Crigler-Najjar syndrome

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INTRODUCTION

Crigler-Najjar syndrome is a rare autosomal recessive disorder of bilirubin conjugation characterized by severe unconjugated hyperbilirubinemia that can result in bilirubin-induced neurologic dysfunction (BIND). BIND includes potentially reversible acute bilirubin encephalopathy, which, if sufficiently severe or prolonged, can progress to static encephalopathy due to neuronal death, commonly known as kernicterus. Other common causes of unconjugated hyperbilirubinemia are Gilbert syndrome, physiologic neonatal jaundice, and hemolytic disorders. (See "Gilbert syndrome" and "Unconjugated hyperbilirubinemia in neonates: Etiology and pathogenesis" and "Classification and causes of jaundice or asymptomatic hyperbilirubinemia".)

This topic reviews the pathophysiology, clinical manifestations, diagnosis, and management of Crigler-Najjar syndrome. The evaluation of an infant, child, or adult with unconjugated hyperbilirubinemia is discussed in detail separately. (See "Evaluation of jaundice caused by unconjugated hyperbilirubinemia in children" and "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia".)

CLASSIFICATION

Crigler-Najjar syndrome is caused by absent or defective uridine diphosphate glucuronosyltransferase-1A1 (UGT1A1), the enzyme responsible for the conjugation of bilirubin.

The phenotype depends on serum bilirubin concentration. It is related to the degree of impairment in hepatic bilirubin-UGT1A1 activity (table 1) and possibly other factors that affect bilirubin production or biliary excretion:

- **Type I** – Patients with severe unconjugated hyperbilirubinemia due to absent or minimal hepatic bilirubin-UGT1A1 activity are traditionally classified as Crigler-Najjar syndrome type I (MIM #218800). The severe unconjugated hyperbilirubinemia begins in the neonatal period and continues throughout life. These patients are at high risk for developing bilirubin-induced neurologic dysfunction (BIND), especially within the neonatal period but also at any age [1]. They do not respond to phenobarbital and require chronic daily phototherapy to maintain serum bilirubin within safe margins.

- **Type II** – Patients with less severe persistent unconjugated hyperbilirubinemia due to reduced hepatic UGT1A1 activity are traditionally classified as Crigler-Najjar syndrome type II (MIM #606785). However, this includes a range of serum bilirubin levels, depending on the individual's hepatic UGT1A1 activity:

  - Patients with moderate reductions in UGT1A1 activity may have high enough serum bilirubin levels to require daily phenobarbital administration to maintain serum bilirubin concentrations within a safe range. Additional interventions may be needed for acute exacerbations triggered by infection, hemolysis, or biliary obstruction. Without active management and interventions during hyperbilirubinemic crises, they are at risk for bilirubin-induced brain injury.

  - A majority of type II patients with milder reductions in hepatic UGT1A1 activity have persistently elevated but generally safe serum bilirubin concentrations without chronic phototherapy or phenobarbital. These patients may choose chronic phenobarbital therapy to manage their jaundice if the jaundice impairs their quality of social life.

EPIDEMIOLOGY

The prevalence of Crigler-Najjar syndrome is approximately 0.6 to 1 case per million live births [2]. The disorder occurs in all races. It is more common in communities with a high frequency of pathogenic *UGT1A1* gene variants due to a founder effect, such as in Old Order Amish and Mennonite populations [1], as well as in children born to consanguineous parents [3,4].

PATHOPHYSIOLOGY

Bilirubin metabolism — The metabolism of bilirubin by the liver comprises five distinct but interrelated stages (figure 1) (see "Bilirubin metabolism"):

- Uptake from the circulation
- Intracellular storage in the hepatocyte
- Conjugation with glucuronic acid
- Biliary excretion
- Reuptake of a fraction of bilirubin glucuronides that is secreted into liver sinusoidal blood

In healthy people, approximately 96 percent of serum bilirubin is unconjugated. Abnormalities in any one or more of the five stages of bilirubin metabolism can result in hyperbilirubinemia, in which there is either an elevation in unconjugated bilirubin alone or of both unconjugated and conjugated bilirubin. The unconjugated fraction alone is increased in disorders with bilirubin overproduction (eg, hemolysis) and with inherited or acquired disorders that specifically affect bilirubin uptake or glucuronidation, including Crigler-Najjar or Gilbert syndromes. In inherited disorders of biliary excretion of conjugated bilirubin (Dubin-Johnson syndrome) and defective reuptake of bilirubin glucuronides from plasma, both conjugated and unconjugated bilirubin accumulate in plasma. Complex clinical disorders, such as hepatitis or cirrhosis, can affect multiple processes, resulting in the accumulation of both unconjugated and conjugated bilirubin. In these settings, the proportion of conjugated bilirubin in plasma increases. (See "Classification and causes of jaundice or asymptomatic hyperbilirubinemia".)

