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Jaundice in the First Month of Life

Authors: **John M. Olsson, MD,** Associate Professor, General Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC; **Karin M. Hillenbrand, MD,** Associate Professor, General Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC; **Pamela Larsen, DrPH, DNSc, FNP,** Department of Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC

Peer reviewer: **Mary Jo Bowman, MD, FAAP, FCP,** Pediatric Emergency Medicine Fellowship Director, Attending Physician, Emergency Department, Nationwide Children's Hospital, Columbus, OH.

Jaundice is an important presentation for the emergency physician to recognize. Physicians should recognize that its presence may be due to an increase in either unconjugated or conjugated bilirubin. Jaundice caused by unconjugated hyperbilirubinemia places the newborn at risk for kernicterus, a potentially devastating neurologic injury; furthermore, jaundice caused by conjugated hyperbilirubinemia may represent a condition requiring urgent medical or surgical intervention. This article comprehensively reviews the differential diagnosis, testing, and therapy for an infant with jaundice.

— The Editor

Introduction

The term "kernicterus" first appeared in the early 1900s; it referred to the yellow staining of the basal ganglia observed at autopsy in extremely jaundiced infants who had died. Increased recognition of Rh hemolytic disease and associated kernicterus in the United States resulted in a very aggressive approach to treating newborn jaundice.[1] It became apparent in the 1980s and 1990s, however, that kernicterus had become a rare complication and that treatment of jaundiced infants might be excessive.[2-4] The American Academy of Pediatrics (AAP) adopted a practice parameter in 1994 that reflected a less aggressive approach to the management of neonatal jaundice.[5] Disconcertingly, new case reports of newborns with kernicterus soon followed, raising questions about the optimal care of jaundiced infants.[6,7] In view of these developments, it is crucial to prevent, identify, and treat hyperbilirubinemia in a timely manner.

Statement of Financial Disclosure

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Epidemiology

Because uniform case definitions for jaundice, hyperbilirubinemia, and kernicterus have not been established, and the conditions are not reportable, their incidence is unknown.[8] It is estimated that 60% of term newborns and 80% of preterm newborns will become clinically jaundiced.[9] Hyperbilirubinemia is the most common reason for rehospitalization during the first month after birth; hospitalization rates for jaundice range from 2.3 to 12.2 per 1000 live births.[10-13] Factors associated with an increased risk of significant neonatal jaundice include gestational age < 38 weeks, Asian race, increasing maternal age, family history of jaundice in a newborn, and the presence of bruising or cephalhematoma.[10,13-16] Boys are more likely than girls to develop jaundice. Breastfeeding infants, those experiencing feeding difficulties, and those with significant weight loss in the first few days after birth also are at increased risk.[10,13-16] Factors associated with decreased risk of severe hyperbilirubinemia include African-American race, gestational age > 40 weeks, maternal smoking during pregnancy, and newborn hospital stay longer than 72 hours.[10,13-16]

Length of birth hospitalization and early discharge practices have been evaluated to determine whether an association with hospital readmission for jaundice exists; study results are conflicting. Large case-control and cohort studies have demonstrated no difference in readmission for newborns discharged less than 24 hours after birth when compared with those who are 24-48 hours old when discharged.[10-12] However, one case-control study did find a significant association between discharge at less than 72 hours and readmission for hyperbilirubinemina.[13]

Most jaundice in the newborn period is due to elevation of unconjugated bilirubin; entities that cause cholestasis are far less common. Idiopathic neonatal hepatitis, the most common etiology of cholestasis, occurs with an estimated frequency of 1/5000-10,000 live births.[17] Biliary atresia, the most common cause of extrahepatic obstructive jaundice and also the most frequent indication for liver transplantation in childhood, occurs in approximately 1/10,000-15,000 live births.[17-19]

Pathophysiology

The production of bilirubin begins with the breakdown of heme proteins. Most heme is derived from hemoglobin released following the destruction of red blood cells. This unconjugated bilirubin is water insoluble, but lipid soluble. In the serum it may be bound to albumin; unconjugated bilirubin that is not bound to albumin can leave the intravascular space and be deposited in skin, resulting in clinical jaundice; it also can cross the blood-brain barrier, where it can exert neurotoxic effects.[14]

Circulating unconjugated bilirubin is transported into hepatocytes. It is subsequently converted by uridine diphosphoglucuronic acid (UDP)-glucuronyl transferase to bilirubin monoglucuronide or bilirubin diglucuronide. These conjugated forms of bilirubin are water soluble and are excreted with the bile into the intestinal tract. Once in the intestinal tract, bilirubin can be excreted in stool, or glucuronidases in the intestine can deconjugate it and allow it to re-enter the enterohepatic circulation.[9]

Normal transitional and maturational processes that occur in the first days after birth result in elevation of bilirubin and mild clinical jaundice in most newborns. Relative polycythemia, coupled with a shortened half-life of fetal red blood cells, results in increased bilirubin production. Transient limitations in the processes of uptake, conjugation, and excretion by the liver result in delayed metabolism of bilirubin to an easily excreted form. In the first days after birth, the newborn intestinal tract lacks normal bacteria that convert conjugated bilirubin to stercobilinogen, a nonreabsorbable form of bilirubin excreted in the feces. In addition, transit of conjugated bilirubin through the gut into the stool is prolonged until feeding is well established, resulting in an increased gut transit time. These factors increase the likelihood that bilirubin in the gut will re-enter the serum through the enterohepatic circulation.

The level of unconjugated bilirubin in normal infants at birth is 1-3 mg/dL, and it rises less than 5 mg/dL/24 hours. Physiologic jaundice becomes clinically apparent on the second or third day of life; bilirubin level peaks between days 2 and 4 at 5-6 mg/dL, and declines to less than 2 mg/dL by 5-7 days. In premature infants, the rise in bilirubin is similar to or a little slower than that found in term infants but continues for a longer duration; this results in average peak levels of 8-12 mg/dL at 5-7 days. Jaundice in premature infants is unusual after 10 days of age.[9]

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Senior Vice President/Group Publisher: Brenda Mooney
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Pathologic states of hyperbilirubinemia exist when the amount of total bilirubin is higher than that expected for the patient's age, or when any elevation of conjugated bilirubin occurs. Most cases of hyperbilirubinemia during the first month of life are caused by elevation of unconjugated bilirubin. Elevation of the level of circulating unconjugated bilirubin is associated with an increased risk of neurotoxicity. While the term "kernicterus" traditionally was a pathologic diagnosis indicating bilirubin staining of brainstem nuclei and the cerebellum, it now is commonly used interchangeably with "bilirubin encephalopathy" to connote the clinical manifestations of bilirubin toxicity in the brain *(see Table 1)*.[7,14] Pathologic changes in the brain that are attributable to bilirubin include yellow staining of the basal ganglia and brainstem nuclei initially, with eventual progression to neuronal loss, reactive gliosis, and atrophy.[9]

The likelihood of neurotoxicity from unconjugated hyperbilirubinemia is increased by factors that facilitate movement of bilirubin from the vascular space to surrounding tissues, such as hypoproteinemia, acidosis, hypothermia, hypoglycemia, and competitive inhibition of albumin binding by drugs, such as sulfonamides or salicylates.[9,20] The risk of toxicity also is increased by factors that alter the permeability of the blood-brain barrier or increase the susceptibility of brain cells to injury (e.g., asphyxia, prematurity, hyperosmolarity, and infection).[9]

Cholestasis, an elevated level of conjugated bilirubin in the serum, occurs when there is mechanical obstruction to bile flow or functional impairment of bilirubin excretion because of hepatocellular injury or ductal disturbance. Functional impairment most commonly arises from virally-induced liver injury or metabolic liver disease. Although the mechanisms are not completely understood, a single process probably underlies the diverse etiologies of cholestasis: an initial insult causes inflammation and progressive damage to liver cells and cells of the biliary tract, which ultimately results in hepatocellular dysfunction or sclerosis of the biliary tree.[17] While conjugated bilirubin is not toxic, its presence usually is indicative of a serious underlying disorder.

