NEONATAL JAUNDICE

Comprehensive Clinical Review

Prof. Eman Badran | Professor of Pediatrics | Fifth Year Medical Students

1. DEFINITIONS & KEY CONCEPTS

1.1 Neonatal Jaundice

Yellowish discoloration of the skin and/or conjunctiva caused by bilirubin deposition in tissues. It becomes clinically visible when Total Serum Bilirubin (TSB) exceeds 1 mg/dL (17.1 µmol/L).

1.2 Significant Neonatal Hyperbilirubinemia

Defined in infants ≥35 weeks gestational age (GA) as TSB >95th percentile on the hour-specific Bhutani nomogram. This level indicates the need for close surveillance or treatment.

1.3 Severe Neonatal Hyperbilirubinemia

Defined as Total Serum Bilirubin (TSB) >25 mg/dL (425 µmol/L) in term newborns. It is associated with an increased risk for Bilirubin-Induced Neurologic Dysfunction (BIND).

Term	Definition
TSB	Total Serum Bilirubin — includes both direct (conjugated) and indirect (unconjugated) fractions
TcB	Transcutaneous Bilirubin — non-invasive screening tool
BIND	Bilirubin-Induced Neurologic Dysfunction — brain damage from free bilirubin crossing the blood-brain barrier
ABE	Acute Bilirubin Encephalopathy — the acute signs of BIND
Kernicterus	Chronic and permanent sequelae of BIND
EHC	Enterohepatic Circulation — reabsorption of bilirubin from the gut
UGT1A1	UDP-glucuronosyltransferase 1A1 — the key enzyme for bilirubin conjugation in the liver

2. BILIRUBIN METABOLISM

2.1 Sources of Bilirubin

Bilirubin is produced from the breakdown of heme-containing proteins:

- 80–90%: Degradation of hemoglobin from old or injured RBCs (via macrophages in the spleen and bone marrow)
- 10–20%: Breakdown of hemoproteins in the liver (catalases, cytochrome oxidases)
- Additional: Ineffective erythropoiesis — destruction of newly formed RBCs within the bone marrow before they enter circulation

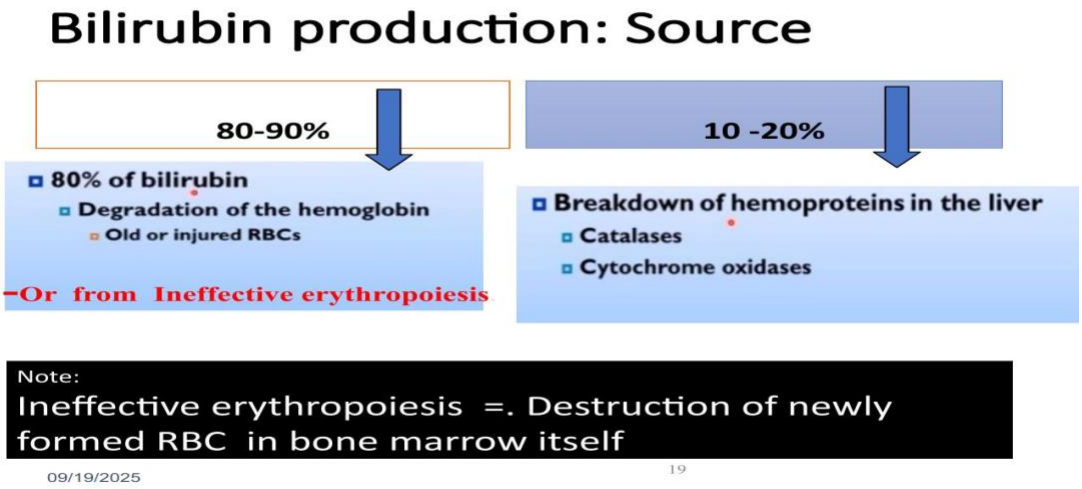


Figure 1: Sources of Bilirubin Production

2.2 Bilirubin Synthesis Pathway

The pathway proceeds in macrophages:

- Macrophages remove old erythrocytes (RBC lifespan = 120 days)
- Hemoglobin is broken down into: Iron (reutilized) + Globin (returned to amino acid pool) + Heme
- Heme → (heme oxygenase) → Biliverdin + CO + Iron
- Biliverdin → (biliverdin reductase) → Bilirubin (released into blood)