Molecular defect — Crigler-Najjar syndrome is caused by homozygous or compound heterozygous pathogenic variants in the *UGT1A1* gene, which encodes uridine diphosphate glucuronosyltransferase 1A1, the only isoform of UGT that contributes significantly to bilirubin conjugation in humans (figure 2) [5].

- **Type I** – Crigler-Najjar syndrome type I is caused by one of many pathogenic variants in the coding sequence of *UGT1A1*, specifically deletions, insertions, missense mutations, or premature stop codons that lead to complete loss or very low levels of hepatic bilirubin-UGT activity and severe unconjugated hyperbilirubinemia (table 1) [6-9]. The variants can be located in any of the five exons comprising the *UGT1A1* messenger ribonucleic acid (mRNA) (figure 2) [10,11]. In addition, variants within introns can result in splicing abnormalities, resulting in loss of the enzyme activity. Genetic alterations located in exon 1 affect the activity of only *UGT1A1*; in contrast, mutations involving exons 2 to 5 affect all isoforms expressed from the *UGT1A* locus, which may affect other UGT1A functions including conjugation of various hormones, drugs, and xenobiotics.

- **Type II** – Crigler-Najjar syndrome type II is caused by pathogenic point mutations in the coding region of *UGT1A1* that reduce but do not abrogate hepatic UGT1A1 enzyme activity [7]. The residual enzyme activity can be boosted by phenobarbital. The enzyme activity and bilirubin conjugation vary depending on the variant. As in type I disease, the mutations may be located in any of the five exons in the *UGT1A1* coding region [7,10].

- **Combined *UGT1A1* coding variant with Gilbert-type promoter defect** – Gilbert syndrome is caused by homozygous insertion of a TA dinucleotide in the **promoter** region of *UGT1A1*, which reduces the production of UGT1A1 to approximately 30 percent of normal, in contrast with the mutations in the coding region that cause the two types of Crigler-Najjar syndrome [12]. Because of the high frequency of the Gilbert-type promoter in the general population (approximately 51 percent of the Western population has at least one Gilbert-type allele), some heterozygous carriers of a structural variant associated with Crigler-Najjar syndrome also carry the Gilbert-type promoter on the other allele. Such combined defects may explain the frequent finding of intermediate levels of hyperbilirubinemia in a range similar to that found in Crigler-Najjar syndrome type II in the family members of patients with Crigler-Najjar syndrome (both types I and II) who are carriers for a structural pathogenic *UGT1A1* variant on one allele but have a Gilbert-type promoter on the other allele [13,14]. Case reports describe a few individuals with this combined genotype who developed episodes of severe hyperbilirubinemia leading to acute bilirubin encephalopathy and kernicterus. (See "Gilbert syndrome".)

CLINICAL MANIFESTATIONS

Type I disease

- **Clinical presentation** – Crigler-Najjar syndrome type I presents with severe and persistent elevations of unconjugated bilirubin within the first few days after birth. Affected patients may be identified through routine newborn bilirubin screening (see "Unconjugated hyperbilirubinemia in term and late preterm newborns: Screening"). The hyperbilirubinemia is usually in the range of 10 to 25 mg/dL (171 to 425 micromol/L) within the first 7 to 10 days of life. If left untreated, it progresses to neurologically dangerous levels, usually after 14 days of life (table 1) [1,15,16]. There is little or no conjugated component, and other liver tests are normal. Stool color is normal, but fecal urobilinogen excretion is diminished due to the marked reduction in the conjugation of bilirubin [3,4,15-20]. There is no evidence of hemolysis or other cause of unconjugated hyperbilirubinemia [21].

Crigler-Najjar syndrome must be distinguished from other causes of unconjugated hyperbilirubinemia in newborns, some of which are far more common than Crigler-Najjar syndrome. Crigler-Najjar syndrome usually can be distinguished from these disorders based on greater severity and persistence of the hyperbilirubinemia. (See "Unconjugated hyperbilirubinemia in neonates: Etiology and pathogenesis".)