Differential Diagnosis of Jaundice

The differential diagnosis of unconjugated hyperbilirubinemia and conjugated hyperbilirubinemia suggest divergent approaches to the clinical diagnosis and management of specific conditions. In the first week of life, unconjugated hyperbilirubinemia is by far the most common cause of jaundice, while conjugated hyperbilirubinemia is seen more frequently as the infant becomes older.

Unconjugated Hyperbilirubinemia. Physiologic jaundice is the most common form of jaundice in the first month of life. Both increased production of bilirubin and a decreased ability to excrete it contribute to physiologic jaundice.[21] The task of defining physiologic jaundice by measuring bilirubin levels is difficult. Maisels recently summarized this controversy, noting that newborn bilirubin values vary a great deal based on race/ethnicity, feeding method, laboratory methods, and age of the infant.[22] In the term infant without risk factors for jaundice, it has been suggested that serum bilirubin values should not exceed 15 mg/dL between 25 and 48 hours, 18 mg/dL between 49-72 hours, and 20 mg/dL beyond 72 hours.[23] Values below these thresholds may be consistent with physiologic jaundice; values above these thresholds suggest a pathologic cause of jaundice or intensification of an otherwise physiologic process. Perhaps the most straightforward method of determining physiologic jaundice is to exclude pathologic processes. The following may suggest a pathologic cause of jaundice rather than a physiologic one: clinical jaundice in an infant younger than 24 hours, serum bilirubin values increasing by more than 0.5 mg/dL per hour or 5 mg/dL per day, conjugated bilirubin values greater than 2.0 mg/dL or 20% of the total serum bilirubin, and clinical jaundice lasting more than two weeks.

Pathologic unconjugated hyperbilirubinemia most often is a result of increased bilirubin production due to a hemolytic process in the newborn. Historically, Rh isoimmunization was the most common cause of hemolysis in the newborn, but it has become rare with the identification of Rh negative women and their treatment with RhO (D) immune globulin (RhoGAM). ABO and minor blood type incompatibilities continue to be frequent causes of hemolysis and jaundice. Glucose-6-phosphate dehydrogenase (G6PD) deficiency has become a significant cause of unexpected kernicterus in the United States.[24] G6PD, and to a lesser degree pyruvate kinase deficiency, occur when abnormally low levels of enzymes found in major pathways of glucose metabolism cause red cell membrane instability and result in hemolysis. While episodes of hemolysis in older children and adults are triggered by a variety of drugs and foods, significant hemolysis due to G6PD deficiency may occur in the newborn without such exposure. Hereditary spherocytosis, elliptocytosis, and similar red blood cell membrane defects also may be associated with hemolysis and jaundice in the first week of life. Other causes of increased bilirubin production include the presence of extravascular blood resulting from traumatic delivery (e.g., cephalhematomas, bruising) and swallowed maternal blood, polycythemia, and sepsis-induced hemolysis. Urinary tract infection should be considered as a cause when an infant presents with unexplained jaundice after the first week of life.[25]

Unconjugated hyperbilirubinemia also may develop as a

Table 1. Clinical Findings of Kernicterus

ACUTE	CHRONIC
Lethargy	Mild neurodevelopmental delays
Poor feeding	Choreoathetoid cerebral palsy
Tone abnormalities	Paralysis of upward gaze
Opisthotonus	Sensorineural hearing loss
High pitched cry	Dental dysplasia
Seizures	
Apnea	
Abnormal auditory brainstem response	

Adapted from Maisels MJ, Newman TB. Kernicterus in otherwise healthy, breast-fed term newborns. *Pediatrics* 1995;96:730-733.

result of impaired conjugation or excretion of bilirubin. Hypothyroidism impairs the normal conjugation of bilirubin, and the resulting jaundice typically presents during the second week of life. Hypopituitarism should be a consideration in an infant presenting with hypoglycemia, hyponatremia, and small genitalia, in addition to jaundice. Crigler-Najjar syndrome is a familial unconjugated hyperbilirubinemia associated with deficiency of glucuronyl transferase. Both type 1 and type 2 usually present in the first three days of life. The type 1 variant generally causes the greater increase in bilirubin. Gilbert syndrome, a condition that more commonly presents during adolescence, results from a reduction in glucuronyl transferase activity, while Lucey-Driscoll syndrome is due to the effect of a maternal serum factor that inhibits the newborn's glucuronyl transferase activity. Infants of diabetic mothers are at increased risk for jaundice, both because of associated polycythemia and from immaturity of the glucuronyl transferase enzyme system.

Finally, prolonged enterohepatic circulation in an infant can result in marked elevations in unconjugated bilirubin. It is most often seen in breast-fed infants, though it occasionally occurs in formula-fed infants who feed poorly or in those not being fed at all. It often is responsible for higher-than-usual bilirubin values in an infant with what appears to be physiologic jaundice. Breast-feeding jaundice presents in the first few days of life as a result of persistent intestinal glucuronidase activity during early breast-feeding when there is limited milk intake. In contrast, breast milk jaundice presents in the second week of life in thriving infants, due to the presence of maternal glucuronidase in breast milk. A serious though uncommon cause of prolonged enterohepatic circulation is intestinal obstruction, either congenital (e.g., small bowel atresia/stenosis) or acquired (e.g., pyloric stenosis).

Conjugated Hyperbilirubinemia. Conjugated hyperbilirubinemia in patients presents as a conjugated or direct bilirubin fraction that is greater than 2 mg/dL or that accounts for greater than 20% of the total bilirubin value. Conjugated hyperbilirubinemia in the newborn is always pathologic. It most commonly presents later in the first month of life; when it presents in the first two weeks, the etiology often is infectious and generally not related to abnormalities of the liver itself.[26]

As opposed to the differential diagnosis of unconjugated hyperbilirubinemia, which calls for an orderly diagnostic evaluation, the differential diagnosis of conjugated hyperbilirubinemia includes a number of conditions that mimic each other. This prompts a work-up that is specific for each condition. Whereas unconjugated hyperbilirubinemia is a transient condition that leaves no lasting effects when properly managed, the causes of conjugated hyperbilirubinemia persist and require a speedy diagnosis to assure the best outcome for the infant.

Extrahepatic biliary disease includes obstructive lesions outside the liver, most of which can be surgically corrected. Biliary atresia, choledochal cyst, bile duct stenosis, neoplasm, and spontaneous perforation of the common bile duct are the most common extrahepatic obstructing lesions. Cholelithiasis is very rare in infants.

Biliary atresia accounts for roughly one-third of cases of conjugated hyperbilirubinemia.[27] The precise cause of biliary atresia is unknown, but histopathology demonstrates obliteration of the extrahepatic bile ducts; occasionally, this is recognized on prenatal ultrasound with the finding of biliary cystic malformations.[28] Biliary atresia is a progressive condition in which ongoing inflammation and fibrosis of the extrahepatic biliary tract eventually cause hepatic failure. The Kasai procedure is the operation of choice to restore normal function and is most successful if performed before the infant is 60 days old.[27]

Intrahepatic biliary disease includes a variety of metabolic, anatomic, infectious, and genetic conditions. Idiopathic neonatal hepatitis is the most frequent diagnosis in this category, although it is being made less often as new metabolic and genetic causes are identified. Inspissated bile syndrome is the result of the accumulation of bile in the canaliculi and bile ducts in infants with hemolytic disease (Rh, ABO), and in some infants receiving total parenteral nutrition.

