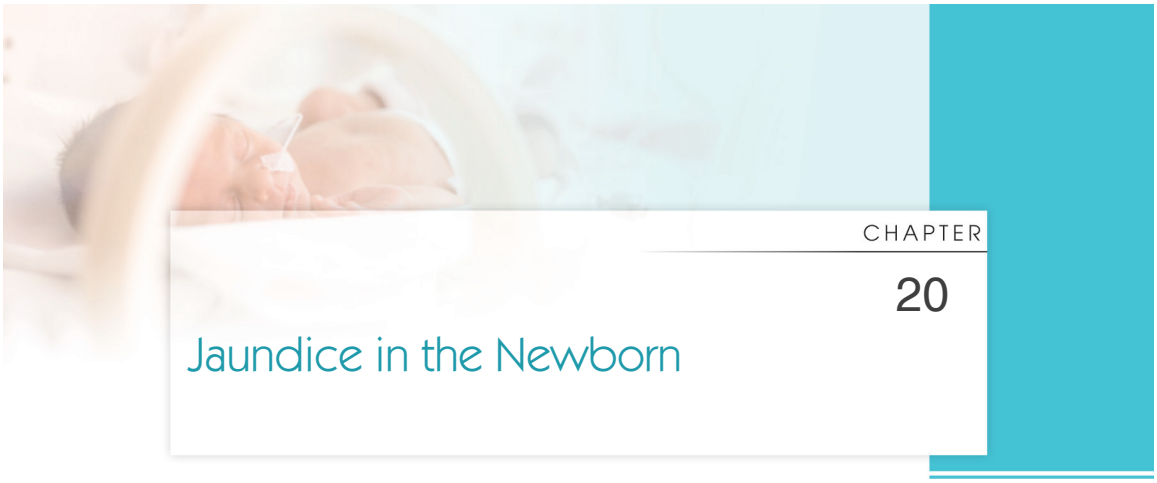


CHAPTER

20

Jaundice in the Newborn

Jaundice is the most common morbidity in the first week of life, occurring in about 60% of term and 80% of preterm newborns. Globally, it ranks 7th among all causes of mortality in the early neonatal period.[1] It is also the most common cause of readmission after discharge from the birth hospitalization. In neonates, jaundice appears when total serum bilirubin (TSB) concentration exceeds 5–7 mg/dl. In most cases, it is benign and does not require any intervention. The primary concern with neonatal jaundice is the risk of bilirubin-induced neurological dysfunction (BIND), which is, fortunately, rare. Nevertheless, a few neonates develop long-term sequelae of BIND that are entirely preventable in most of them.

PHYSIOLOGICAL JAUNDICE

Jaundice attributable to the physiological immaturity of neonates to handle a high burden of bilirubin is termed 'physiological jaundice.' Neonatal bilirubin production is 2–3-fold that of adults, owing to increased hematopoiesis and a shortened RBC lifespan. The enzymes for bilirubin conjugation (UGT1A1) have little activity in neonates. Enterohepatic circulation is also enhanced due to deficient intestinal flora and high intestinal beta-glucuronidase activity, causing the reabsorption of conjugated bilirubin.

In term neonates, physiological jaundice usually appears between 24 and 72 hours of life, rises to a peak level of 12–15 mg/dl by 3 days, and then starts falling. In preterm neonates, the peak level occurs between 3 and 7 days, and TSB can rise over 15 mg/dl. It may take weeks before the TSB falls under 2 mg/dl in both term and preterm neonates. Jaundice in most neonates is physiological and rarely requires treatment.

PATHOLOGICAL JAUNDICE

'Pathological jaundice' is an arbitrarily and loosely defined term for bilirubin levels beyond the normal physiological range

that generally requires further investigation and treatment. It includes:

- Visible jaundice in the first 24 hours of life (however, slight jaundice appearing on the face by 18–24 hours is common and may be considered physiological).
- Presence of jaundice on arms and legs on day 2 of life
- Yellow palms and soles at any age
- Presence of jaundice on arms and legs on day 2 of life
- Yellow palms and soles at any age
- TSB more than 95th centile as per age-specific bilirubin nomogram
- Rise of TSB more than 0.3 mg/dl/hour on day 1 and 0.2 mg/dl/hour beyond 24 hours
- Any jaundice with features of BIND
- Clinical jaundice persisting beyond 2 weeks in term and 3 weeks in preterm neonates.