- **Complications** – If the hyperbilirubinemia is not treated promptly and effectively, affected neonates may develop acute bilirubin encephalopathy, which is potentially reversible but can progress to kernicterus, which is characterized by bilirubin staining and death of neurons and static encephalopathy. Patients who avoid these sequelae during childhood with optimal medical management remain at risk to develop late-onset bilirubin-induced neurologic dysfunction (BIND) in adolescence or adult life [3,22]. (See "Unconjugated hyperbilirubinemia in neonates: Risk factors, clinical manifestations, and neurologic complications", section on 'Risk factors for neurotoxicity'.)

  Patients with type I disease often develop hepatic fibrosis, as demonstrated in case series of patients undergoing liver transplantation, in which 40 to 60 percent had fibrosis of varying severity [1,23]. Although the mechanism for hepatocellular injury has not been established, the fibrosis score in one study correlated with the lifetime mean bilirubin concentration [1].

  Biliary stones develop in 40 to 50 percent of patients with type I disease [1]. These pigmented stones develop because a fraction of the photo-isomers of bilirubin excreted in bile revert to water-insoluble bilirubin IX-alpha. Because biliary excretion of bilirubin photo-isomers is a major pathway of bilirubin elimination in type I patients under phototherapy, biliary obstruction by pigment stones can rapidly increase serum bilirubin to dangerous levels. Therefore, the diagnosis of cholelithiasis should prompt urgent cholecystectomy.

Type II disease

- **Clinical presentation** – Affected patients may present with jaundice during the neonatal period (similar to those with type I disease), later in childhood, or adulthood. Patients may come to medical attention because of an acute episode of jaundice (often triggered by fasting, an intercurrent illness, or general anesthesia) or when hyperbilirubinemia is identified as an incidental finding on laboratory testing. BIND is uncommon in patients with type II disease [17,24-26] but may occur in neonates, children, or adults if hyperbilirubinemia is not adequately controlled during acute exacerbations.

Crigler-Najjar syndrome type II responds to phenobarbital, and the hyperbilirubinemia is usually less severe than in type I disease. Bilirubin concentrations are usually 8 to 20 mg/dL (136 to 340 micromol/L) but can rise to levels as high as 40 mg/dL (680 micromol/L) during acute exacerbations [27]. Other liver function tests are normal (table 1).

Residual bilirubin-UGT activity is generally less than 10 percent. Because of a relatively low affinity of the mutant UGT1A1 for bilirubin, the enzyme is catalytically effective only in the presence of hyperbilirubinemia [6]. Although only approximately 50 percent of the bilirubin produced is conjugated and excreted into the bile, the bile is pigmented [17,28].

DIAGNOSIS

When to suspect Crigler-Najjar syndrome — Crigler-Najjar syndrome is suspected in a newborn infant or child presenting with severe, persistent unconjugated hyperbilirubinemia (no conjugated component) and no evidence of hemolysis or underlying liver disease. Because it is a rare autosomal recessive disease, it is more likely in infants from the populations with a high prevalence of pathogenic *UGT1A1* variants due to a founder effect (eg, Old Order Amish and Mennonite people), as well as in children born to consanguineous parents.

Genetic testing — The diagnosis is established by molecular testing for pathogenic variants in the *UGT1A1* gene. Deoxyribonucleic acid (DNA) extracted from peripheral blood leukocytes, buccal scrapings, or any other tissue can be used to make a genetic diagnosis in both affected patients and heterozygous carriers. For families with confirmed or suspected Crigler-Najjar syndrome, prenatal testing can be performed on chorionic villus samples or amniotic cells [29]. A list of laboratories that provide genetic testing is available here.

Because Crigler-Najjar syndrome can result from point mutations, insertions, or deletions within any of the five exons comprising the *UGT1A1* coding region, as well as splicing abnormalities, all exons and their flanking intronic regions should be sequenced. In addition, the promoter region containing the TATAA element should also be sequenced because the presence of a Gilbert-type promoter (UGT1A1*28) would reduce quantitative expression of UGT1A1.

Distinguishing type I from type II disease

- **Clinical distinction** – As a general rule, type II is associated with lower serum bilirubin concentrations, but values can overlap with type I, especially if there is underlying hemolysis (table 1). Therefore, serum bilirubin concentrations do not reliably distinguish between Crigler-Najjar syndromes type I and II in all cases. For practical

purposes, if regular phototherapy is needed to keep the patient's serum bilirubin below the dangerous range, the patient should be considered to be type I.