Metabolic disorders include disorders of amino acid, lipid, and carbohydrate metabolism. Classic galactosemia, a deficiency of galactose-1-phosphate uridyl transferase, may present with jaundice, hepatomegaly, vomiting, lethargy, irritability, cataracts, feeding difficulties, or poor weight gain. Cystic fibrosis causes cholestasis by its associated mucous plugging of the bile ducts. $Alpha_1$-antitrypsin is a serum proteolytic enzyme inhibitor. Patients with a homozygous deficiency state, protease inhibitor ZZ phenotype (PiZZ), have greatly reduced quantities of $alpha_1$-antitrypsin; as a result, 10-15% develop progressive giant cell hepatitis.

Infectious considerations include hepatitis, urinary tract infection, and sepsis. Infectious hepatitis represents the second leading cause of conjugated hyperbilirubinemia, and accounts for about 20% of cases. Urinary tract infection and sepsis can be associated with conjugated hyperbilirubinemia as well as with unconjugated hyperbilirubinemia.[25,29]

Caroli disease (nonobstructive dilatation of the intrahepatic bile ducts) and congenital hepatic fibrosis are examples of anatomic disorders causing conjugated hyperbilirubinemia. Genetic/chromosomal conditions associated with conjugated hyperbilirubinemia include Down syndrome and Donahue syndrome. Finally, toxic hepatitis secondary to total parenteral nutrition is a common cause of cholestatic jaundice in neonatal intensive care unit patients.

Clinical Features

The history and physical examination of the jaundiced newborn should characterize the onset and progression of the jaundice, determine risk factors, and identify features that suggest an etiology. Characteristic clinical findings for selected diagnoses in the differential are presented in the Table "Clinical Features and Diagnostic Studies for the Jaundiced Newborn" on the card inserted with the issue.

History. *Clarify the onset and duration of jaundice.* Jaundice presenting in the first 24 hours after birth is suggestive of a

hemolytic disorder; congenital infections also may present with jaundice at this time. Physiologic jaundice is the most common cause of jaundice during the first week, and usually becomes clinically evident on the second or third day. Unconjugated hyperbilirubinemia presenting after the first week is usually due to ingestion of breast milk, but also could suggest hemolysis due to G6PD deficiency, Crigler-Najjar syndrome, hypothyroidism, or intestinal obstruction.[9] The many entities that result in conjugated hyperbilirubinemia are also increasingly likely in the latter half of the first month.

Review the history of the pregnancy. Prematurity increases the likelihood of jaundice, as well as the risk for neurologic sequelae. Infants born to Asian or Native American women have an increased risk for clinically significant jaundice, as do those born to women with diabetes. Maternal infection during pregnancy or at the time of delivery increases the possibility of infectious hepatitis, sepsis, and urinary tract infection in the neonate.

Determine maternal blood type and review maternal screening labs. All mothers should have ABO and Rh blood type determined during pregnancy, and should be screened for isoimmunization. Maternal laboratory studies during pregnancy may be a clue to congenital infection, such as syphilis or rubella.

Ask about the delivery history. Difficult or instrumented deliveries (i.e., those involving forceps or vacuum-assisted extraction) are associated with an increased incidence of bruising or cephalhematoma with subsequent jaundice. Delay in clamping the umbilical cord can result in polycythemia in the newborn. Intrapartum fever and other signs of maternal infection noted during labor and delivery may be clues to neonatal infection.

Identify familial causes of jaundice. Spherocytosis is inherited in an autosomal dominant fashion; clues in the history include family members with chronic anemia, jaundice, or a history of splenectomy. Both race and family history may provide clues to G6PD deficiency, which is inherited as an autosomal recessive (AR) trait. History of a sibling affected with jaundice in the early neonatal period suggests the presence of hemolysis due to blood group incompatibility or G6PD deficiency. Crigler-Najjar, Alagille, Gilbert, and Lucey-Driscoll syndromes and Byler disease are all inherited disorders that result in jaundice.

Characterize infant feeding and elimination patterns. Breastfeeding infants are at increased risk for jaundice during the first week after birth, especially those with significant weight loss. Supplementation of breastfeeding with glucose water is associated with increased bilirubin levels and should be discouraged.[9] Intake of breast milk also is associated with jaundice later in the first month. Infrequent or absent stools or persistence of meconium stools for more than two or three days after birth suggest inadequate feeding. Infrequent stooling also may be a clue to bowel obstruction or other causes of constipation, such as hypothyroidism or Hirschsprung disease.

Inquire about the color of stool and urine. Urine of an adequately fed newborn should be pale yellow or clear. Dark yellow urine may suggest inadequate volume intake by the newborn, while dark brown urine may be a clue to excretion of bilirubin and may suggest cholestatic causes of jaundice. Persistently acholic or clay-colored stools suggest biliary obstruction, particularly biliary atresia, although infants with severe idiopathic neonatal hepatitis can have transient impairment of bile excretion. Consistently pigmented stool effectively rules out biliary atresia.[17]

Characterize the infant's behavior. Lethargy, vomiting, or seizures may be clues to sepsis, a metabolic disorder, or evolving neurotoxicity from hyperbilirubinemia, all of which must be quickly identified and treated. Metabolic disorders or infection — especially urinary tract infection — also may present less acutely with temperature instability, poor feeding, or inadequate growth, or the infant may be asymptomatic except for jaundice.

Investigate whether symptoms of bilirubin encephalopathy are present. Symptoms of kernicterus that may manifest acutely during the newborn period are listed in Table 1.

Identify medications that may have been administered to the infant either directly or via breast milk. Antibiotics can increase enterohepatic circulation of bilirubin and contribute to jaundice. Sulfonamides and salicylates compete with unconjugated bilirubin for albumin binding. Inadvertent administration of excessive amounts of vitamin K can trigger hemolysis.

Physical Examination

Assess the Extent of Jaundice. The examination of the newborn should take place in a well-lit area. Jaundice can be ascertained if the blanching caused by pressure on the skin reveals an underlying yellow color. It also is important to note the degree of jaundice of the sclerae and mucous membranes, though its presence only indicates that hyperbilirubinemia is present, not its severity. Once serum levels of bilirubin rise above 5 mg/dL, visible cutaneous newborn icterus is noted, usually beginning on the face and progressing caudally.[30,31] Efforts to correlate the progression of jaundice to specific serum bilirubin levels have been unsuccessful.[32,33]

Identify other pertinent skin findings. Bruising represents a source of extravascular blood. Petechiae reflecting thrombocytopenia might suggest congenital infection, sepsis, or hemolytic anemia.

Determine weight compared to birth weight and state of hydration. Inadequate caloric intake causes increased enterohepatic circulation and results in hyperbilirubinemia; dehydration can intensify hyperbilirubinemia.

Identify any dysmorphic features. Down syndrome and Alagille syndrome have distinctive features.

Examine the patient's head. Cephalhematomas or other scalp bleeding may contribute to jaundice. Microcephaly or macrocephaly may be seen in congenital infection. An exceptionally large anterior fontanelle may be associated with hypothyroidism.

Listen to the heart. Cardiovascular examination should include assessment for signs of severe anemia, which might be associated with a hemolytic process. Heart murmurs consistent with peripheral pulmonic stenosis are found in Alagille syndrome.

Examine the abdomen for hepatosplenomegaly or masses.

Hepatomegaly may be evidence of congenital infection or metabolic disease. Splenomegaly may be seen in G6PD or other hemolytic disease. Masses may be felt with neoplasms or choledochal cysts.

Perform a thorough neurological examination. Infants with significant elevations in serum bilirubin may demonstrate lethargy, drowsiness, and poor feeding; overt neurologic signs such as altered cry, change in muscle tone, or seizures warrant immediate attention as they signal an infant at risk for kernicterus.

