A 5-week-old Caucasian male infant who was born at 37 weeks' gestation has been receiving phototherapy with a blanket at home since his discharge at 2 days of age. Indirect bilirubin levels peaked at 18 mg/dL (308 mcmol/L) at 3 days of age and subsequently stabilized at 12 mg/dL (205 mcmol/L) after phototherapy was discontinued. Direct bilirubin levels remain less than 1 mg/dL (17.1 mcmol/L). His blood type is O-negative, and his mother's blood type is B-positive. An initial blood smear was normal, without evidence of hemolysis, and the reticulocyte count was 1% (0.01). The hematocrit at birth was 52% (0.52) and is now 44% (0.44). He is exclusively breastfed, growing appropriately, neurologically normal, and thriving. Physical examination shows scleral icterus, jaundiced skin under the diaper, and moist mucous membranes; no organomegaly, pallor, tachycardia, or other skin findings are evident. Urine is clear yellow, and stools are mushy and yellow-brown. He is the first baby for this mother, and no pregnancy, labor, or delivery complications occurred. Family history is positive for hypertension, diabetes, and neonatal jaundice in the mother and her twin brother, both of whom required phototherapy for 6 days after birth.

Of the following, the condition that is MOST likely contributing to jaundice in this infant is

1	Crigler-Najjar syndrome type I
2	Gilbert syndrome
3	Hypothyroidism
4	Lucey-Driscoll syndrome
5	Pyloric stenosis

You selected 3, the correct answer is 2.

The presence of jaundice beyond 3 weeks of age most often is associated with human milk feedings. However, more prolonged jaundice, as described for the infant in the vignette, requires additional evaluation because it may be a presenting sign for serious disease that requires urgent diagnosis or intervention (eg, biliary atresia, hypothyroidism, pyloric stenosis, cystic fibrosis). A complete history and physical examination supplemented with laboratory testing generally is sufficient to determine the diagnosis. The differential diagnosis for prolonged jaundice includes human milk jaundice, excessive bilirubin production, impaired bilirubin conjugation, increased enterohepatic circulation, and cholestasis syndromes (Table).

Gilbert syndrome is a defect in the gene for the enzyme uridinediphosphoglucuronate glucuronosyltransferase (UGT), which is responsible for conjugation of bilirubin within the hepatocyte. It affects about 6% of adults and typically presents during adolescence with mild indirect hyperbilirubinemia. This defect also has manifested in neonates who have additional icterogenic conditions. The most common polymorphism in Caucasians is an additional TA insertion in the TATAA box of the UGT 1A1 gene promotor (Figure). Homozygous individuals for the promotor defect have seven repeats-$(TA)_7TAA$ (7/7)-instead of the usual six repeats-$(TA)_6TAA$. The additional TA repeat leads to reduction in UGT activity and mild hemolysis. However, the promotor defect frequently is insufficient to cause clinical jaundice. Breastfeeding, ABO incompatibility, glucose-6-phosphate dehydrogenase deficiency, or hereditary spherocytosis in combination with the $(TA)_7TAA$ promotor defect has been associated with an increased incidence of elevated bilirubin levels in some populations of newborns. The infant described in the vignette most likely has human milk jaundice that is exacerbated by a defect in the 1A1 UGT gene (ie, Gilbert syndrome).

Genetic variations in the promotor or coding area defect of the UGT 1A1 gene, environmental factors, and the multifactorial nature of neonatal jaundice may account for the variation in hyperbilirubinemia among different newborn populations who have defects of the UGT 1A1 gene. For example, the most prevalent defect in neonates from Japan, Korea, and China involves the actual coding area of the UGT 1A1 gene (Figure). Specifically, there are missense mutations within the coding area, the most common being a G * A transition at nucleotide 211. This transition causes arginine to replace glycine at position 71. In contrast to the promotor defect in Caucasian infants, infants who have this coding area defect have higher bilirubin levels than those without the defect; additional icterogenic factors such as human milk are unnecessary to catalyze the effect, although exacerbation may occur.