For patients with suspected type II disease, a trial of phenobarbital should be performed to confirm the diagnosis. The administration of phenobarbital can help to differentiate between Crigler-Najjar syndromes type I and II. In most patients with type II disease, the serum bilirubin concentration can be reduced by more than 25 percent by administration of phenobarbital, which presumably works by inducing residual UGT1A1 activity (table 1) [17,30]. A response to phenobarbital is not observed in patients with type I disease. (See 'Phenobarbital' below.)

- **Genetic testing** – Whenever possible, the diagnosis and type should be confirmed by genetic testing. Type I disease is caused by premature translational stop codons, translational frameshift, or nonsynonymous (missense) mutations causing the substitution of a single amino acid. On the other hand, type II disease is always caused by missense mutations, which result in amino acid substitutions that markedly reduce the catalytic activity of UGT1A1, without completely abolishing it. Coexistence of a Gilbert-type TATAA element can further enhance hyperbilirubinemia by reducing expression of the protein. (See 'Genetic testing' above and 'Molecular defect' above.)

- **Other tests** – In a small minority of cases, genetic testing does not reveal a pathogenic variant that permits confident prediction of absence or functional deficit of UGT1A1. In such cases, or if genetic testing is not available, type I and type II disease can be distinguished by high-pressure liquid chromatography or thin-layer chromatography of bile collected from the duodenum through an orally placed duodenal catheter or an upper gastrointestinal endoscope. In patients with type I disease, conjugated bilirubin is absent or present only in trace amounts, reflecting the lack of UGT1A1 activity (table 1). Patients with type II disease have detectable amounts of conjugated bilirubin. They also have an increased fraction of bilirubin monoglucuronides (>10 percent), similar to individuals with Gilbert syndrome [28,31]. By contrast, in healthy individuals without these conditions, up to 90 percent of bilirubin conjugates in bile are bilirubin diglucuronide; the remaining are bilirubin monoglucuronide.

DIFFERENTIAL DIAGNOSIS

- **Neonates** – Crigler-Najjar syndrome must be distinguished from other causes of unconjugated hyperbilirubinemia in newborns, including benign neonatal hyperbilirubinemia, breast milk jaundice, lactation failure jaundice, Lucey-Driscoll

syndrome, and isoimmune-mediated hemolysis (Rh or ABO incompatibility), which are far more common than Crigler-Najjar syndrome. Crigler-Najjar syndrome usually can be distinguished from these disorders based on greater severity and persistence of the hyperbilirubinemia as well as exclusion of hemolytic disease. (See "Unconjugated hyperbilirubinemia in neonates: Etiology and pathogenesis" and "Bilirubin metabolism", section on 'Conjugation of bilirubin'.)

- **Children and adults** – Patients with Crigler-Najjar syndrome type II may present in infancy, childhood, or adulthood, with chronic jaundice caused by unconjugated hyperbilirubinemia. The differential diagnosis for this presentation includes:

  - Gilbert syndrome – Patients with Gilbert syndrome develop hyperbilirubinemia at times of stress or fasting. Serum bilirubin concentrations are generally <3 mg/dL (51 micromol/L), with a conjugated component.

  - Hemolytic disorders – Hemolytic disorders can cause unconjugated hyperbilirubinemia due to bilirubin overproduction. However, serum bilirubin concentrations are generally <8 mg/dL (136 micromol/L).

  - Drugs – Drugs can impair bilirubin uptake (eg, rifamycin or probenecid) or impair bilirubin conjugation (eg, protease inhibitors, ketoconazole and amitriptyline). (See "Evaluation of jaundice caused by unconjugated hyperbilirubinemia in children" and "Gilbert syndrome".)

MANAGEMENT OF TYPE I DISEASE

Goals of treatment — To avoid the risk of bilirubin-induced neurologic dysfunction (BIND), treatment goals are to maintain [1]:

- Serum total bilirubin <20 mg/dL (340 micromol/L). Lower thresholds are needed for preterm infants. (See "Unconjugated hyperbilirubinemia in preterm infants <35 weeks gestation".)