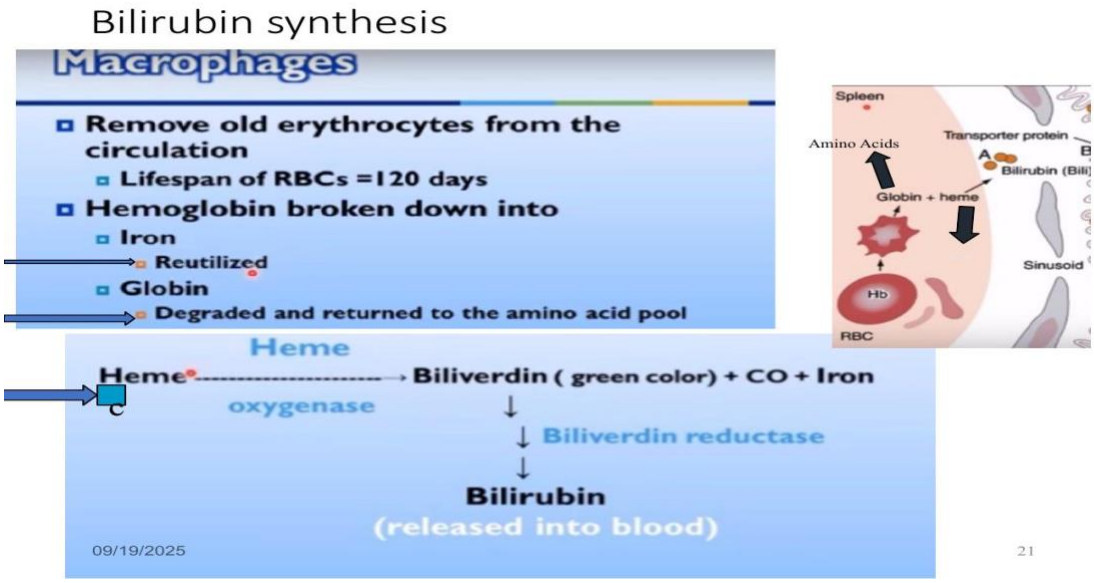


Figure 2: Bilirubin Synthesis — from RBC breakdown to bilirubin release

2.3 Unconjugated Bilirubin in Plasma

After release into the bloodstream:

- Bound to albumin (reversible binding) for transport to the liver
- Can be displaced from albumin by: Drugs (diazepam/Valium, ceftriaxone, sulfa drugs) and Free fatty acids
- Displaced (free) bilirubin is lipid-soluble and can cross the blood-brain barrier — this is the toxic form

2.4 Hepatic Uptake and Conjugation

- Bilirubin is transported to the liver via carrier proteins, primarily OATP-2 (organic anion transporter protein)
- Inside hepatocytes: bilirubin dissociates from albumin
- Conjugation is catalyzed by UGT1A1 (uridine diphosphate-glycosyltransferase 1A1)
- Result: Water-soluble conjugated (direct) bilirubin → excreted into bile
- Phenobarbital enhances bile flow and UGT1A1 activity

2.5 Ethnic Variation in Conjugation

Polymorphisms in the UGT1A1 gene affect enzyme activity:

- Differences in the number of thymine-adenine (TA) repeats in the gene promoter region
- Vary among individuals of Asian, African, and Caucasian ancestry
- These polymorphisms can decrease UGT1A1 enzyme activity → increased total bilirubin levels

2.6 Conjugation Abnormalities

- UGT1A1 polymorphism
- Crigler-Najjar Syndrome (Types I and II) — severe UGT1A1 deficiency

- Gilbert Syndrome — mild UGT1A1 reduction
- Inhibitory factors for hepatic UGT1A1: substances in breast milk (→ breast milk jaundice); maternal plasma factors (→ Lucey-Driscoll syndrome)

2.7 Bilirubin Metabolism in Adults

In adults, conjugated bilirubin excreted in bile reaches the gut where:

- Gut bacteria reduce it to colorless urobilinogen
- 85% → oxidized in the colon to stercobilinogen → excreted in feces
- 15% → absorbed into portal blood → enters enterohepatic circulation → re-excreted by the liver
- Some urobilinogen enters systemic blood → excreted in urine as urobilin (gives yellow color)