Crigler-Najjar type I syndrome, like type II, is a rare disease that leads to very high levels of bilirubin soon after birth. Bilirubin encephalopathy and death may occur. Crigler-Najjar type I syndrome is due to complete absence of UGT 1A1 enzyme activity and is caused by mutations in any of the five exons coding for the UGT 1A1 enzyme (Figure). The inheritance pattern is autosomal recessive. Treatment requires exchange transfusion, phototherapy, and possibly liver transplantation. The infant in the vignette could have inherited the disease in an autosomal recessive pattern, but the bilirubin concentration stabilized at moderate levels at 5 weeks of age. In contrast, a progressive increase is seen with Crigler-Najjar syndrome whenever phototherapy is stopped.

Untreated primary hypothyroidism can be associated with prolonged jaundice in about 10% of affected newborns. Indirect hyperbilirubinemia predominates. UGT activity is low, although the mechanism is unclear. It has been speculated that the absence of thyroid hormone delays UGT and bilirubin transport development. The infant in the vignette does not demonstrate the clinical manifestations of primary congenital hypothyroidism: lethargy, hypotonia, edema, inactivity, poor feeding, cyanosis, mottled skin, coarse hair, hoarse cry, constipation, large tongue, large fontanelles, umbilical hernia, abdominal distention, or hypothermia. Of note, prolonged direct hyperbilirubinemia has been associated with central hypothyroidism and hypopituitarism.

Lucey-Driscoll syndrome (transient familial neonatal hyperbilirubinemia) is a rare familial disorder. Serum from mothers of affected infants contains high concentrations of an unidentified inhibitor of UGT that crosses the placenta to the fetus. All infants of mothers who have the inhibitor are affected. After birth, severe hyperbilirubemia occurs and may cause bilirubin encephalopathy and kernicterus. Exchange transfusion, aggressive phototherapy, and clearance of the inhibitor from the infant during the first weeks after birth resolve the hyperbilirubinemia. The infant in the vignette did not have severe hyperbilirubinemia or require exchange transfusion in the first days after birth.

Pyloric stenosis is a common disorder that is seen in 1 to 3 per 1,000 live births. Males are affected four times more often than are females. Firstborn infants also account for about 50% of those affected. Symptoms and signs may present after several weeks of age and include emesis, dehydration, metabolic alkalosis, and jaundice. Jaundice is predominately due to indirect hyperbilirubinemia and is present in 10% to 25% of infants at the time that vomiting begins. Jaundice resolves quickly after surgical intervention. UGT activity is decreased; some affected infants have the same UGT 1A1 promoter defect found with Gilbert syndrome. Because the infant in the vignette is gaining weight, thriving, and has no emesis or dehydration, pyloric stenosis is not likely contributing to the jaundice.

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

Content Specification(s):

Know the pathogenesis, clinical course, diagnosis and management of human-milk jaundice.
Understand the differential diagnosis, evaluation and approach to management of infants with indirect hyperbilirubinemia.