- Maintain serum bilirubin/albumin (B/A) ratio:

  - <0.7 mol/mol (molar ratio), or
  - <6.15 mg/g (mass ratio)

  This target provides a margin of safety below the threshold that is associated with kernicterus (unsafe B/A molar ratio is ≥1 mol:mol) [1].

To convert the mass ratio to molar ratio, use the following conversions:

- Bilirubin in mg/dL × 17 = Bilirubin in micromol/L
- Albumin in g/dL × 152 = Albumin in micromol/L

Thus, 1 g of albumin binds approximately 8.8 mg of unconjugated bilirubin; therefore, the target B/A mass ratio is ≤6.15 mg bilirubin:g albumin (8.8 × 0.7 = 6.15).

The B/A ratio provides an important index of neurologic risk because it reflects the amount of unbound ("free") bilirubin, which crosses the blood-brain barrier and causes BIND.

General measures — General measures to help control hyperbilirubinemia and avoid acute exacerbations include:

- Avoid dehydration; check serum bilirubin during any significant acute illness or if jaundice worsens
- Avoid drugs that displace bilirubin from albumin-binding sites; unsafe drugs include some commonly used antibiotics and contrast agents (see this list of safe and unsafe drugs) [1,32]

Therapy for chronic unconjugated hyperbilirubinemia — Crigler-Najjar syndrome type I is characterized by severe chronic unconjugated hyperbilirubinemia, with acute exacerbations. The acute exacerbations may be triggered by a variety of factors that increase bilirubin production or interfere with its elimination, including fasting and infection. (See 'Treatment of acute exacerbations' below.)

Patients are managed with chronic daily phototherapy (table 2). Additional measures including plasmapheresis are required for acute exacerbations to avoid BIND. (See 'Treatment of acute exacerbations' below.)

Liver transplantation is curative, and we suggest referral for discussion of transplantation, which should be performed between the age of one year and early to mid-adolescence to minimize the risk of BIND. (See 'Early referral for liver transplantation' below.)

Phototherapy — Phototherapy is effective and widely used for the treatment of unconjugated hyperbilirubinemia of any cause, including Crigler-Najjar syndrome, and it is the primary chronic intervention for patients with Crigler-Najjar syndrome type I during infancy and childhood. Early diagnosis and initiation of phototherapy within the first one or two weeks of life effectively maintains chronic serum bilirubin concentrations and B/A ratios below thresholds that are associated with BIND and is associated with dramatic improvement in neurologic

outcomes, based on observational evidence from case series [1]. In the absence of phototherapy, virtually all infants with type I disease develop BIND and die by 18 months of age (see 'Prognosis' below). Phototherapy has minimal risks, but has substantial treatment burden for the patient and family, and must be combined with other measures to prevent and treat acute exacerbations of hyperbilirubinemia. (See 'Treatment of acute exacerbations' below.)

Phototherapy acts by converting a portion of bilirubin IX-alpha-ZZ into its configurational isomers, photocyclization products (lumirubin), and photo-oxidation products, which are then excreted in the bile without requiring conjugation. Of the three types of photoproducts, the configurational isomers become reconverted to bilirubin IX-alpha-ZZ, which is partly absorbed in the intestine and undergoes enterohepatic circulation [33]. (See "Bilirubin metabolism".)

The technique involves exposure to an array of light-emitting diodes (LEDs) or fluorescent lamps (peak emission 450 to 600 nm) placed 30 to 45 cm from the skin in infants (exposing 60 to 70 percent of the body surface) and 45 to 60 cm in children and adults (exposing 35 to 50 percent of the body surface). Irradiance at skin surface should be 40 to 100 microW/cm^2, as measured with a photometer. Neonates are exposed to the lights for 15 to 20 hours per day, while children and adults are exposed for 7 to 13 hours per day [1]. Exposure to sunlight also provides additional effective phototherapy. However, despite using an optimized phototherapy array, at puberty, phototherapy becomes less effective because of thickening of the skin, increased skin pigmentation, and decreased surface area in relation to body mass, as indicated by an increasing B/A molar ratio, which may reach potentially dangerous values during adolescence [1]. (See 'Goals of treatment' above.)

Bilirubin passes the placental barrier bidirectionally, so that newborns born to mothers with Crigler-Najjar syndrome have serum bilirubin levels similar to those of their mothers [34]. Based on the combined published experience of 17 deliveries in 12 mothers with Crigler-Najjar syndrome (four with type I and eight with type II disease), recommendations for management during pregnancy include regular prenatal monitoring and adjusting maternal phototherapy duration to keep the mother's bilirubin levels below 11.7 mg/dL (200 micromol/L) and B/A molar ratios below 0.5 [35].