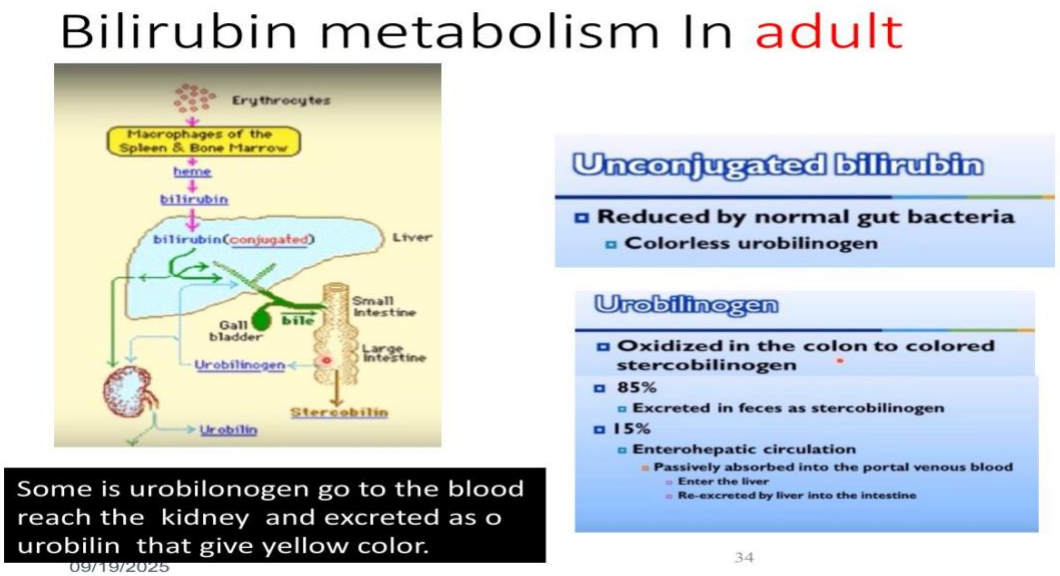


Figure 3: Bilirubin Metabolism in Adults — full pathway from RBC to excretion

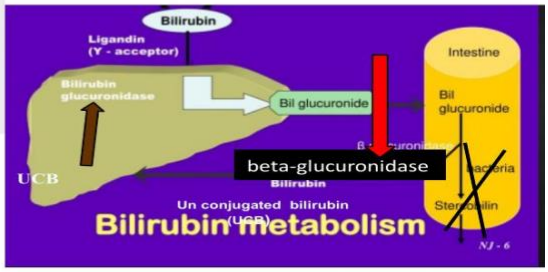
2.8 Neonatal Bilirubin Metabolism — Enterohepatic Circulation (EHC)

> ⚠ **Key Neonatal Difference: Neonates have beta-glucuronidase in their intestinal mucosa — an enzyme absent (or low) in adults.**

- Beta-glucuronidase deconjugates conjugated bilirubin back to unconjugated bilirubin (UCB)
- UCB is then partially reabsorbed through the intestinal wall and recycled into circulation — this is the EHC of bilirubin
- This significantly increases total bilirubin levels in newborns
- EHC is exaggerated by: intestinal obstruction, delayed passage of meconium, fasting (decreases transit time)

Bilirubin metabolism in neonate (Entero- hepatic circulation EHC)

- Neonates have beta-glucuronidase in the intestinal mucosa
- It deconjugates the conjugated bilirubin to **unconjugated bilirubin** (UCB)



UCB fraction is partially reabsorbed through the intestinal wall and recycled into the circulation, a process known as the “EHC of bilirubin".
undergoes EHC

Excessive amounts of bilirubin are available for reabsorption in : obstruction of the upper intestinal tract, delayed passage of meconium, or fasting (decrease transient time)

Figure 4: Neonatal Bilirubin Metabolism — the Enterohepatic Circulation (EHC)

3. TYPES OF NEONATAL JAUNDICE

3.1 Physiologic Jaundice

Mechanisms

- Increased bilirubin production: increased RBCs, shortened RBC lifespan (70–90 days vs adult 120 days), ineffective erythropoiesis
- Hepatic immaturity: immature uptake (paucity of ligandin), decreased UGT1A1, decreased hepatic excretion
- Increased enterohepatic circulation: high beta-glucuronidase activity

Characteristics (all 4 must be present)

- Has a Pattern: peaks day 3–4 in term neonates; day 5–7 in preterm
- Baby is well — clinically stable, feeding normally
- Rate of rise: <0.2 mg/dL/hour, <5 mg/dL/day; mean peak <15 mg/dL
- May be exaggerated (especially in breastfed infants — see breast feeding jaundice below)
- Usually disappears by day 4–5 in term (rarely 7–10 days); by day 7–9 in preterm (rarely up to 2 weeks)

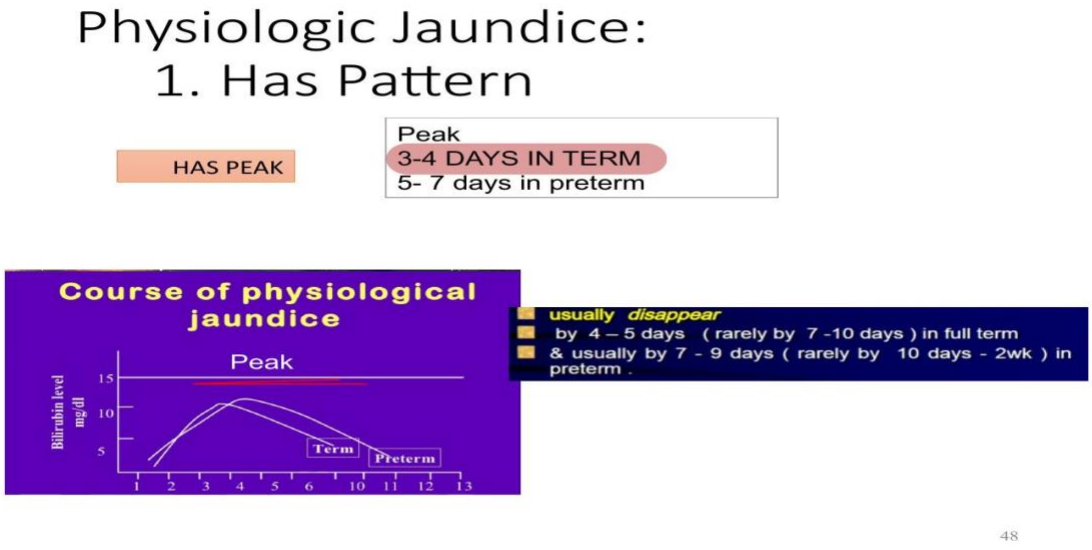


Figure 5: Course of Physiological Jaundice — Term vs. Preterm bilirubin peak patterns

3.2 Breast Feeding Jaundice (BFJ)

Occurs in the first few days of life. Caused by inadequate intake, not by breast milk itself.