Diagnostic Evaluation

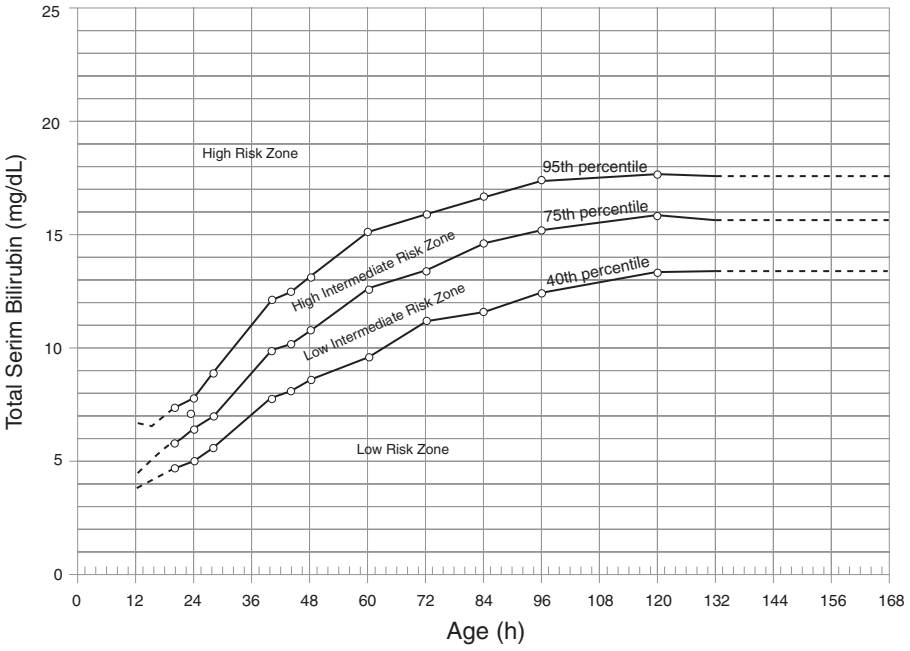
Assess the Total Bilirubin Level. The diagnostic evaluation of the jaundiced newborn begins with quantification of total bilirubin, which in many instances will be the only test required. Total serum bilirubin (TSB) estimations include both conjugated and unconjugated components, although most bilirubin in the early newborn period is unconjugated.

Either serum or plasma can be used as the specimen for assessing total bilirubin. Hemolysis may interfere with some laboratory methods for measuring bilirubin, resulting in a falsely low value. Specimens should be protected from light if there will be a delay before processing.[20] Data regarding the difference between bilirubin values obtained from venous or capillary samples is conflicting; current recommendations suggest that either may be used to measure TSB and that it is not necessary to obtain a venous specimen to "confirm" the result from a capillary sample.[14]

Various methods for measuring bilirubin in the lab are used; since most are not precise, small changes in TSB may reflect imprecision of the measurement method and not an actual change in the patient's condition.[20] Significant variability also exists between laboratories, which should be taken into account when infants are transferred from one institution to another. Instruments that measure bilirubin are typically calibrated to levels of 25 or 30 mg/dL. Higher levels are increasingly less precise, but because bilirubin levels in this range should consistently result in evaluation and intervention, the imprecision poses little problem.[14] Clinicians should become familiar with the method used in their own laboratory, as well as its limitations.[20]

Most laboratory methods are less accurate for assessing the level of conjugated than of total bilirubin; however, for most infants the portion of conjugated bilirubin is low, and an accurate assessment of total bilirubin is adequate. TSB results during the first week of life should be interpreted in relation to the infant's age in hours *(see Figure 1)*.[14,34] The majority of tables and nomograms that provide reference ranges for neonatal hyperbilirubinemia are based on TSB rather than specifically on the unconjugated fraction.

Figure 1. Risk Designation of Term and Near Term Well Newborns Based on Hour-specific Serum Bilirubin Values



The high-risk zone is designated by the 95th percentile track. The intermediate-risk zone is subdivided to upper- and lower-risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. (Dotted extensions are based on < 300 TSB values/epoch.)

Reprinted with permission from: Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics* 1999;103:6-14.

Portable handheld devices that allow transcutaneous measurement of bilirubin (TCB) are becoming increasingly popular in the newborn nursery setting. Studies have documented that the results from these devices are equivalent to measurements of TSB in term and near-term infants (35-42 weeks) and across racial groups for detection of clinically significant jaundice.[35,36] Most provide measurements within 2-3 mg/dL of the TSB measurement and can replace measurement of TSB, especially if the value is less than 15 mg/dL.[14] Phototherapy alters bilirubin in the skin; therefore, transcutaneous assessment of bilirubin is inaccurate in infants who have been treated in this manner.[14] As with TSB, results of TCB should be interpreted in relation to age in hours. Transcutaneous devices have been shown to save time and money, reduce blood sampling, and can accurately predict a high-risk population of newborns prior to nursery discharge.[35,37]

Although studies evaluating the use of TCB devices have focused primarily on a pre-discharge nursery population, use in outpatient settings also has been described.[37-39] Outpatient use generally has been limited to routine follow-up and surveillance. Available studies suggest accuracy in this setting and demonstrate that the use of the devices could reduce the frequency of outpatient blood sampling for bilirubin assessment. As with studies done in inpatient settings, outpatient use of TCB devices has been limited to infants during the first week after birth. Use of this technology in emergency department and acute care settings

and for infants older than 7 days has not been reported.

For most jaundiced newborns, a clinical evaluation, coupled with assessment of total bilirubin, will be sufficient. Further evaluation to determine the cause of jaundice should be considered if:

- jaundice appears in the first 24-36 hours;
- serum bilirubin rises more than 5 mg/dL/24 hours;
- bilirubin measurement exceeds 12 mg/dL in a term infant or 10-14 mg/dL in a preterm infant;
- there is a family history of hemolytic disease, such as G6PD deficiency;
- the infant's history includes vomiting, lethargy, poor feeding, light-colored stools, or dark urine;
- physical exam reveals pallor, hepatomegaly, splenomegaly, or signs of kernicterus; or
- therapy is required.[9]

In this subgroup of jaundiced infants, the following diagnostic studies should be considered.

Obtain a complete blood count, which may reveal anemia as a clue to hemolysis, or polycythemia as the source for jaundice. Evaluate for hemolysis in infants who present with jaundice in the first 24-36 hours after birth, as well as for those with a rapidly rising total serum bilirubin, and those who present with anemia in addition to jaundice. A smear of the peripheral blood may reveal nucleated red blood cells, spherocytes, fragmented cells, and other evidence of ongoing hemolysis. The reticulocyte count in a hemolyzing newborn may be normal or elevated.

Anemia with hemolysis occurring in the first few days after birth is usually the result of hemolytic disease of the newborn, arising from incompatibility of maternal and infant ABO or Rh blood types. For infants born to Rh-negative mothers, cord blood testing for blood group and Rh type and a direct antiglobulin (Coombs) test is indicated to identify infants with Rh isoimmunization at risk for hemolysis. Similar testing often is performed for infants delivered to women with O blood type to identify those infants with A or B blood type incompatibility who may subsequently develop hemolysis.[14] A positive direct Coombs test is consistent with hemolysis caused by ABO, Rh, or minor blood group incompatibility.[9]

Infants with anemia and jaundice presenting after the first several days may have other causes of hemolysis. Considerations include spherocytosis, elliptocytosis, G6PD deficiency, and pyruvate kinase deficiency.

Clinicians should evaluate for G6PD deficiency in significantly jaundiced infants when there is a family history of the disorder, a consistent ethnic or geographic family origin, or a poor response to phototherapy. During periods of active hemolysis, G6PD is released from lysed cells and levels are elevated above baseline; therefore, a normal level in an actively hemolyzing infant does not rule out deficiency. A repeat level should be measured at 3 months of age if suspicion for the disorder exists.[14]

The fraction of bilirubin that is conjugated should be determined when jaundice persists or presents after two weeks of age, and for infants with other evidence of liver dysfunction.