Causes

Increased production	• Polycythemia. • Extravasated blood (hematomas or internal hemorrhage-pulmonary/intracranial/gastrointestinal) • Hemolytic diseases (immune-mediated, red cell membrane enzymatic defects, hemoglobinopathies)
Decreased clearance	• Increased enterohepatic circulation (GI obstruction) • Cholestasis (due to anatomical causes like biliary atresia, or inborn errors of metabolism like tyrosinemia, galactosemia, etc.)

IDENTIFYING HIGH-RISK NEONATES

Approximately 5–10% of neonates develop clinically significant jaundice that requires treatment to lower the TSB levels. Factors that increase the risk of developing significant jaundice include:

- Lower gestational age (<40 weeks)
- Hemolytic disease
- History of phototherapy in parents or sibling
- Scalp hematoma or significant bruising
- Exclusively breastfed infant with suboptimal milk intake
- Down syndrome
- Macroscopic infant of a diabetic mother

All neonates should be visually inspected for jaundice at least every 12 hours during the initial 3–5 days of life. Those with the risk factors listed above should be identified and kept under close monitoring.

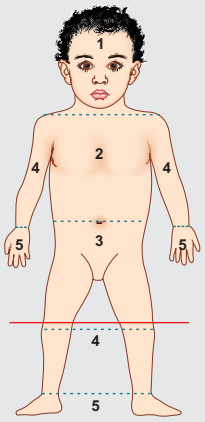
The new American Academy of Pediatrics (AAP) 2022 guidelines recommend that transcutaneous bilirubin (TcB) or TSB value be obtained for all neonates between 24 and 48 hours of life, and post-discharge surveillance be decided based on the difference between this value and the corresponding phototherapy (PT) cutoff. The suggested intervals also consider gestational age at discharge and hyperbilirubinemia neurotoxicity risk factors (listed below).[2]

Estimation of Serum Bilirubin

1. **Visual inspection:** Visual inspection of jaundice (Table 20.1) can help estimate the serum bilirubin levels using Kramer's rule, and if done diligently, has reasonable accuracy (comparable to TcB). The absence of jaundice on visual inspection reliably excludes jaundice. However, it cannot be relied upon at higher TSB levels and following phototherapy.
2. **Transcutaneous bilirubinometry:** TcB measures the reflected light spectra from bilirubin in the skin and subcutaneous tissues.

Table 20.1: Visual inspection of jaundice

1. Examine the baby in bright natural light or bright white fluorescent light.
2. The baby should be naked. Ensure there is no yellow or off-white background.
3. Examine blanched skin and gums or sclerae.
4. Note the extent of jaundice (Kramer's zone).
5. Note the depth of jaundice (Light staining as lemon yellow; deep staining as orange-yellow).



Kramer's zones	Approximate TSB level	
	Light staining jaundice	Deep staining jaundice
1. Face and neck	5–7 mg/dl	7–9 mg/dl
2. Chest and upper abdomen	7–9 mg/dl	9–11 mg/dl
3. Lower abdomen and thighs	9–11 mg/dl	11–13 mg/dl
4. Legs and arms/ forearms	11–13 mg/dl	14–16 mg/dl
5. Palms and soles	13–15 mg/dl	17 mg/dl or more

Although it cannot substitute TSB, it is a good screening tool to determine whether serum bilirubin level should be measured. It is quick and noninvasive and reduces painful sampling needs by almost 30%. TcB values correlate well with TSB (lie within 3 mg/dl) at levels below 15 mg/dl.[2] Above that, TcB tends to underestimate the TSB. TcB level above 15 mg/dl or lying within 3 mg/dl of the PT threshold warrants TSB measurement.

TcB can be used for neonates of all gestations[3] and in mixed racial populations. Measurements are affected by the skin's melanin content; depending on the instrument, it may overestimate or underestimate TSB in dark-skinned neonates. For the same reason, it is believed to be unreliable for skin bleached from PT; however, it can be used for rebound measurements taken 24 hours after stopping PT.

Measurement of Serum Bilirubin

High-performance liquid chromatography (HPLC) remains the gold standard for the estimation of TSB. However, this test is available for research purposes only. Laboratory estimation of TSB is usually performed by the van den Bergh reaction. It has marked inter-laboratory variability, with the coefficient of variation being up to 10–12%. Novel methods for bilirubin measurement include spectrophotometry, optical imaging of conjunctiva, and exhaled carbon monoxide (CO) spectroscopy. CO is produced in equimolar amounts when heme is degraded, and ETCO >2 ppm may help identify infants undergoing hemolysis.[4]

Indications of TSB measurement:

- Jaundice in the first 24 hours of life.
- Confirmation of high TcB levels before initiating therapy.
- Monitoring during and up to 24 hours after phototherapy.

