

Jaundice and Hyperbilirubinemia in the Newborn

Jaundice is observed during the 1st wk of life in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin.

Although bilirubin may have a physiologic role as an antioxidant, elevated levels of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates potentially serious hepatic disorders or systemic illnesses.

ETIOLOGY:

Unconjugated hyperbilirubinemia may be caused or increased by any factor that ;-

(1) Increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, and shortened red cell life as a result of immaturity or transfused cells, increased enterohepatic circulation, infection).

(2) Damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency);

(3) Competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation); or

(4) Leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, and prematurity).

The toxic effects of elevated serum levels of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation:

1- Hypoproteinemia.

2- Displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam.

3 Chuen-Lin herbal tea.

4- Acidosis.

5- Increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia.

Neurotoxic effects are directly related not only to the permeability of the blood-brain barrier and nerve cell membranes, but also to neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases whereas breast-feeding and dehydration increase serum levels of bilirubin.

Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic circulation after deconjugation by intestinal glucuronidase.

Drugs such as oxytocin and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia.

DIFFERENTIAL DIAGNOSIS

Jaundice, consisting of either indirect or direct bilirubin, that is present at birth or appears within the 1st 24 hr of life requires immediate attention and may be due to erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital infections, including syphilis, cytomegalovirus, rubella, and toxoplasmosis. Hemolysis is suggested by a rapid rise in serum bilirubin (>0.5 mg/dL/hr), anemia, pallor, reticulocytosis, hepatosplenomegaly, and a positive family history.

Jaundice that 1st appears on the 2nd or 3rd day is usually physiologic but may represent a more severe form. Familial non-hemolytic icterus (Crigler-Najjar syndrome) and early-onset breast-feeding jaundice are seen initially on the 2nd or 3rd day. Jaundice appearing after the 3rd day and within the 1st wk suggests bacterial sepsis or urinary tract infection.

Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the 1st day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

The differential diagnosis for persistent jaundice during the 1st mo of life includes hyperalimentation-associated cholestasis, hepatitis, cytomegalic inclusion disease, syphilis, toxoplasmosis, familial non-hemolytic icterus, congenital atresia of the bile ducts, galactosemia, or inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several wk, as in infants with hypothyroidism or pyloric stenosis.

PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)

Under normal circumstances, the level of indirect-reacting bilirubin in umbilical cord serum is 1–3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus, jaundice becomes visible on the 2nd–3rd day, usually peaking between the 2nd and 4th days at 5–6 mg/dL and decreasing to below 2 mg/dL between the 5th and 7th days of life. Jaundice associated with these changes is designated physiologic and is believed to be the result of increased bilirubin production from the breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver. Overall, 6–7% of full-term infants have indirect bilirubin levels >12.9 mg/dL and less than 3% have levels >15 mg/dL. Risk factors for elevated indirect hyperbilirubinemia include maternal age, race (Chinese, Japanese, Korean, and Native American), maternal diabetes, prematurity, drugs (vitamin K3, novobiocin), altitude, Polycythaemia, male sex, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), oxytocin induction, breast-feeding, weight loss (dehydration or caloric deprivation), delayed bowel movement, and a family history/sibling who had physiologic jaundice.

Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10–14 days of life. Persistent indirect hyperbilirubinemia beyond 2 wk suggests hemolysis, hereditary glucuronyl transferase deficiency, breast-milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated with pyloric stenosis may be due to caloric deprivation, deficiency of hepatic UDP-glucuronyl transferase, or an increase in the enterohepatic circulation of bilirubin from an ileus.

PATHOLOGIC HYPERBILIRUBINEMIA

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity.

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels.

The development of kernicterus (bilirubin encephalopathy) is dependent on the level of indirect bilirubin, duration of exposure to elevated levels, the cause of jaundice, and the infant's well-being.