Conjugated hyperbilirubinemia exists when the direct-reacting fraction of bilirubin exceeds 20% of the total, or when direct-reacting bilirubin is > 2 mg/dL. For infants found to have an elevation of conjugated bilirubin, an evaluation for causes should be done expeditiously.

Clinicians should obtain tests for liver function and hepatocellular injury, such as coagulation studies and liver enzymes. Elevated liver enzymes indicate hepatocyte injury but are nonspecific regarding the cause of jaundice. Tests to evaluate liver function or damage are not warranted if direct bilirubin is normal.[40]

The liver should be imaged using ultrasonography to identify a choledochal cyst, liver tumor, or other mass, and to visualize the gallbladder and biliary tract. Bile duct perforation and cholelithiasis, though rare, may be identified with ultrasonography. In biliary atresia, the gallbladder may be small or cannot be seen, but this finding is not specific.[17]

Clinicians also should obtain a nuclear hepatobiliary scan. A dynamic study of bile flow is necessary to evaluate for biliary atresia. This study assesses uptake of a technetium-labeled isotope by the liver and its excretion into the biliary tract and subsequently into the intestinal tract. In biliary atresia, uptake is normal but excretion into the intestine is absent; unlike with neonatal hepatitis, uptake may be impaired but excretion should eventually occur.[17] Administration of phenobarbital for several days prior to the study enhances excretion of the isotope. Definitive diagnosis when biliary atresia is suspected is done by exploratory laparotomy with direct cholangiography.

Finally, consider measuring the serum albumin level. Albumin binds to unconjugated bilirubin in the serum, preventing its transport into the brain; therefore, some authorities advocate measuring serum albumin levels in infants for whom phototherapy is being contemplated.[14] A low serum albumin level (< 3.0 mg/dL) could be considered one risk factor that might lower the threshold for treatment. Some studies have indicated that the ratio of bilirubin to albumin (B/A ratio) might be used to modify decisions regarding initiation of exchange transfusion for extreme hyperbilirubinemia.[14] Other factors to consider when assessing patients for the risk of neurotoxicity include the total serum bilirubin level and the susceptibility of CNS cells to damage.[14] Studies correlating the B/A ratio to developmental outcome are limited and conflicting; no studies have directly demonstrated that serum albumin level is a predictor of neurodevelopmental outcome in infants with hyperbilirubinemia.[14,41]

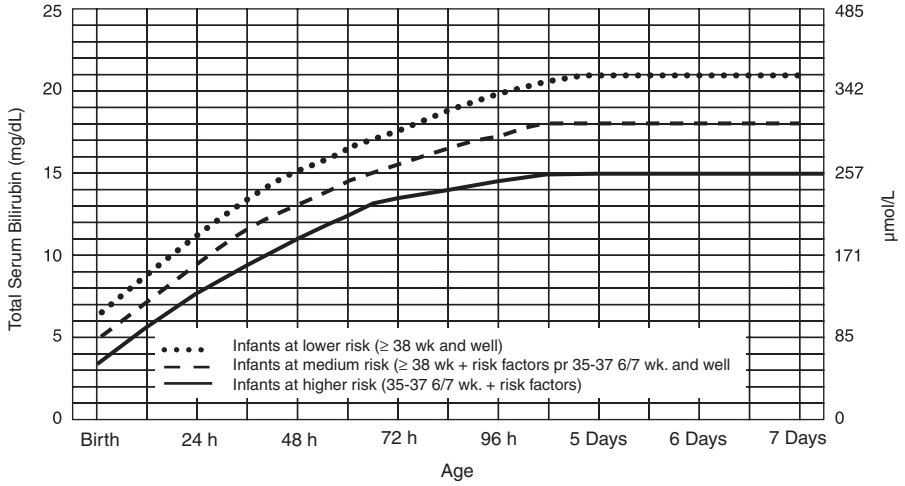
Other studies that may be useful for diagnosing specific etiologies of hyperbilirubinemia are found *on the card*.

Management

The clinical approach to jaundice in the first month of life has three aspects: prevention, managing the infant with unconjugated hyperbilirubinemia, and managing the infant with conjugated hyperbilirubinemia.

Prevention Strategies. Emergency physicians encountering jaundiced infants should be aware of early detection efforts car-

Figure 2. Guidelines for Phototherapy in Hospitalized Infants of 35 or More Weeks Gestation



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured).
- For well infants 35-37 6/7 wk 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 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

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ried out in the newborn nursery. These prevention strategies are necessary because visual assessment of jaundice is difficult, especially in infants with darkly pigmented skin. It is in part due to errors in visual assessment that healthy term infants in significant numbers continue to develop kernicterus.

Primary prevention efforts recommended by the AAP include encouraging mothers to breast feed their infants frequently for the first several days without water or dextrose water supplementation. Testing all pregnant women for ABO and Rh blood types and performing a serum screen for unusual isoimmune antibodies is a secondary prevention effort.[14]

One strategy to prevent kernicterus is to identify babies who are at risk for severe hyperbilirubinemia by measuring the bilirubin at the time of discharge in all infants. Bhutani and colleagues found that a predischarge hour-specific serum bilirubin determination was useful for predicting which infants were at increased risk for developing severe hyperbilirubinemia.[34] Serum bilirubin can be plotted for a given postnatal age in hours on a graph based on Bhutani's normal infant data. *(See Figure 1.)* The 40% of infants whose bilirubin levels fall in the low-risk zone are unlikely to develop severe hyperbilirubinemia, while infants whose bilirubin levels fall in the higher zones are at increased risk. In addition, clinical risk factors should be considered because combining clinical risk data with serum bilirubin values improves the clinician's ability to predict severe hyperbilirubinemia compared to age-specific bilirubin levels alone.[42] Determining the relative risk for severe hyperbilirubinemia is important in setting the time of follow-up at discharge. Infants at higher risk whose discharge bilirubin values do not meet criteria for immediate phototherapy should be seen by their primary physician in 1-2 days. BiliTool™, a web-based instrument (www.bilitool.org) that determines risk level based on age in hours and the bilirubin value, may be useful in determining appropriate follow-up.[43]

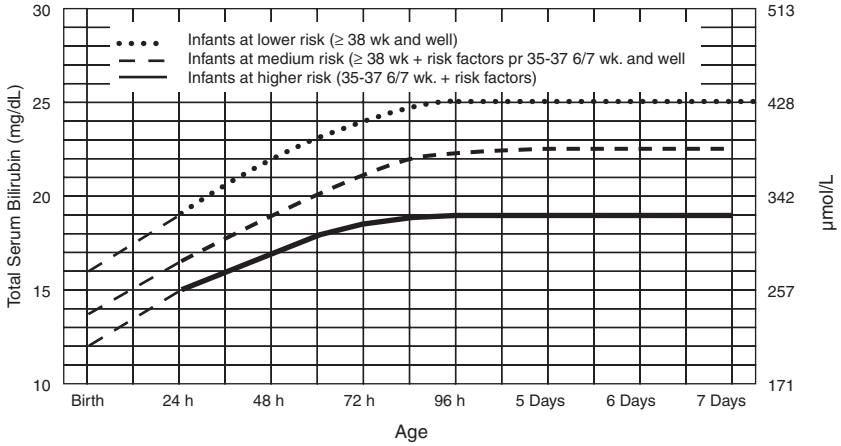
Managing the Infant with Hyperbilirubinemia. Management and disposition will differ depending on whether the infant has unconjugated or conjugated hyperbilirubinemia. Once the type and degree of hyperbilirubinemia have been identified, appropriate treatment can be undertaken.