- Elevated unconjugated bilirubin — can exaggerate physiologic jaundice
- Associated with mild dehydration: weight loss >8% of birth weight (day 3–4), possible elevated serum Na, dehydration fever

Management of BFJ

- Improve/increase breastfeeding frequency (every 2–3 hours)
- No water or dextrose supplementation

- Formula supplementation is acceptable
- May need phototherapy — shared decision with parents

3.3 Breast Milk Jaundice (BMJ)

Develops AFTER the first 4–7 days of life. Distinct from Breast Feeding Jaundice.

- Caused by inhibitory factors in breast milk (substances that inhibit UGT1A1) and high beta-glucuronidase activity in milk
- May be familial (2–4% of breastfed infants)
- Persists longer than physiologic jaundice — can last 3–12 weeks
- Rarely causes BIND unless bilirubin >25 mg/dL
- Has no other identifiable cause — diagnosis of exclusion
- Genetic factors may play a role

3.4 Prolonged Jaundice

Defined as clinically significant jaundice (TSB within 35 µmol/L [≈2 mg/dL] of the phototherapy threshold) persisting beyond 14 days of life.

Causes — Unconjugated (Indirect) Hyperbilirubinemia

- Hemolytic disease (G6PD deficiency, ABO/Rh incompatibility)
- Congenital hypothyroidism
- Genetic syndromes: Crigler-Najjar, Gilbert syndrome
- UGT1A1 gene polymorphisms (ethnic variation)
- Breast milk jaundice

Causes — Conjugated (Direct) Hyperbilirubinemia

- Cholestatic liver diseases (e.g., biliary atresia — requires early surgical intervention)
- Metabolic/infectious causes: inborn errors of metabolism, sepsis, UTI

⚠ Always check direct (conjugated) bilirubin when jaundice persists >14 days. Direct bilirubin >17 µmol/L (≈1 mg/dL) is ABNORMAL and may indicate cholestasis.

3.5 Pathologic Jaundice

🚨 Pathologic jaundice is a MEDICAL EMERGENCY

Features suggesting pathologic jaundice

- Onset of jaundice <24 hours of birth
- Rapid rise: >0.3 mg/dL/hour in first 24 hours, or >0.2 mg/dL/hour thereafter
- Signs of illness: lethargy, poor feeding, vomiting, apnea, tachypnea, temperature instability, excess weight loss
- Jaundice in a term newborn after two weeks of age
- Direct (conjugated) bilirubin >1 mg/dL

Causes — Increased Production

- Isoimmune-mediated hemolysis: ABO or Rh(D) or minor blood group incompatibility

- Inherited RBC membrane defects: hereditary spherocytosis, elliptocytosis
- Erythrocyte enzymatic defects: G6PD deficiency, pyruvate kinase deficiency, congenital erythropoietic porphyria
- Viral or bacterial infections (sepsis)
- Polycythemia
- Sequestration of blood: cephalohematoma
- Ineffective erythropoiesis
- Inherited biochemical abnormalities: Galactosemia

Causes — Decreased Clearance/Excretion

- Crigler-Najjar syndrome types I and II
- Gilbert syndrome
- OATP-2 polymorphism
- Congenital hypothyroidism
- GI/Liver diseases including metabolic liver disease

Causes — Increased Enterohepatic Circulation

- NPO (nothing by mouth)
- Intestinal obstruction
- Any cause of decreased intestinal transit time

G6PD Testing Notes

- Do a G6PD enzyme assay in all babies with jaundice that doesn't respond to phototherapy, or appears without obvious risk factors
- Caution: test may be falsely normal during acute hemolysis (young circulating RBCs still have enough enzyme)
- If suspicion remains: repeat testing at 3 months of age

4. BILIRUBIN-INDUCED NEUROLOGIC DYSFUNCTION (BIND)

4.1 Pathophysiology

Free (unbound) bilirubin crosses the blood-brain barrier and binds to brain tissue, causing both molecular and cytological injuries to brain cells.

4.2 Acute Signs — Acute Bilirubin Encephalopathy (ABE)

- Change in level of consciousness: irritability alternating with increasing lethargy → coma
- Poor feeding → cessation of feeding
- Hypertonia: retrocollis (neck arching backward), opisthotonus (back arching)
- Shrill (high-pitched) cry
- Bicycling movements (possible seizures)
- Fever

4.3 Chronic Sequelae — Kernicterus

Kernicterus is the chronic and PERMANENT consequence of BIND. It is preventable with early recognition and prompt treatment.