PREVIOUS NEXT

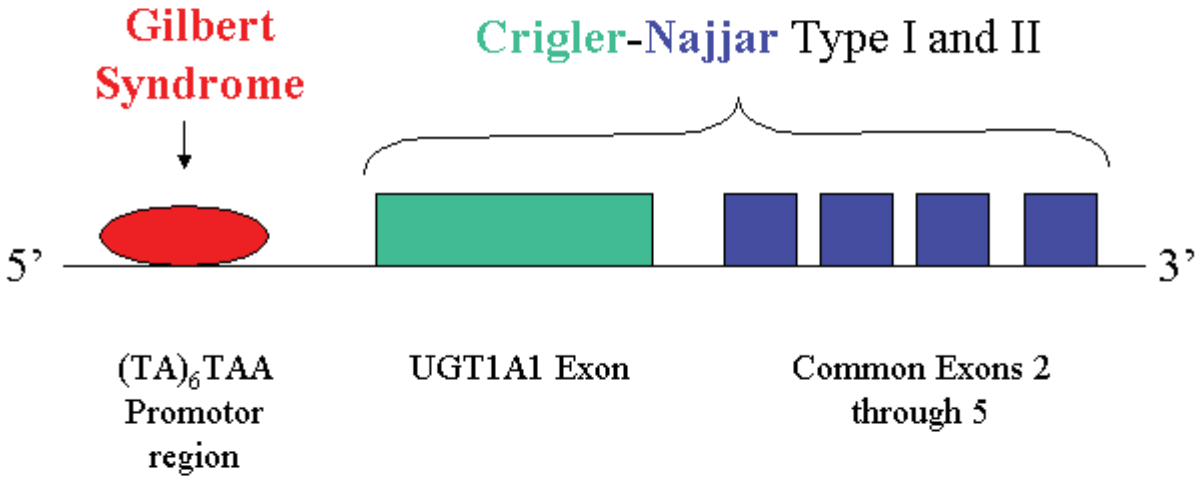
Question 9 -- Table 1

Selected Causes of Jaundice Beyond 3 Weeks of Age

Human Milk Jaundice	Bilirubin Conjugation Defects	Hemolytic Defects	Cholestasis due to Hepatocellular Disorders	Cholestasis due to Ductal Disturbances
	Gilbert syndrome Crigler-Najjar syndrome type I Crigler-Najjar syndrome type II Transient familiar neonatal hyperbilirubinemia (Lucey-Driscoll syndrome) Pyloric stenosis Hypothyroidism	Erythrocyte Enzyme Defects • Glucose-6-phosphate deficiency • Pyruvate kinase deficiency and others Erythrocyte Structural Defects • Hereditary spherocytosis and others Infection • Bacterial, viral, and protozoal	Primary Hepatitis • Neonatal giant cell hepatitis • Infectious hepatitis (viral, bacterial, protozoal) Toxic Hepatitis • Bacterial sepsis or urinary tract infection • Parenteral alimentation Metabolic Disorders • Alpha-1-antitrypsin deficiency • Galactosemia • Tyrosinemia • Fructosemia • Glycogen storage disease type IV • Lipid storage diseases -- Niemann-Pick disease -- Gaucher disease -- Wolman disease Cerebrohepatorenal syndrome (Zellweger syndrome) Trisomy 18 Cystic fibrosis Familial idiopathic cholestasis (Byler disease) Hemochromatosis Idiopathic hypopituitarism	Bile plug syndrome Extrahepatic biliary atresia Alagille syndrome Intrahepatic biliary atresia Extrahepatic obstruction and choledochal cyst Hepatic or biliary tract tumors Cystic disease

Close

Figure. Human UGT1A1 promoter, exon 1A1 and common exons 2 through 5.



An apparently healthy male was born vaginally to a gravida 2 African-American mother at 38 weeks' gestation. No apparent risk factors for hyperbilirubinemia are noted. He is scheduled to be discharged with his mother 25 hours after birth. Nursing notes indicate jaundice on the face and upper trunk. The infant is breastfeeding well, has passed meconium, and is voiding regularly. Following nursery protocol, transcutaneous bilirubin concentration is measured at 8.0 mg/dL (136.8 mcmol/L), which you assess for the risk of subsequent significant hyperbilirubinemia using the hour-specific bilirubin nomogram (Figure).

Of the following, the MOST appropriate plan of action at this time is to

1	consult an audiologist
2	delay discharge and repeat the bilirubin measurement in 8 to 12 hours
3	institute phototherapy
4	send the infant home after scheduling a follow-up evaluation in 1 week
5	send the infant home after scheduling a follow-up evaluation in 2 days

You selected 1, the correct answer is 2.

The bilirubin concentration measured in the infant in the vignette corresponds to the 95th percentile on the nomogram, which places the infant in the high intermediate risk category for development of severe hyperbilirubinemia. Although the infant's history presents no risk factors, hemolysis is the most common underlying reason for early hyperbilirubinemia, and incompatibility in the ABO blood grouping is responsible for most cases. Screening tests for blood group incompatibility should be ordered and the history reviewed for jaundice in the sibling or family. Because follow-up requires accurate bilirubin measurements, measuring total serum bilirubin at this time, delaying discharge, and obtaining another measurement prior to discharge would be most helpful in planning care and follow-up.