Unconjugated Hyperbilirubinemia. The first task of the physician in the emergency department is to determine if the bilirubin value represents physiologic jaundice or some form of pathologic jaundice. This can easily and practically be accomplished by plotting the hour-specific bilirubin on a graph for determining the need for phototherapy. *(See Figure 2.)* By definition, an infant meeting the criteria for phototherapy has pathologic jaundice, even if it is simply an exaggeration of a physiologic process, as in the breastfeeding infant who is feeding poorly. Physiologic jaundice does not require additional evaluation or treatment. Careful review of feeding practices, whether by bottle or breast, is essential to help provide counseling that enables the infant to feed effectively and thrive. Lactation consultants can assist breastfeeding women and are available in most communities.

Phototherapy is a method of providing a spectrum of light that causes bilirubin to undergo a photoisomerization reaction to form lumirubin, a substance that can be excreted without further metabolism. Naked infants with shielded eyes are placed under either a specially designed light-emitting diode light or banks of fluorescent lights.[44] Optimal phototherapy employs lights with a wavelength predominantly in the blue-green spectrum (430-490 nm).[45] Intensive phototherapy is best accomplished using a combination of fluorescent tubes above and a fiberoptic pad or special blue fluorescent tubes below the baby. Home phototherapy with a BiliBlanket® should only be used if serum bilirubin levels remain below those recommended for inpatient phototherapy. Exposing infants to sunlight as a means of providing phototherapy is expressly discouraged by the AAP because it is less effective than standard phototherapy and exposes the infant to the risk of skin damage and dehydration.[14]

It is vital that the emergency physician recognize an extreme-

Figure 3. Guidelines for Exchange Transfusion in Infants 35 or More Weeks Gestation



- The dashed lines for the first 24 hours indicate uncertainly due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dL (85 mcmol/L) above these lines.
- Risk factors — isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

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ly high bilirubin value in an infant who might require exchange transfusion. This can be determined by plotting the hour-specific bilirubin on a graph that serves as a guideline for exchange transfusion *(see Figure 3)*, or by finding a serum bilirubin of 25 mg/dL or higher at any time. The infant with pathologic jaundice who meets criteria for exchange transfusion requires urgent admission to a Level 3 neonatal intensive care unit or to a pediatric intensive care unit for intensive phototherapy and possible exchange transfusion.

Exchange transfusion is an uncommon procedure today due to the administration of RhoGAM and the use of phototherapy. Exchange transfusion involves the slow removal and replacement of twice the infant's blood volume through umbilical catheters, with close monitoring of physiological parameters. The once significant and frequent complications of exchange transfusion have lessened with anticipatory vigilance and the increased utilization of cardiopulmonary monitoring. More complications occur in infants who are ill at the time of exchange transfusion than in those who are healthy. Complications include apnea, bradycardia, hypocalcemia, infection, hypertension, mechanical problems involving umbilical catheters, and thrombocytopenia. Given that many of these complications are unavoidable, it is best to initiate intensive phototherapy early enough that an exchange transfusion does not become necessary.[46]

Intravenous gamma globulin, administered at a dose of 1 gm/kg over two hours, demonstrably decreases serum bilirubin values and the need for exchange transfusion in patients with ABO and Rh isoimmune hemolytic anemia.[47] Gamma globulin may be considered for use in infants whose bilirubin values continue to rise rapidly in spite of intensive phototherapy.

Phenobarbital induces hepatic glucuronyl transferase, thereby increasing conjugation and excretion of bilirubin. However, a study that showed it to be beneficial required administration to the mother in cases in which severe hemolysis was anticipated prenatally.[48] Because phenobarbital is not effective immediately, and early exposure to phenobarbital may affect future cognitive development, its routine use is not recommended in the treatment of unconjugated hyperbilirubinemia.

Synthetic metalloporphyrins have been shown to reduce bilirubin production by competitively inhibiting the enzyme heme oxygenase.[49] One study showed that a single dose of Sn-mesoporphyrin reduced the need for phototherapy in jaundiced term and near-term newborns, as well as the need for follow-up testing.[50] However, the safety of metalloporphyrins has not yet been established and they are not clinically available.

Conjugated Hyperbilirubinemia. The definition, differential diagnosis, and diagnostic evaluation of conjugated hyperbilirubinemia have been described. Though the diagnosis-specific work-up is often best done as part of an inpatient admission, basic laboratories addressing metabolic and hepatic function can be obtained in the emergency room. Once conjugated hyperbilirubinemia has been identified and basic studies have been obtained, the infant should be promptly referred, in collaboration with the primary care provider, to a pediatric unit capable of conducting the full diagnostic evaluation. Timely recognition and evaluation is essential in treating both the medical and surgical etiologies of conjugated hyperbilirubinemia.

Clinical Outcomes

A recent evidence-based review suggests that a relationship between height of serum bilirubin and likelihood of developing kernicterus does exist. Most of the infants with kernicterus studied had a bilirubin level of greater than 20 mg/dL and 50% of infants with kernicterus had peak bilirubin levels up to 29.9 mg/dL. Still, a large number of infants with very high bilirubin levels had no evidence of kernicterus and were neurologically normal on short-term follow-up.[41]

Neurodevelopmental outcomes of near-term and term newborns with hyperbilirubinemia are unclear because of methodological differences in studies used to evaluate these outcomes. There was no association between peak bilirubin level and IQ when

using a large population data set.[2] Only transient mild and nonspecific motor abnormalities were noted occasionally in infants with higher bilirubin values. Other population-specific studies showed a higher prevalence in central nervous system abnormalities in infants with a bilirubin level greater than 20 mg/dL. Abnormal testing on the Denver Developmental Screening Test also was seen in these infants, though there is no evidence that these neurological problems persist into early childhood.[36]

Several well-constructed studies demonstrate a relationship between hearing impairment and high bilirubin levels.[51,52] Most of these studies report resolution of the hearing impairment with treatment of the hyperbilirubinemia.

Prognosis for infants with conjugated hyperbilirubinemia is disease-specific. Infants with biliary atresia with correctable lesions have a good prognosis with direct drainage. Those without a correctable lesion still may benefit from a Kasai procedure, although they will generally develop portal hypertension and require liver transplantation. Of infants who present with sporadic cases of idiopathic neonatal hepatitis, 60-70% recover with no lasting hepatic dysfunction, while only 20-30% of infants with the familial type do so. Progression to chronic liver disease with cirrhosis is more common in the familial type, frequently necessitating liver transplantation. Death from hemorrhage or sepsis may occur in these infants prior to liver transplantation.[17]

Disposition

Clinicians should admit all jaundiced infants who require intensive phototherapy or exchange transfusion in consultation with their primary care physicians. Consultation with neonatology or pediatric critical care is advisable in cases in which exchange transfusion is considered.

Follow-up should be arranged within 24-48 hours for those infants with increased unconjugated bilirubin values that do not meet criteria for inpatient care. Communication with the primary care physician can facilitate this process.

The infant's primary care physician should be consulted regarding conjugated hyperbilirubinemia. Once immediate infectious causes have been eliminated, the infant's physician may choose to pursue an expeditious outpatient evaluation or to admit the infant to the hospital.

Summary

Jaundice is a common clinical problem in infants during the first month of life. Distinguishing unconjugated hyperbilirubinemia from conjugated hyperbilirubinemia as a cause of jaundice is essential to developing a differential diagnosis and appropriate management plan.

Close collaboration and follow-up with the infant's primary care physician is important once jaundice has been identified by the emergency physician. By working together, the emergency physician and the primary care physician can assure timely evaluation and treatment of the jaundiced infant, assuring the best possible outcome.

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CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a credit letter. When your evaluation is received, a credit letter will be mailed to you.