> **Key Message: Life-long complications of severe neonatal hyperbilirubinemia are PREVENTABLE by early recognition and prompt early treatment.**

CLINICAL CASE VIGNETTE

3-day-old male (73 hrs), BW=2.7 kg, born at 36 wks, exclusively breastfed. Mother presents because baby is sleepy and feeding less. On exam: hard to arouse, shrill cry, jaundiced. Weight 2.3 kg.
TSB: 25 mg/dL (425 µmol/L) | Indirect: 23 mg/dL | Hgb: 13.5 g/dL | Direct Coombs: Negative
Diagnosis: BIND (Acute Bilirubin Encephalopathy)

5. BILIRUBIN MEASUREMENT

5.1 When to Measure TSB

- If jaundice appears <12 hours of age (always urgent)
- Baby with jaundice <24 h or rapid rise → always get a serum TSB (not just TcB)
- All babies ≥12 h old must have TSB or TcB measured before discharge
- If discharged before 12 h (e.g., home births) → arrange bilirubin check within the first day

5.2 Newborn Screen Testing

If maternal blood group (ABO and Rh) and red cell antibody screen are positive or unknown at delivery, newborn testing should include:

- Total Serum Bilirubin (TSB)
- Hemoglobin, reticulocyte count, blood smear
- Direct Antiglobulin Test (DAT) and blood group
- Preferably obtained from cord blood
- Monitor closely for early (<24 hours) hyperbilirubinemia

5.3 When to Confirm TcB with Serum TSB

Situation	Action Required
TcB within 50 µmol/L (≈3 mg/dL) of phototherapy threshold	Confirmatory serum TSB required
TcB above 250 µmol/L (≈14.6 mg/dL)	Confirmatory serum TSB required
TcB clearly below threshold and baby is well	TcB alone is acceptable (interpret with clinical context)
Jaundice <24 h or rapid rise	Always get serum TSB regardless of TcB result

6. ASSESSMENT OF RISK FOR SEVERE HYPERBILIRUBINEMIA

6.1 Risk Factors for Significant Hyperbilirubinemia

General Risk Factors (AAP/CPS Guidelines 2025)

- Lower gestational age
- Jaundice in the first 24 hours after birth
- Predischarge TcB or TSB concentration close to the phototherapy threshold
- Hemolysis from any cause (rapid TSB/TcB rise >0.3 mg/dL/hour in first 24 h or >0.2 mg/dL/hour thereafter)
- Phototherapy before discharge
- Parent or sibling who required phototherapy or exchange transfusion
- Family history or genetic ancestry suggestive of inherited RBC disorders, including G6PD deficiency
- Exclusive breastfeeding with suboptimal intake
- Scalp hematoma or significant bruising
- Down syndrome
- Macrosomic infant of a diabetic mother

High-Risk Factors for Hyperbilirubinemia Neurotoxicity

> ⚠ **These risk factors LOWER the threshold for treatment with phototherapy**

- Gestational age <38 weeks (risk increases with decreasing GA)
- Albumin <3.0 g/dL
- Isoimmune hemolytic disease (positive direct antiglobulin test), G6PD deficiency, or other hemolytic conditions
- Sepsis
- Significant clinical instability in the previous 24 hours

6.2 The 6-Step Assessment Protocol (AAP/CPS 2025)

Step 1: Newborn Screen

Test for maternal blood group and red cell antibody; obtain TSB, Hgb, reticulocyte, DAT if maternal antibody screen is positive or unknown.

Step 2: Risk Factor Assessment

Evaluate all clinical risk factors as listed above. Infants with risk factors require closer monitoring.

Step 3: Know Phototherapy Thresholds

Use hour-specific, gestational age-specific phototherapy threshold charts (Figures 6 and 7 below).

Step 4: Measure TSB/TcB Before Discharge

Every baby should have TSB or TcB measured at ≥12 hours of life.

Calculate Δ-TSB

Δ-TSB = Treatment threshold − Measured bilirubin

This tells you how far the baby is from needing treatment and guides follow-up timing.

Δ-TSB (mg/dL)	Δ-TSB (µmol/L)	Meaning	Action
≤1.8	≤30	Very close to treatment line — HIGH RISK	Urgent: start phototherapy or recheck in 6–12 h
1.9–3.5	31–60	May reach treatment line soon	Recheck in 12–24 h; sooner if risk factors
3.6–5.9	61–100	Below threshold but needs watching	Recheck in 1–2 days
>6.0	>100	Well below treatment threshold	Routine follow-up in 2–3 days

> **Rule of 30: If Δ-TSB ≤30 µmol/L (≈1.8 mg/dL), act urgently. Consider early phototherapy if risk factors present even when slightly below threshold.**

Step 5: Communicate Clearly to Families

- Give parents written + verbal information in their first language
- Include: baby's bilirubin level(s), age at testing, calculated Δ-TSB, next steps
- Teach warning signs: jaundice in first 24 h, poor feeding, excessive sleepiness, dark urine, pale stools

Step 6: Support Breastfeeding

- Early skin-to-skin contact
- Frequent feeding (8–12 times/day)
- Monitor weight, urine, and stool output
- Arrange community resources (lactation clinics, hotlines)

6.3 Risk Zone Nomogram

Use the Bhutani nomogram to determine the bilirubin risk zone at discharge (for infants >35 weeks):

- High-risk zone (>95th percentile) → urgent follow-up
- High-intermediate zone (75th–95th) → early follow-up
- Low-intermediate zone (40th–75th) → routine follow-up
- Low-risk zone (<40th percentile) → standard follow-up

6.4 Post-Discharge Follow-Up

- Infants discharged before 48 hours → seen within 2 days of discharge
- Infants with significant risk factors for severe hyperbilirubinemia → seen within 1 day