Oral calcium phosphate as an adjunct to phototherapy — We routinely treat patients with type I disease with oral calcium salts as an adjunct to phototherapy. Recommended total daily doses are:

- Adults and children >40 kg body weight – 100 mmol calcium daily
- Children <40 kg – 2.5 mmol/kg body weight calcium daily

The calcium salts are given in three or four divided doses, administered as an equimolar mixture of calcium phosphate and calcium carbonate (which converts phosphates to amorphous calcium phosphate in the intestines). Formulations of these calcium salts and conversions are included in the footnote to the table (table 2).

The calcium phosphate binds bilirubin IX-alpha-ZZ generated in the intestine from configurational isomers excreted as a result of phototherapy, thereby disrupting the enterohepatic recycling of bilirubin [36]. In a case series in patients with Crigler-Najjar syndrome type I who were being treated with phototherapy, oral calcium administration (17.1 g calcium salts as a powder in adults) resulted in an average of 18 percent reduction in serum bilirubin from the levels achieved by phototherapy alone [24]. In contrast, patients with Crigler-Najjar syndrome type II who had not been on phototherapy did not have any reduction of serum bilirubin, suggesting that calcium acts by binding unconjugated bilirubin IX-alpha-ZZ generated from its configurational isomers produced by phototherapy. (See 'Phototherapy' above.)

Orlistat — Orlistat is rarely used clinically due to its modest effect on serum bilirubin levels and gastrointestinal side effects. In a placebo-controlled crossover trial in patients with Crigler-Najjar syndrome types I and II, there was an average of 9 percent reduction of serum bilirubin in 44 percent of patients [37].

Early referral for liver transplantation — We suggest referral for discussion of prophylactic liver transplantation early in the course of Crigler-Najjar syndrome type I [38].

Liver transplantation is the only definitive treatment and rapidly normalizes serum bilirubin levels [1,30,39,40]. Survival rates for children undergoing liver transplantation (all causes) are generally >90 percent at one and five years, although reliable data are not available for the subset of patients who are transplanted for Crigler-Najjar syndrome, who represent <1 percent of pediatric liver transplant patients [41]. One registry with outcomes for liver transplant in more than 60 patients with Crigler-Najjar syndrome reported 5- and 10-year survival rates of 96 percent [42]. Transplant from a living donor is an option and may permit elective transplantation while the child is healthy [40].

The optimal timing of liver transplantation has not been established, but it is generally recommended that liver transplantation should be considered after the age of one year, preferably in early or mid-adolescence. The decision should be made collaboratively by the expert clinicians, patient, and family, including these considerations:

- Deferring liver transplantation until adolescence is reasonable, provided that serum bilirubin concentrations can be maintained in a safe range, ie, serum bilirubin significantly

below 20 mg/dL (340 micromol/L) and serum B/A molar ratio <0.7 mol:mol.

In many patients, this can be accomplished by optimizing the technique and adherence to phototherapy and expert management of acute hyperbilirubinemic crises. An advantage of deferring liver transplant until adolescence is that another therapy may be developed in the interim (eg, gene therapy) and, if so, this would avoid the need for prolonged immunosuppression. (See 'Investigational therapies' below.)

- By contrast, transplantation during childhood may be beneficial for patients whose hyperbilirubinemia is not well controlled despite concerted efforts to optimize phototherapy and management of acute hyperbilirubinemic crises, as indicated by serum bilirubin levels persistently above 20 mg/dL (340 micromol/L) or spikes to 25 mg/dL (425 micromol/L) during intercurrent illnesses. For these patients, early liver transplantation is suggested to reduce the risk for BIND, which may not be fully reversible once it is established [30].

In the small case series available, approximately one-quarter of patients managed with phototherapy and plasmapheresis alone developed BIND before or during adolescence [1,30,43]. Although standardization of phototherapy protocols and establishment of criteria for urgent care are expected to prevent BIND, the patients remain at lifelong risk and, therefore, liver transplantation is recommended before or at adolescence. (See 'Prognosis' below.)