JAUNDICE ASSOCIATED WITH BREAST-FEEDING

Significant elevation in unconjugated bilirubin develops in an estimated 2% of breast-fed term infants after the 7th day of life, with maximal concentrations as high as 10–30 mg/dL reached during the 2nd–3rd week. If breast-feeding is continued, the bilirubin gradually decreases but may persist for 3–10 wk at lower levels. If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal levels within a few days. With resumption of breast-feeding, bilirubin levels seldom return to previously high levels. Phototherapy may be of benefit. Although uncommon, kernicterus can occur in patients with breast-milk jaundice. The etiology of breast-milk jaundice is not entirely clear, but may be attributed to the presence of glucuronidase in some breast milk. This syndrome should be distinguished from an early-onset, accentuated unconjugated hyperbilirubinemia known as breast-feeding jaundice which occurs in the 1st week of life, in breast-fed infants who normally have higher bilirubin levels than formula-fed infants. Hyperbilirubinemia (>12 mg/dL) develops in 13% of breast-fed infants in the 1st wk of life and may be due to decreased milk intake with dehydration and/or reduced caloric intake. Giving supplements of glucose water to breast-fed infants is associated with higher bilirubin levels, in part because of reduced intake of the higher caloric density of breast milk.

Frequent breast-feeding (>10/24 hr), discouraging 5% dextrose or water supplementation, and ongoing lactation support may reduce the incidence of early breast-feeding jaundice.

Kernicterus

Kernicterus, or bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. Disruption of the blood-brain barrier by disease, asphyxia, and other factors and maturational changes in blood-brain barrier permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but kernicterus is rare in healthy term infants and in the absence of hemolysis if the serum level is <25 mg/dL. In previously healthy, predominantly breast-fed term infants, kernicterus has developed when bilirubin levels exceed 30 mg/dL, although the range is wide (21–50 mg/dL). Onset is usually in the 1st wk of life, but may be delayed to the 2nd–3rd wk. The risk in infants with hemolytic disease is directly related to serum bilirubin levels. The duration of exposure needed to produce toxic effects is unknown. Little evidence suggests that a level of indirect bilirubin <25 mg/dL affects the IQ of healthy term infants without hemolytic disease. Nonetheless, the more immature the infant is the greater the susceptibility to kernicterus.

CLINICAL MANIFESTATIONS.

Signs and symptoms of kernicterus usually appear 2–5 days after birth in term infants and as late as the 7th day in premature infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrated, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched. Rigidity is rare at this late stage.

Clinical Features of Kernicterus.

ACUTE FORM

Phase 1 (1st 1–2 days): poor sucking, stupor, hypotonia, seizures.

Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever

Phase 3 (after the 1st wk): hypertonia

CHRONIC FORM

First year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills. After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss.

PATHOLOGY:-

The surface of the affected brain is usually pale yellow. On pathologic section, certain regions are characteristically stained yellow by unconjugated bilirubin, particularly the corpus subthalamicum, hippocampus and adjacent olfactory areas, striate bodies, thalamus, globus pallidus, putamen, inferior clivus, cerebellar nuclei, and cranial nerve nuclei.

INCIDENCE AND PROGNOSIS.

By pathologic criteria, kernicterus will develop in 1/3 of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25–30 mg/dL. Overt neurologic signs have a grave prognosis; more than 75% of such infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common.

PREVENTION.

Although kernicterus has been thought to be a disease of the past, there are recent reports of neurotoxic effects of bilirubin in term and near-term infants discharged as healthy newborns. Some experts recommend universal screening for hyperbilirubinemia in the 1st 24–48 hr of life to detect infants at high risk for severe jaundice and bilirubin-induced neurologic dysfunction

The American Academy of Pediatrics (AAP) has identified potentially preventable causes of kernicterus: (1) early discharge (<48 hr) with no early follow-up (within 48 hr of discharge); this problem is particularly important in near-term infants (35–37 wk gestation); (2) failure to check the bilirubin level in an infant noted to be jaundiced in the 1st 24 hr; (3) failure to recognize the presence of risk factors for hyperbilirubinemia; (4) underestimation of the severity of jaundice by clinical (visual) assessment; (5) lack of concern regarding the presence of jaundice; (6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy.

TREATMENT OF HYPERBILIRUBINEMIA.

Regardless of the cause, the goal of therapy is to prevent indirect-reacting bilirubin related neurotoxicity while not causing undo harm. Phototherapy and, if unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below the pathologic levels.

Because phototherapy may require 6–12 hr to have a measurable effect, it must be started at bilirubin levels below those indicated for exchange transfusion. When identified, underlying medical causes of elevated bilirubin and physiologic factors that contribute to neuronal susceptibility should be treated (antibiotics for septicemia and correction of acidosis).