> ⚠ **Visual assessment of jaundice is UNRELIABLE. Always confirm with bilirubin measurement.**

Causes of Kernicterus — Preventable Failures (from Pediatrics literature)

- Failure to check bilirubin level if onset in first 24 hours

- Early discharge (<48 hrs) without follow-up within 48 hrs
- Visual assessment underestimated severity
- Delay in testing jaundiced newborns or treating elevated levels
- Lack of concern for jaundice or parental concern
- Failure to note risk factors

7. MANAGEMENT

7.1 Guidelines

- AAP Guidelines 2022: https://publications.aap.org/pediatrics (Pediatrics 2022; 150(3):e2022058865)
- Canadian Paediatric Society (CPS) Guidelines 2025: https://cps.ca
- NICE Guidelines (UK) — also available
- Mobile apps: https://hyperbili.com (Canadian), https://peditools.org/bili2022/ (AAP 2022)

7.2 Phototherapy

Goal and Mechanism

- Treat neonatal hyperbilirubinemia and prevent neurotoxicity
- Decreases the need for exchange transfusion
- Exposes the skin of the jaundiced baby to blue or cool white light of wavelength 425–475 nm
- The toxic bilirubin molecule isomerizes (changes shape) to a non-toxic, water-soluble product that can be excreted without conjugation

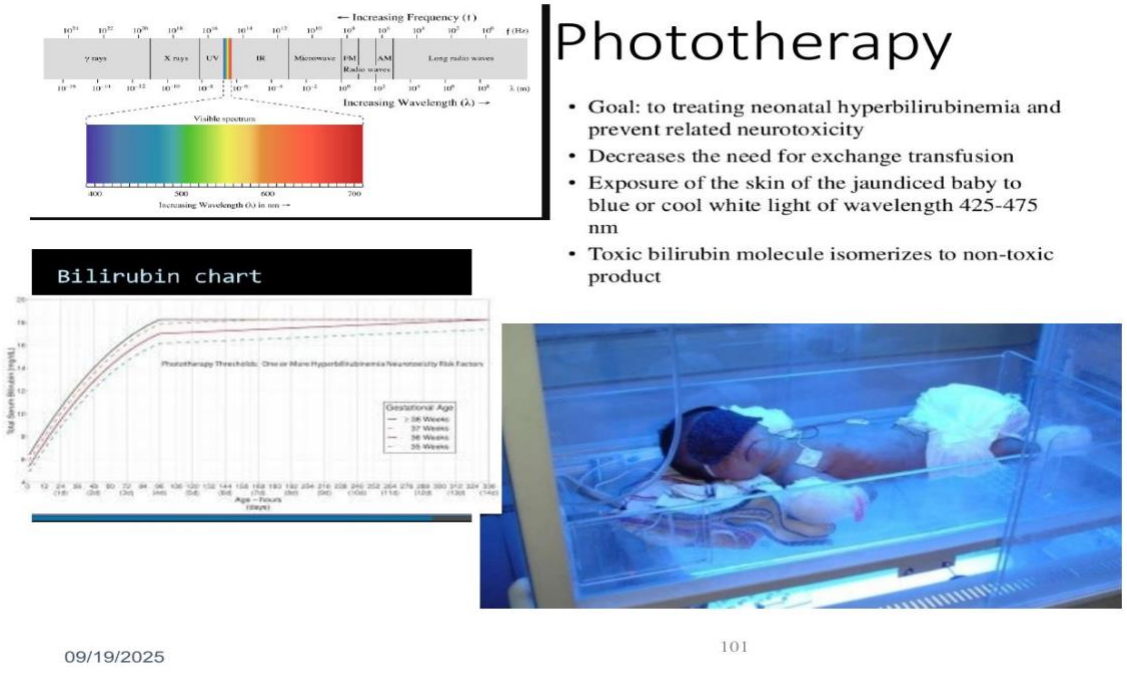


Figure 6: Phototherapy — mechanism (light spectrum), bilirubin chart, and a neonate receiving phototherapy

Phototherapy Thresholds

Use the hour-specific, gestational age-specific threshold charts. Two separate charts exist:

- Chart 1 (Figure 7): Infants with NO hyperbilirubinemia neurotoxicity risk factors
- Chart 2: Infants with ≥1 hyperbilirubinemia neurotoxicity risk factor (lower thresholds)

Intensive phototherapy is recommended at the TSB phototherapy threshold based on gestational age, risk factors, and age in hours.