APPROACH TO A JAUNDICED NEONATE

Thorough history taking and examination usually guide lab investigations in cases of pathological jaundice (detailed in Table 20.2). However, treatment should never be delayed, and phototherapy or exchange transfusion should be initiated as soon as possible when indicated. While no cause may be found in many cases, a cause for jaundice should be sought after in all neonates requiring phototherapy.[5]

Table 20.2: History, examination and laboratory tests		
History	*Examination*	*Laboratory tests*
• Family history suggestive of hemolytic anemia/liver disease/sibling with jaundice • Antenatal history to indicate TORCH infections, gestational diabetes mellitus, intake of drugs that displace bilirubin or that trigger hemolysis in G6PD deficiency • Birth history suggestive of trauma or asphyxia • Feeding history (milk or formula, adequacy) and history suggestive of pyloric stenosis or intestinal obstruction	• Gestational assessment • Features suggestive of dehydration/ low caloric intake • Pallor/petechiae/ bruising/enclosed hemorrhage • Hepatosplenomegaly • Signs of infection (congenital/ acquired)	• Essential—Blood typing (mother and infant), direct Coombs' test, peripheral smear, G6PD levels • Optional—Direct bilirubin levels, TSH, sepsis screen, metabolic workup

THERAPEUTIC OPTIONS

Phototherapy

Phototherapy (PT) remains the mainstay of treating hyperbilirubinemia in neonates. It can be provided using compact fluorescent lamps (CFL), high-intensity light-emitting diodes (LED), fiber-optic units, and halogen lights. CFL is the most used device with its easy availability and low cost. However, the use of LEDs has increased recently. Although their efficacy in reducing TSB levels is similar compared to conventional sources as per 2 meta-analyses,[6,7] they have several advantages such as a longer life, narrow emission spectrum, less infrared radiation (thus less water loss), and less heat production (allowing the device to be placed closer to the infant thus increasing the irradiance). Halogen lights are unsafe to use as they produce much heat and may lead to thermal injury. Fiber-optic devices are designed to transmit light from LED or halogen sources to pads or blankets via flexible optic fibers. They provide higher irradiance than fluorescent lamps and produce minimal heat but would not cover adequate surface area for stand-alone use. Typically used to provide under-surface PT to increase the efficacy of the overhead source (e.g. Biliblanket), they may also be used for continuing PT in neonates undergoing ET.

Efficacy of PT mainly depends on the light source (irradiance of light, spectrum of wavelength), the exposed body surface area, and the underlying cause of jaundice. Effective PT requires at least 30 μW/cm^2/nm irradiance, with a wavelength between 460 and 490 nm (matches the absorption spectrum of bilirubin). The PT unit should be kept as close to the baby as possible for greater irradiance.[5] Light rays should be perpendicular to the baby in an incubator to minimize reflectance. Moreover, the irradiance of PT units should be periodically measured, at several points on the unit, as it decays with time. Reflective white curtains have been shown to cause a greater decline in TSB and may even decrease the length of hospital stay.[8] Maximizing the exposed surface area by removing all clothes and minimizing the area covered by diapers is essential. Turning the infant to expose unbleached skin does not improve the efficacy of PT. The baby's eyes should be covered with a small patch, temperature monitored, and breastfeeding continued, minimizing interruptions to less than 30 minutes. Routine fluid or feed supplementation is not required.

The rate of decline of TSB with PT depends on the spectral power (average irradiance across the surface area) and the cause of jaundice. Effective PT causes a decrease in TSB by at least 2 mg/dl within 4–6 hours of initiation. Lack of fall in TSB or rising levels indicates ongoing hemolysis.

Indications

1. TSB levels at or above the phototherapy threshold.
2. Neonates with features of BIND while exchange transfusion is being arranged.
3. Home-based LED phototherapy is now considered a feasible option for discharged neonates whose TSB is not more than 1 mg/dl above PT cutoff and are otherwise well, with no risk factors for bilirubin neurotoxicity (only if daily monitoring of TSB can be ensured).[2]

The PT thresholds are based on AAP nomograms (2022), which have separate charts for neonates with and without hyperbilirubinemia neurotoxicity risk factors (gestation <38 weeks, serum albumin <3 g/dl, sepsis, isoimmune hemolytic disease, and significant clinical instability in last 24 hours). Each chart has separate cutoff lines for different gestations (>35 weeks), with higher cutoffs for lower gestational age neonates. Readers may refer to the AAP publication for the charts.[2]

The 2022 AAP guidelines have raised thresholds for each gestation compared to the 2004 guidelines, recognizing that neurotoxicity occurs way above the previous thresholds. However, using higher cut-offs also entails ensuring adherence to rigorous follow-up, which may not be possible in resource-limited settings.[2]

No evidence-based guidelines exist for neonates below 35 weeks of gestation for initiating PT or exchange transfusion. Consensus-based guidelines from NICE (2010), Norwegian guidelines, and the AAP Committee on Fetus and Newborn are available. *We follow the NICE guidelines for neonates below 35 weeks gestation in our unit*. NICE guidelines can be accessed at https://www.nice.org.uk/guidance/cg98/evidence/full-guideline-245411821.