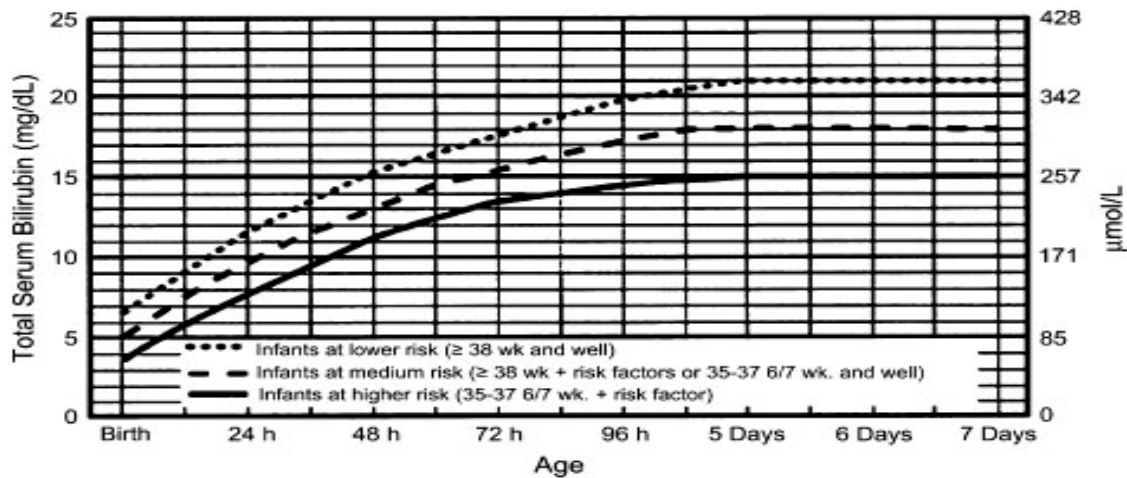


Fig. 1. Phototherapy guideline from the 2004 practice parameter of the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin. Risk factors include isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin less than 3.0g/dL (if measured). For well infants (35^{6/7}–37^{6/7} wks), 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} wks. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2004;114:304; with permission. © Copyright 2004 by the American Academy of Pediatrics.)

Phototherapy

Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to a high intensity of light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420–470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. The other major product from phototherapy is lumirubin, which is an irreversible

structural isomer converted from native bilirubin and can be excreted by the kidneys in the unconjugated state.

The therapeutic effect of phototherapy depends on the light energy emitted in the effective range of wavelengths, the distance between the lights and the infant, and the surface area of exposed skin, as well as the rate of .

The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic and nonhemolytic jaundice. When indications for exchange transfusion are present, phototherapy should not be used as a substitute; however, phototherapy may reduce the need for repeated exchange transfusions in infants with hemolysis.

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrimia, overheating, dehydration (increased insensible water loss, diarrhea), hypothermia from exposure, and a benign condition called bronze baby syndrome.

Phototherapy is contraindicated in the presence of porphyria. Before initiating phototherapy, the infant's eyes should be closed and adequately covered to prevent light exposure and corneal damage. Eye shields should be fitted properly to avoid pressure injury to the closed eyes, corneal excoriation if the eyes can be opened under the binding, and nasal occlusion.

The term bronze baby syndrome refers to a sometimes-noted dark, grayish-brown skin discoloration in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may be due to photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immunoglobulin

The administration of intravenous immunoglobulin is an adjunctive treatment for hyperbilirubinemia due to isoimmune hemolytic disease. Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions including phototherapy. Intravenous immunoglobulin (0.5–1.0 g/kg/dose; repeat in 12 hr) has been shown to reduce the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.

Metalloporphyrins:

A potentially important alternative therapy is the use of metalloporphyrins for hyperbilirubinemia. The metalloporphyrin Sn-mesoporphyrin (SnMP) offers promise as a drug candidate. The proposed mechanism of action is by competitive enzymatic inhibition of the rate limiting conversion of heme-protein to biliverdin (an intermediate metabolite to the production of unconjugated bilirubin) by heme-oxygenase. A single intramuscular dose on the 1st day of life may reduce the need for phototherapy. Such therapy may be beneficial when jaundice is anticipated, particularly in patients with ABO incompatibility or G6PD deficiency or when blood products are discouraged as with Jehovah's Witness patients

Exchange Transfusion.

Double volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and if the risk of kernicterus exceeds the risk of the procedure. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, NEC, infection, graft versus host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range

Various factors may affect the decision to perform a double volume exchange transfusion in an individual patient. The appearance of clinical signs suggesting kernicterus is an indication for exchange transfusion at any level of serum bilirubin. A healthy full-term infant with physiologic or breast-milk jaundice may tolerate a concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level.