CME Objectives

The CME objectives for *Pediatric Emergency Medicine Reports* are to help physicians:

a.) Quickly recognize or increase index of suspicion for specific conditions;

b.) Describe the epidemiology, etiology, pathophysiology, historical and physical examination findings associated with the entity discussed;

c.) Correctly formulate a differential diagnosis and perform necessary diagnostic tests;

d.) Apply state-of-the-art therapeutic techniques (including the implications of pharmacologic therapy discussed) to patients with the particular medical problems discussed;

e.) Provide patients with any necessary discharge instructions.

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CME Questions

111. A 72-hour-old breastfeeding newborn is evaluated in the emergency department for jaundice, and is found to have a total serum bilirubin of 10.1. The infant is well-appearing, but today's weight is 5% below the birth weight. There are no specific risk factors identified for severe hyperbilirubinemia. The best course of action now is to:
    A. encourage follow-up with the primary provider in the next 48 hours.
    B. admit immediately for phototherapy.
    C. arrange for home phototherapy with a "BiliBlanket".
    D. send additional blood tests for blood group incompatibility and G6PD deficiency.
    E. advise discontinuation of breastfeeding and begin feedings with standard infant formula.

112. An infant born to a mother with 0 type, Rh positive blood develops jaundice with a bilirubin of 12 at 18 hours of age. Which of the following is the most likely etiology of hyperbilirubinemia for this infant?
    A. Hemolysis due to ABO blood group incompatibility
    B. Hemolysis due to Rh incompatibility
    C. Inadequate initiation of feeding
    D. Extensive bruising and cephalohematoma
    E. Physiologic jaundice

113. Kernicterus:
    A. can be manifested by failed newborn hearing test.
    B. refers to yellow staining of the frontal and temporal lobes seen on autopsy.
    C. is less likely to occur in sick, stressed, or premature newborns.
    D. has been eliminated by the use of RhoGAM in Rh negative mothers.
    E. does not occur in breastfed infants.

114. Causes of cholestasis in the newborn include:
    A. Rh disease and ABO incompatibility.
    B. G6PD deficiency and thalassemia.
    C. galactosemia and tyrosinemia.
    D. Crigler-Najjar syndrome and Lucey-Driscoll syndrome.
    E. breastfeeding jaundice and breast milk jaundice.

115. Which of the following is the *most common* cause of clinical jaundice during the first month of life?
    A. Physiologic jaundice
    B. Breastfeeding
    C. Blood type incompatibility
    D. Viral hepatitis
    E. Idiopathic neonatal hepatitis

116. Which of the following infants should undergo further evaluation for jaundice?
    A. A 4-day-old breast feeding infant with icteric sclerae
    B. A 5-day-old infant with TSB of 12 and direct bilirubin of 0.9
    C. An 18-hour-old, bottle feeding, term infant with jaundice limited to the face
    D. An O-positive infant delivered to an A-positive mother
    E. A 2-day-old infant whose parents are both sickle cell trait carriers

117. A 9-day-old infant is jaundiced with a TSB of 19.7 and DB of 0.6. Which of the following would be the best study to order?
    A. Liver enzymes (AST and ALT)
    B. Coagulation studies (PT and PTT)
    C. Liver ultrasound
    D. CBC and examination of the smear
    E. Urine for reducing substances

118. Which of the following tests provides the *most specific* information for diagnosing biliary atresia?
    A. Hepatobiliary scintigraphy
    B. Liver ultrasound
    C. Measurement of direct bilirubin
    D. MRI of the biliary system
    E. Direct cholangiography

119. The most important reason to treat jaundice caused by unconjugated hyperbilirubinemia is to:
    A. prevent ongoing destruction of liver cells.
    B. prevent permanent skin discoloration.
    C. prevent visual impairment.
    D. prevent neurologic sequelae.
    E. prevent progression of underlying surgical disorders.

120. A 3-day-old newborn has a total bilirubin of 21.3, with a direct fraction of 0.6. The infant is breastfeeding, and currently weighs 9% less than at birth. Examination of a smear of the peripheral blood reveals no evidence of hemolysis. The most appropriate initial management of this infant is to:
    A. admit for intensive phototherapy and support of lactation.
    B. refer to a gastroenterologist for liver biopsy.
    C. admit to an intensive care unit for an urgent exchange transfusion.
    D. begin oral phenobarbital at 5mg/kg/day.
    E. advise discontinuation of breastfeeding and follow-up in 24 hours.

Answers: 111. A; 112. A; 113. A; 114. C; 115. A; 116. C; 117. D; 118. E; 119. D; 120. A

PEDIATRIC Emergency Medicine Reports
The Practical Journal of Pediatric Emergency Medicine

Jaundice

Clinical Features and Diagnostic Studies for the Jaundiced Newborn

UNCONJUGATED HYPERBILIRUBINEMIA		
Diagnostic Consideration	**Clinical Clues**	**Diagnostic Studies to Consider**
Blood group incompatibility	Jaundice in the first 24-36 hours after birth Rapid rise in bilirubin Maternal blood type O or Rh-negative	Maternal and infant blood typing Direct antiglobulin (Coombs) test
G6PD deficiency	Positive family history, or high-risk ethnicity Onset of jaundice after 72 hours of age May occur after administration of medication but also spontaneously Splenomegaly	G6PD level
Spherocytosis	Family history of anemia, jaundice, splenectomy	Smear Osmotic fragility test
Urinary tract infection	Jaundice persists or presents after a week of age Temperature instability Poor feeding or growth May be asymptomatic except jaundice	Urine culture
Hypothyroidism	Large anterior fontanel Umbilical hernia Constipation Lethargy, hypotonia Poor growth	Thyroid function studies
Crigler-Najjar syndrome	Family history Early onset or persistence of severe unconjugated hyperbilirubinemia without hemolysis	Liver biopsy; hepatic enzyme assay DNA studies
Intestinal obstruction	Poor feeding, vomiting, constipation	Ultrasound Barium study Rectal biopsy (for Hirschsprung disease)

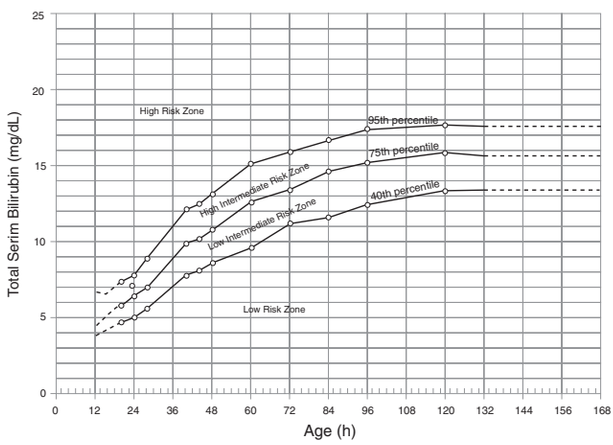
CONJUGATED HYPERBILIRUBINEMIA		
Diagnostic Consideration	**Clinical Clues**	**Diagnostic Tests to Consider**
Biliary atresia	Light colored "acholic" stools	Nuclear hepatobiliary scan Direct cholangiography Liver biopsy
Choledochal cyst	Right upper quadrant mass	Liver ultrasound
Alagille syndrome	Family history Characteristic facial features Murmur of pulmonary stenosis	Liver biopsy
Galactosemia	Lethargy, vomiting, seizures Sepsis, especially with *Escherichia coli* Cataracts Unexplained metabolic acidosis	Urine for reducing substances Newborn metabolic screening Specific enzyme assay
Other inborn errors of metabolism	Lethargy, vomiting, seizures Unexplained acidosis or hypoglycemia	Newborn metabolic screening Urine for organic acids Serum amino acids Carnitine level Specific enzyme or metabolite assays
Cystic fibrosis	Gastrointestinal, respiratory, infectious, and/or growth problems	Sweat chloride analysis
Alpha$_1$-antitrypsin deficiency	Family history	Alpha-1-antitrypsin phenotype
Urinary tract infection	Temperature instability Poor feeding or growth May be asymptomatic except jaundice	Urine culture
Infectious hepatitis	Jaundice in the first 24 hours Maternal history of infection during pregnancy Persistent jaundice Specific clues on physical examination Travel, immigration from high-risk areas	Review maternal serologies Urine for cytomegaloviral (CMV) culture Specific serologies for herpes simplex, Epstein-Barr virus, toxoplasmosis, syphilis, hepatitis
Toxic hepatitis	History of total parenteral nutrition	

Clinical Findings of Kernicterus

ACUTE	CHRONIC
Lethargy	Mild neurodevelopmental delays
Poor feeding	Choreoathetoid cerebral palsy
Tone abnormalities	Paralysis of upward gaze
Opisthotonus	Sensorineural hearing loss
High pitched cry	Dental dysplasia
Seizures	
Apnea	
Abnormal auditory brainstem response	

Adapted from Maisels MJ, Newman TB. Kernicterus in otherwise healthy, breast-fed term newborns. *Pediatrics* 1995;96:730-733.