Contraindications

Congenital porphyria (or a family history of porphyria) is an absolute contraindication to initiating PT. Severe blistering and agitation on exposure to PT should alert for the presence of this disease.

The presence of conjugated hyperbilirubinemia, especially in sick LBW babies, should not be considered a contraindication to starting PT.

Monitoring

Neonates undergoing PT should be assessed for hydration status, hypo/hyperthermia, deteriorating feeding pattern, and features of BIND. Hemoglobin or hematocrit levels should be measured for all neonates receiving PT. After initiation of PT, TSB levels should be measured every 4–6 hours initially and then every 6–12 hours once the TSB is stable or declining. PT may be discontinued once TSB falls 2 mg/dl below the PT threshold at which it was initiated, as per the 2022 AAP recommendations.[2]

Following discontinuation of PT, rebound hyperbilirubinemia may occur, and rebound TSB should be measured at least 12 hours after discontinuation of PT (preferably 24 hours, in which case TcB can be used). In neonates at higher risk for rebound hyperbilirubinemia (gestation below 38 weeks, PT initiated within 48 hours of life, hemolytic disease), TSB may be obtained after 6 hours.

Adverse Effects

PT is a remarkably safe therapy that has stood the test for decades. PT does not use UV light, and exposure is mostly harmless. It may cause transient diarrhea or an erythematous rash. In neonates

with conjugated hyperbilirubinemia, it may lead to dark brown discoloration of the skin (bronze baby syndrome) due to the accumulation of photoproducts of bilirubin. Recent studies suggest PT may not be as harmless as it is thought to be and may be sub-clinically carcinogenic and genotoxic.[9] Oxidative injury to cell membranes and DNA may occur, especially in extremely LBW neonates. It thus becomes essential to minimize the duration of PT whenever possible and limit its use to evidence-based indications.

Exchange Transfusion

Double volume exchange transfusion (DVET) is the most effective method for rapidly removing bilirubin. It replaces 85% of circulating RBCs and causes a fall in TSB by about 50% immediately post-procedure.[10] After equilibration occurs with extravascular bilirubin, TSB usually would return to 2/3rd of the pretransfusion level. For infants with Rh isoimmunization, DVET has the added advantage of removing circulating and bound maternal antibodies from the baby's serum.

DVET is usually performed by a pull-and-push technique using the umbilical venous route. The umbilical catheter should be inserted just enough to get a free flow of blood. Individual aliquot volume should not exceed 10% of blood volume, with a maximum of 20 ml for a 3 kg term infant. A blood warmer is recommended to prevent hypothermia during the procedure. TSB levels should be measured at 2 and 6 hours after transfusion, and then 12 hourly until PT can be discontinued (Table 20.3).

Table 20.3: Type and volume of blood for exchange transfusion

S.No.	*Condition*	*Type of blood*
1.	Rh isoimmunization	Rh negative and blood group 'O' or that of baby Suspended in AB plasma Cross-matched with the baby's and mother's blood
2.	ABO incompatibility	Rh compatible and blood group 'O' *(not that of the baby)* Suspended in AB plasma Cross-matched with the baby's and mother's blood

(*Contd.*)

Table 20.3: Type and volume of blood for exchange transfusion (*Contd.*)		
S.No.	*Condition*	*Type of blood*
3.	Other conditions (G6PD deficiency, non-hemolytic, other isoimmune hemolytic jaundice	Baby's group and Rh type Cross-matched with the baby's and mother's blood

- Volume of blood: Twice the blood volume of the baby (total volume: 160–180 ml/kg).
- To prepare blood for DVET, mix two-thirds of the total volume as packed red blood cells and one-third as plasma.

Indications

- Acute bilirubin encephalopathy (irrespective of TSB level).
- TSB levels above exchange cutoff (based on AAP nomograms, as described above)
- In Rh-isoimmunized neonates, if cord bilirubin is 5 mg/dl or cord Hb is 10 g/dl. (However, if the baby shows signs of hydrops or cardiac decompensation in the presence of low PCV (<35%), partial exchange transfusion with 50 ml/kg of packed cells should be done to restore the oxygen-carrying capacity of the blood.)
- DVET may also be considered when the bilirubin-to-albumin ratio exceeds age-specific cutoffs.