Audiology testing is not useful in determining clinical management of bilirubin at this level. Abnormal test results at this time suggest a false-positive result or congenital hearing loss. Guidelines from the American Academy of Pediatrics do not suggest phototherapy for infants at medium risk for hyperbilirubinemia if the bilirubin concentration remains below 10 mg/dL (171 mcmol/L) at 25 hours after birth. A total serum bilirubin is preferred for accuracy in serial measurements. Using total serum bilirubin is essential if phototherapy becomes necessary; skin color and transcutaneous measurements are not accurate when used in conjunction with phototherapy.

Discharging a baby who has jaundice near the 95th percentile at this age with follow-up delayed for 1 week places the child at risk for developing bilirubin levels that exceed those recommended for phototherapy and that may cause brain injury. Additionally, discharge at this age requires follow-up in 1 to 3 days for many reasons unrelated to icterus. Sending the child home with re-evaluation in 2 days without assessing the rate of bilirubin increase and the cause for the jaundice places the child at risk of developing potentially toxic bilirubin levels before being seen again.

Reference:

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

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.

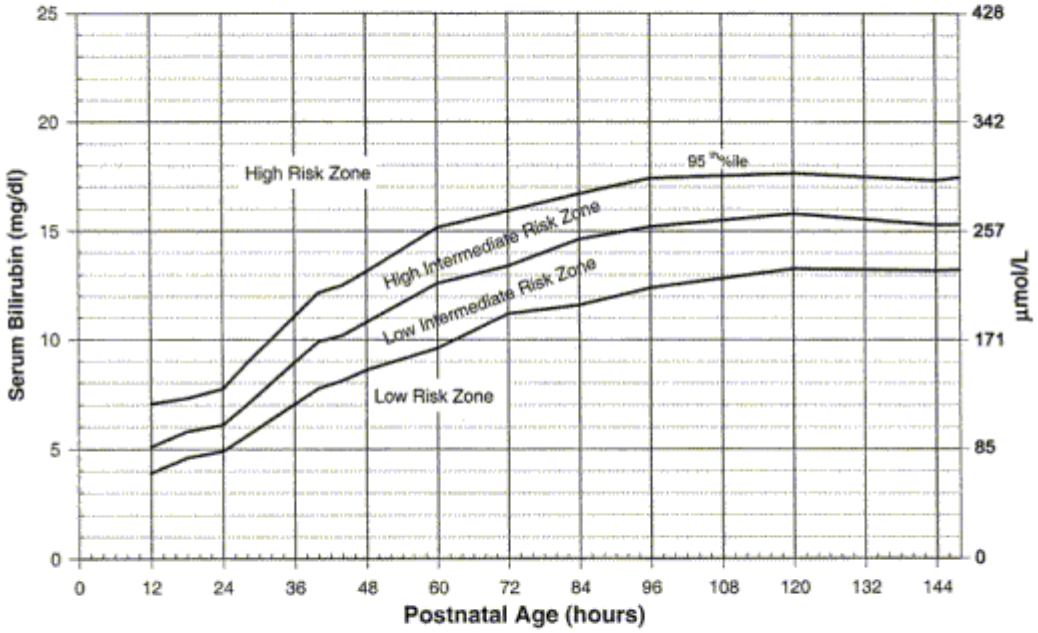
Figure. Hour-specific nomogram for assessing bilirubin levels. Reprinted with permission from Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics*. 1999;103:6-14.

Content Specifications:

Understand bilirubin physiology in the fetus and neonate
Know the factors associated with an increase in neonatal serum bilirubin concentrations
Understand the indications for use, the mechanism of action, the efficacy, and the dose-response relationship of phototherapy in the treatment of neonatal hyperbilirubinemia

PREVIOUS NEXT

Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values



Subcommittee on Hyperbilirubinemia, Pediatrics 2004;114:297-316

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