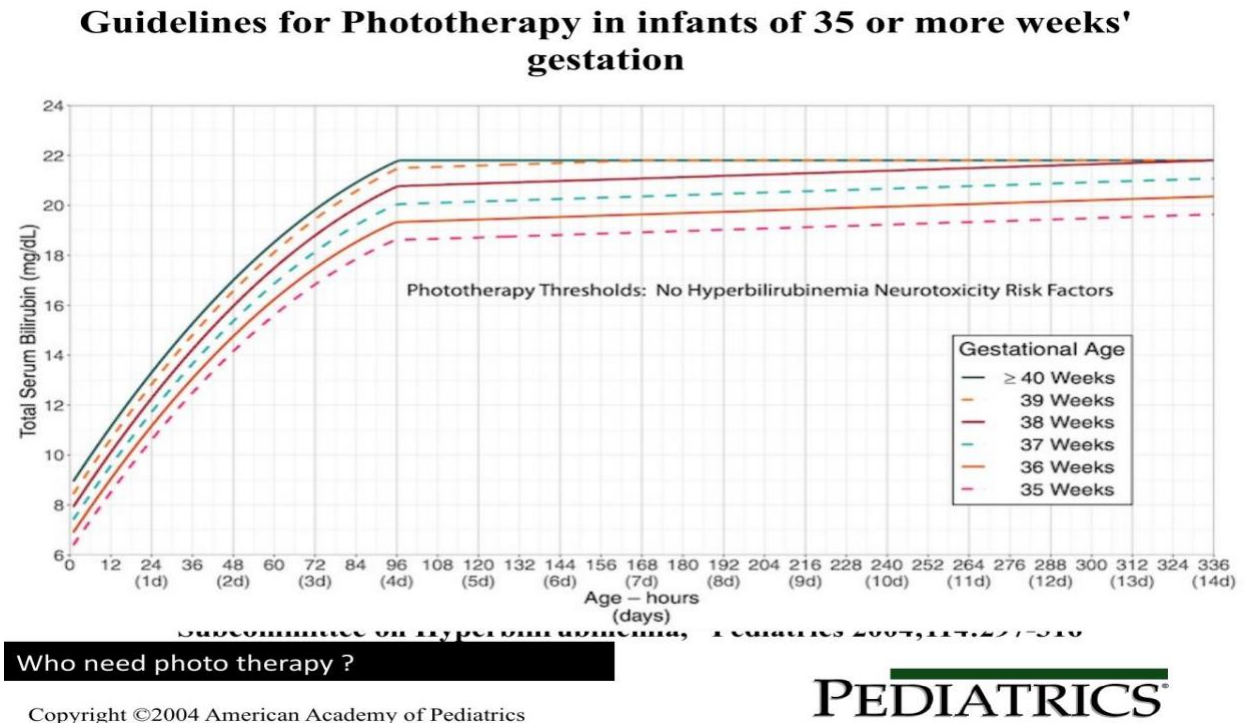


Figure 7: AAP Phototherapy Thresholds for Infants ≥35 Weeks Gestation (No Neurotoxicity Risk Factors) — stratified by gestational age

Adverse Effects of Phototherapy

Phototherapy is safe and lifesaving. Possible but weak associations with:

- Asthma, Allergies, Blood cancers, Epilepsy

Evidence is weak and confounded. Clinical message: Benefits outweigh risks — use phototherapy whenever the threshold is reached.

7.3 Intravenous Immune Globulin (IVIG)

- Dose: 0.5 to 1 g/kg over 2 hours; may be repeated in 12 hours if necessary
- Recommended for infants with isoimmune hemolytic disease AND TSB level rising despite phototherapy
- Also recommended when TSB is within 2–3 mg/dL of the exchange transfusion threshold

7.4 Exchange Transfusion

Indications

- Bilirubin levels >25 mg/dL not responding to phototherapy
- Evidence of Acute Bilirubin Encephalopathy
- TSB at or above exchange transfusion threshold charts (accounting for risk factors)

Exchange transfusion thresholds are also gestational-age specific:

- Chart without risk factors: thresholds range from ~16–28 mg/dL depending on GA and age in hours
- Chart with neurotoxicity risk factors: lower thresholds apply

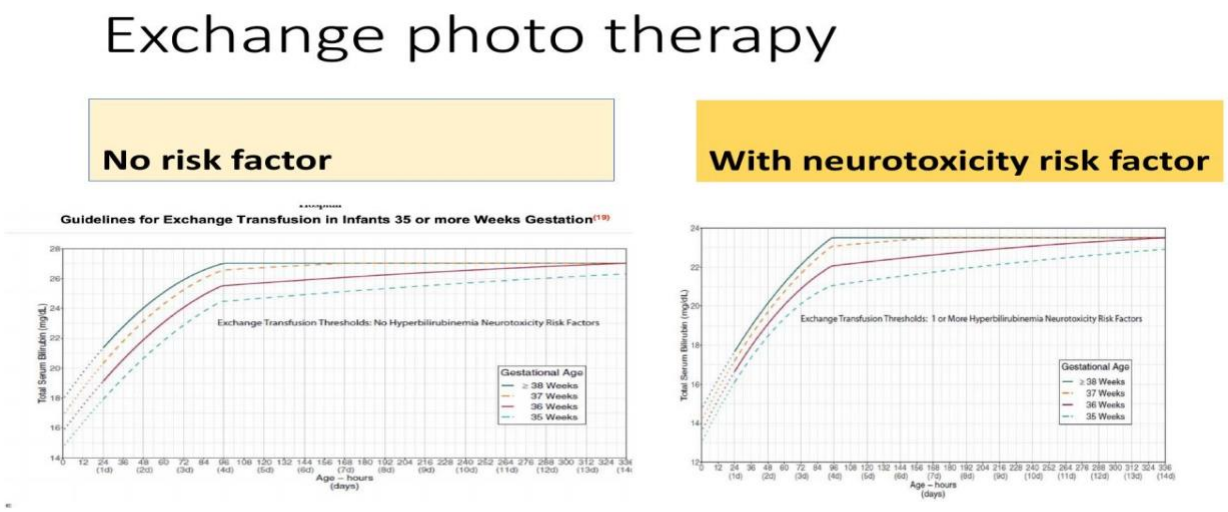


Figure 8: Exchange Transfusion Thresholds — Left: No risk factors; Right: With neurotoxicity risk factors (by gestational age, 35+ weeks)