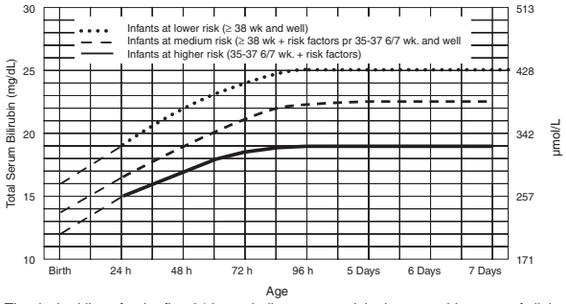
Risk Designation of Term and Near Term Well Newborns Based on Hour-specific Serum Bilirubin Values



The high-risk zone is designated by the 95th percentile track. The intermediate-risk zone is subdivided to upper- and lower-risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. (Dotted extensions are based on < 300 TSB values/epoch.)

Reprinted with permission from: Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics* 1999;103:6-14.

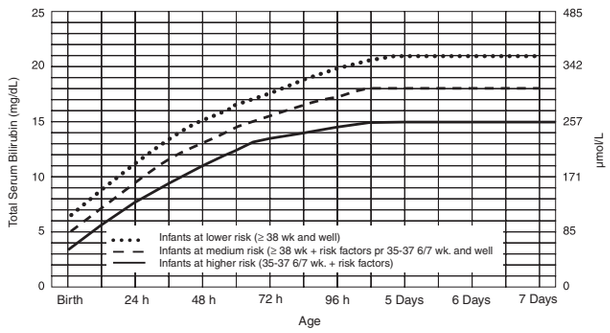
Guidelines for Exchange Transfusion in Infants 35 or More Weeks Gestation



- The dashed lines for the first 24 hours indicate uncertainly due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dL (85 mcmol/L) above these lines.
- Risk factors — isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio.
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk) can individualize TSB levels for exchange based on actual gestational age.

Reprinted with permission from: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114:297-316.

Guidelines for Phototherapy in Hospitalized Infants of 35 or More Weeks Gestation



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured).
- For well infants 35-37 6/7 wk 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 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Reprinted with permission from: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114:297-316.

Supplement to *Pediatric Emergency Medicine Reports*, December 2007: "Jaundice in the First Month of Life." *Authors:* **John M. Olsson, MD,** Associate Professor, General Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC; **Karin M. Hillenbrand, MD,** Associate Professor, General Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC; **Pamela Larsen, DrPH, DNSc, FNP,** Department of Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC. *Pediatric Emergency Medicine Reports' "Rapid Access Guidelines."* **Senior Vice President and Group Publisher:** Brenda Mooney. **Editor-in-Chief:** Ann Dietrich, MD, FAAP, FACEP. **Associate Publisher:** Lee Landenberger. For customer service, call: **1-800-688-2421.** This is an educational publication designed to present scientific information and opinion to health care professionals. It does not provide advice regarding medical diagnosis or treatment for any individual case. Not intended for use by the layman.

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The Practical Journal of Pediatric Emergency Medicine

CUMULATIVE INDEX

Volume 12, Numbers 1-12, Pages 1-156

January-December 2007

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P

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S

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CME Evaluation

Please take a moment to answer the following questions to let us know your thoughts on the CME program. Fill in the appropriate space and return this page in the envelope provided. **You must return this evaluation to receive your letter of credit. ACEP members — Please see reverse side for option to mail in answers.** Thank you.

CORRECT ● INCORRECT ⊘ ✓ ✗ ⚠

1. If you are claiming physician credits, please indicate the appropriate credential: ○ MD ○ DO ○ Other _____

After participating in this program, I am able to:	Strongly Disagree	Disagree	Slightly Disagree	Slightly Agree	Agree	Strongly Agree
2. Quickly recognize or increase index of suspicion for specific conditions.	○	○	○	○	○	○
3. Understand the epidemiology, etiology, pathophysiology, historical and physical examination findings associated with the entity discussed.	○	○	○	○	○	○
4. Correctly formulate a differential diagnosis and perform necessary diagnostic tests.	○	○	○	○	○	○
5. Apply state-of-the-art therapeutic techniques (including the implications of pharmacologic therapy discussed) to patients with the particular medical problems discussed.	○	○	○	○	○	○
6. Provide patients with any necessary discharge instructions.	○	○	○	○	○	○
7. The test questions were clear and appropriate.	○	○	○	○	○	○
8. I am satisfied with customer service for the CME program.	○	○	○	○	○	○
9. I detected no commercial bias in this activity.	○	○	○	○	○	○
10. This activity reaffirmed my clinical practice.	○	○	○	○	○	○
11. This activity has changed my clinical practice.	○	○	○	○	○	○

If so, how? _____

12. How many minutes do you estimate it took you to complete this entire semester (6 issues) activity? Please include time for reading, reviewing, answering the questions, and comparing your answers with the correct ones listed. _____ minutes.

13. Do you have any general comments about the effectiveness of this CME program?

_____

I have completed the requirements for this activity.

Name (printed) _____ **Signature** _____

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In accordance with ACEP requirements, below we provide the option for ACEP members to submit their answers to this CME activity. If you wish to submit answers to this activity, please refer to Vol. 12, Nos. 7-12, or to the answer sheet included in Vol. 12, No. 12, and circle the correct responses.

JULY 2007

Pediatric eye trauma

61. A B C D E
62. A B C D E
63. A B C D E
64. A B C D
65. A B C D E
66. A B C D E
67. A B C D E
68. A B C D E
69. A B C D E
70. A B C D E

AUGUST 2007

Critical rashes

71. A B C D
72. A B C D
73. A B C D E
74. A B C D
75. A B C D E
76. A B C D E
77. A B C D E
78. A B C D E
79. A B C D E
80. A B C D E

SEPTEMBER 2007

Physical abuse of children

81. A B C D
82. A B C D
83. A B C D
84. A B C D
85. A B C D
86. A B C D
87. A B C D
88. A B C D
89. A B C D
90. A B C D

OCTOBER 2007

Foodborne illness

91. A B C D
92. A B C D
93. A B C D
94. A B C D
95. A B C D
96. A B C D
97. A B C D
98. A B C D
99. A B C D
100. A B C D

NOVEMBER 2007

Sports-related injuries

101. A B C D
102. A B C D
103. A B C D E
104. A B C D
105. A B C D
106. A B C D
107. A B C D
108. A B C D
109. A B C D
110. A B C D

DECEMBER 2007

Jaundice

111. A B C D E
112. A B C D E
113. A B C D E
114. A B C D E
115. A B C D E
116. A B C D E
117. A B C D E
118. A B C D E
119. A B C D E
120. A B C D E