Orthotopic, auxiliary, and auxiliary partial orthotopic liver transplantation have been used effectively for patients with Crigler-Najjar syndrome type I [44]. Deceased liver donors and living related donors, including heterozygotes for Crigler-Najjar syndrome type I, have been used successfully [44-46]. In one series of patients with noncirrhotic metabolic liver diseases treated with auxiliary liver transplantation, five-year patient and graft survivals were 90 and 70 percent, respectively [47]. In addition, case reports have described "domino" liver transplantation, in which the liver from a patient with maple syrup urine disease was successfully transplanted into a patient with Crigler-Najjar syndrome [1]. Another report describes an exchange of liver segments between patients with propionic acidemia and Crigler-Najjar syndrome type I, resulting in correction of both disorders [48].

Treatment of acute exacerbations — Acute exacerbations of hyperbilirubinemia may be triggered by a variety of factors including fasting, infection, hemolysis, cholelithiasis, cholecystitis, or general anesthesia. These circumstances increase bilirubin production (hemolysis), reduce bile flow and bilirubin elimination (fasting, cholelithiasis, cholecystitis), and/or reduce plasma albumin (albumin is a negative acute phase reactant), thereby increasing the B/A ratio.

Initial management — Acute exacerbations of hyperbilirubinemia require hospitalization for continuous high-intensity phototherapy, hydration, and correction of any underlying fluid and electrolyte abnormalities (table 2). Concomitant conditions that increase bilirubin production, eg, hemolytic disorders or blood sequestered in subcutaneous tissues or intestine, as well as biliary obstruction by gallstones, should be excluded. Oral calcium salts should be continued during the acute crisis (or instituted if not previously given), if possible. (See 'Oral calcium phosphate as an adjunct to phototherapy' above.)

Persistent hyperbilirubinemia

Albumin infusion — If continuous intensive phototherapy does not achieve the target B/A molar ratio of <0.7, albumin infusion (1 to 2 g/kg/dose) should be performed to reduce the risk of BIND by decreasing unbound (free) plasma bilirubin. Drugs that displace bilirubin from albumin should be avoided. Special caution should be used for intravenous bolus dosing, which results in rapid spike of plasma concentration of the drug.

Plasmapheresis — If, despite the above treatments, the B/A ratio increases to ≥0.9, plasmapheresis should be instituted to reduce the B/A ratio to <0.7 [1]. In neonates, exchange transfusion can be used and may be more effective than plasmapheresis.

Investigational therapies

- **Gene therapy** – Introduction of a nonpathogenic *UGT1A1* gene has the potential for curing the genetic defect leading to Crigler-Najjar syndrome, particularly because even 5 to 10 percent of *UGT1A1* activity is sufficient to maintain serum bilirubin in a safe range.

  The safety and efficacy of *UGT1A1* gene therapy was evaluated in an open-label phase 1 to 2 study in five young adults with Crigler-Najjar syndrome and severe hyperbilirubinemia (NCT03466463) [49]. All participants had been managed with daily phototherapy (7 to 12 hours daily) and two with adjunctive phenobarbital. Gene therapy was administered via a recombinant adeno-associated virus (rAAV) vector at one of two doses (high dose 2×10^{12} vector genomes [vg]/kg body weight or low dose 5×10^{12} vg/kg). Early results (78 to 80 weeks after treatment) show that, for the two participants in the low-dose cohort, serum bilirubin concentrations transiently decreased but then rebounded to pretreatment levels by 16 weeks. However, for the three participants in the high-dose cohort, the mean total bilirubin concentrations were 20.5±3.3 mg/dL (351±56 micromol/L) with phototherapy at baseline and declined to 8.7±1.9 mg/dL (149±33 micromol/L) without phototherapy at least 78 weeks after vector administration. There were transient increases in liver enzymes, managed with immunosuppressive therapy, and no serious adverse events.

While these observations suggest that rAAV-based gene therapy is safe and may be effective in the treatment for severe Crigler-Najjar syndrome, there are some important concerns and potential limitations of this approach:

- The presence of preexisting neutralizing anti-AAV antibodies excludes a significant percentage of Crigler-Najjar patients from this approach.
- Long-term efficacy is uncertain due to disappearance or silencing of the episomal vectors, as indicated by continuous decline of expression of the therapeutic gene product of rAAV vectors in a five-year follow-up study of patients with hemophilia A [50].
- Recipients of rAAV gene therapy develop cross-reacting neutralizing antibodies, which preclude repeat administration of any rAAV serotype [50].
- Gene therapy may increase oncogenic potential, suggested by observations of random integration of fragments of rAAV found in preclinical mouse studies [51] and AAV2 integrations observed in human hepatocellular carcinomas [52].