7.5 Follow-Up After Hyperbilirubinemia

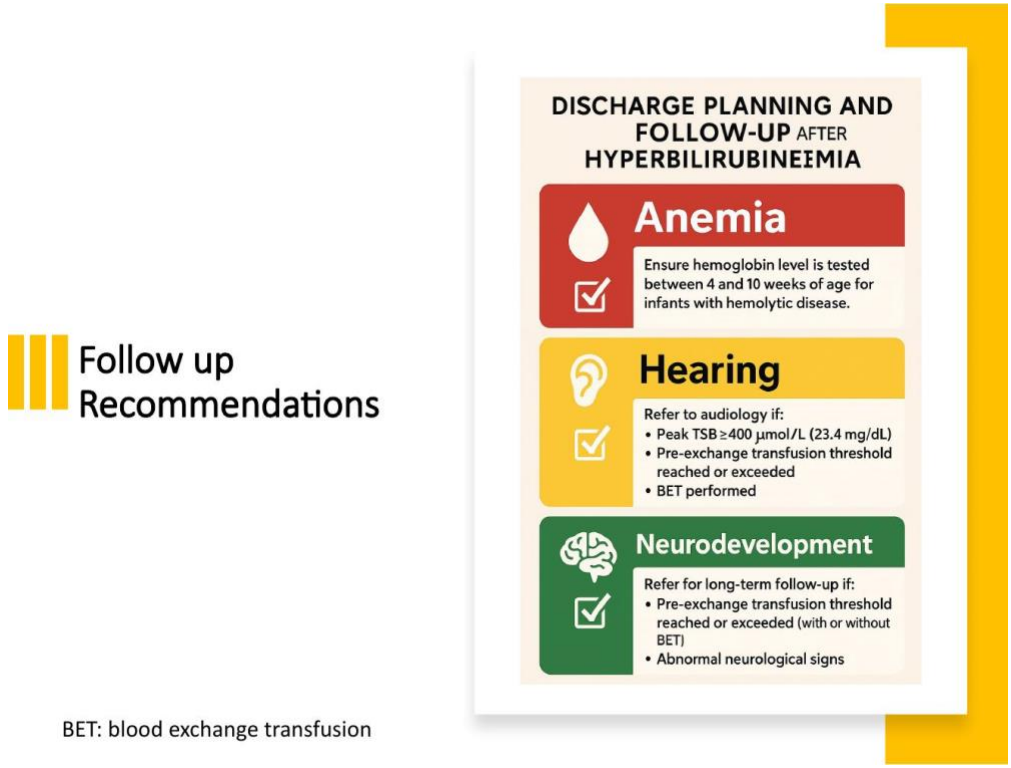


Figure 9: Discharge Planning and Follow-Up After Hyperbilirubinemia

Specific follow-up recommendations:

- Anemia: ensure hemoglobin is tested between 4 and 10 weeks of age for infants with hemolytic disease

- Hearing: refer to audiology if peak TSB ≥400 µmol/L (23.4 mg/dL), or pre-exchange transfusion threshold reached/exceeded, or BET was performed
- Neurodevelopment: refer for long-term follow-up if pre-exchange transfusion threshold was reached or exceeded (with or without BET), or if abnormal neurological signs are present

8. QUICK REFERENCE SUMMARY

Physiologic vs. Pathologic vs. Breast Milk Jaundice

Feature	Physiologic	Breast Milk Jaundice	Pathologic
Onset	Day 2–3	Day 4–7	<24 hours
Duration	5–7 days (term)	3–12 weeks	Variable
Baby's status	Well	Well	May be ill
Type of bili	Indirect (unconjugated)	Indirect (unconjugated)	Direct or indirect
Key feature	Has peak; resolves	Persists after physiologic phase	Rapid rise or early onset
Action	Monitor	Monitor; rarely needs phototherapy	URGENT workup

Treatment Summary

Treatment	Details
Phototherapy	First-line treatment; blue light 425–475 nm; start at gestational age- and hour-specific threshold
IVIG	For isoimmune hemolysis; 0.5–1 g/kg; if TSB rising despite phototherapy or within 2–3 mg/dL of exchange threshold
Exchange Transfusion	For TSB >25 mg/dL, no response to phototherapy, or signs of ABE; replaces sensitized RBCs and removes bilirubin
Breastfeeding Support	Core intervention for BFJ; 8–12 feeds/day; no water/glucose supplementation

Prepared from lecture by Prof. Eman Badran — Based on AAP 2022 & CPS 2025 Guidelines