A new 'escalation of care' bilirubin threshold has been recently introduced at TSB 2 mg/dl below the exchange threshold. Above this threshold, intensive phototherapy and intravenous hydration are recommended, and in case of isoimmune hemolytic disease, using 0.5–1 g/kg IVIG can also be considered. We do not use IVIG for hemolytic jaundice in our unit.[2]

The adverse effects of ET include infection, electrolyte disturbances (hypocalcemia, hypomagnesemia, hypernatremia, hyperkalemia), portal vein thrombosis, thrombocytopenia, coagulopathy, GVHD, NEC, arrhythmias, and a mortality risk of 0.5–2%.

Bilirubin-induced Neurological Damage

Unbound/free bilirubin can cross the intact blood–brain barrier (BBB) and cause damage by inducing apoptosis and causing neuronal necrosis. The key factors promoting its toxicity are the low water solubility of bilirubin and its tendency to aggregate and precipitate at physiologic pH.

Factors that increase the amount of unbound bilirubin (drugs such as ceftriaxone that displace bilirubin from albumin) or factors that increase the permeability of BBB (such as anoxia, hypercarbia, and hyperosmolality) increase the risk of BIND. Premature infants have a more permeable blood-brain barrier as well as a lower affinity of albumin for bilirubin and may develop neuronal damage at lower TSB levels.

Acute bilirubin encephalopathy (ABE) is used to describe the acute manifestations of bilirubin toxicity—enlisted in Table 20.4—seen in the first weeks after birth. Modified BIND scoring is done in our unit to objectively assess and monitor these babies.

Clinical Features of ABE

Preterm neonates may not display the classical signs of ABE. Thus, close monitoring and a high index of suspicion are essential. All neonates with suspected ABE should also be evaluated for other causes of encephalopathy, such as asphyxia, sepsis, and meningitis, that can coexist with hyperbilirubinemia.

MRI in ABE or kernicterus shows a pathognomonic image of bilateral symmetric high-intensity signal in the globus pallidus. Similar changes have been reported in subthalamic nuclei, auditory brainstem, and cerebellar nuclei. All neonates with features of BIND or high bilirubin levels in the presence of risk factors should undergo hearing evaluation with auditory brainstem response (ABR) audiometry to rule out auditory involvement.

The term kernicterus is reserved for the chronic and permanent clinical sequelae of bilirubin toxicity. It is classically described

Table 20.4: Acute manifestation of bilirubin

Early	*Subtle signs like lethargy, hypotonia, poor suckle, or high-pitched cry*	
Intermediate	Tone variable (usually hypertonia), irritability, fever, seizures	Almost all infants who survive this phase are likely to develop chronic bilirubin encephalopathy; an emergent ET may reverse CNS changes in some.
Advanced	Pronounced hypertonia (opisthotonos, retrocollis), weak or shrill cry, apnea, seizures, coma	Affected infants die from intractable seizures or respiratory failure.

as a tetrad of choreoathetoid cerebral palsy with neuromotor impairment, sensorineural hearing loss, upward gaze palsy, and dental enamel dysplasia.

PROLONGED JAUNDICE

The persistence of significant jaundice for more than 2 weeks in term and 3 weeks in preterm neonates is termed prolonged jaundice. The first step in these neonates is to rule out cholestasis. After that, other common causes, such as breastmilk jaundice, hypothyroidism, and continuing hemolysis (due to ABO/Rh incompatibility or G6PD deficiency or from extravasated blood in cephalhematomas), need to be considered.

Breast milk jaundice is a common and mostly benign cause, occurring in up to 30% of infants. It is observed in infants otherwise gaining adequate weight. A few proposed theories for its occurrence are high free fatty acid concentration in breast milk (causing bilirubin displacement from albumin), high beta-glucuronidase activity, and inhibition of UGT1A activity by breast milk contents. Interruption of breastfeeding is seldom required.

A mutation in the promotor region of UGT1A1 causes Gilbert syndrome. It is typically not detected until after puberty. The appearance of mild jaundice seen at times of stress (without concurrent evidence of hemolysis), with response to phenobarbital, would point towards the diagnosis.

Infants with Criggler–Najjar syndrome type I have almost nil UGT1A1 activity and develop severe jaundice requiring exchange transfusion in the first week of life. There is no response to phenobarbital, and these infants must be managed on home PT, usually at night in the post-neonatal period. Liver transplantation is the only curative treatment option. Criggler–Najjar syndrome type II patients have less severe jaundice that responds to phenobarbital and less commonly develop kernicterus.

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