In addition, further study is required to determine the optimal protocol and whether the response varies with baseline characteristics, including *UGT1A1* activity.

Alternatively, autologous hepatocytes obtained from the patient can be genotypically corrected and transplanted back into the donor (ex vivo gene therapy). Most of these potential approaches have not yet reached the stage of clinical application.

- **Hepatocyte transplantation** – Hepatocyte transplantation is continuing to be investigated as a minimally invasive alternative to liver transplantation. Based on initial experimental studies in rodent models [53,54], isolated normal hepatocytes are introduced in the portal venous system, from which hepatocytes flow into the liver and integrate into the hepatic cords. Hepatocyte transplantation in a patient with Crigler-Najjar syndrome type I resulted in reduction of serum bilirubin levels to approximately 50 percent of pretransplant levels [55]. After nearly three years, serum bilirubin levels began to rise and the patient was treated successfully with auxiliary liver transplantation. This was followed by hepatocyte transplantation therapy in a number of patients with various inherited liver diseases, including five with Crigler-Najjar syndrome type I [56-58]. These studies showed that hepatocyte transplantation is safe and feasible but, in the absence of preparative treatment, offers only partial amelioration of liver-based inherited metabolic diseases. Subsequent animal experiments showed that X-irradiation of a part of the recipient liver before transplantation and post-transplant administration of a mitotic

stimulant can result in extensive hepatic repopulation by the donor hepatocytes and complete correction of hyperbilirubinemia [59]. Studies to evaluate host preconditioning by hepatic irradiation to enhance the effect of hepatocyte transplantation for the treatment of inherited metabolic disorders are underway [59]. Clinical use of this technique is limited by the loss of effect over time, shortage of donor organs for hepatocyte isolation, and need for prolonged immunosuppression to prevent allograft rejection. (See "Hepatocyte transplantation".)

Prognosis — Prior to the introduction of phototherapy and plasmapheresis to lower the serum bilirubin concentration, almost all patients with Crigler-Najjar syndrome type I died during the first 18 months of life due to BIND [15,60]. Since these methods were introduced, a majority of patients survive past puberty without significant brain damage but remain at lifelong risk of BIND, which is typically triggered by an acute increase in serum bilirubin due to intercurrent illness, reduction of serum albumin levels, or failure to adhere to optimized phototherapy regimen [16,18,30,61]. Reasons for treatment failure during adolescence and adulthood include the reduction of body surface area relative to body volume with somatic growth, thickening of the skin (both of which render phototherapy less effective), and progressive liver disease (which interferes with bile flow and bilirubin elimination) [30]. Liver transplantation has resulted in long-term survival and is the only curative therapy presently available [30,39].

During the last 25 years, the prospect of preventing BIND has improved because of standardization of phototherapy equipment and protocol, clearer delineation of phototherapy goals based on B/A molar ratio, and establishment of criteria for instituting plasmapheresis. Successful pregnancy has been described in women with Crigler-Najjar syndrome type II. [35,62]. Finally, pediatric liver transplantation for Crigler-Najjar syndrome type I has been available more readily and has been highly successful, leading to the cure of the disease [1,39,44,48].

MANAGEMENT OF TYPE II DISEASE

General measures — Because patients with Crigler-Najjar syndrome type II are unlikely to develop bilirubin-induced neurologic dysfunction (BIND), they can be managed with phenobarbital and do not require routine phototherapy. Patients with mild disease may be able to maintain safe serum bilirubin concentrations without any chronic therapies. Before implementing this supportive management strategy, the diagnosis of type II disease should be firmly established by genetic analysis and a therapeutic trial of phenobarbital. (See 'Distinguishing type I from type II disease' above.)

Supportive care includes educating the patient about the risks of acute exacerbations of hyperbilirubinemia during fasting or illness, as well as checking serum bilirubin during any significant intercurrent illness or if jaundice develops or worsens.

Chronic treatment with phenobarbital is appropriate for many type II patients. Also, in occasional cases, serum bilirubin may reach dangerous levels during intercurrent illnesses, which may require acute measures to reduce the bilirubin level and bilirubin/albumin (B/A) ratio. (See 'Phenobarbital' below and 'Treatment of acute exacerbations' below.)

Phenobarbital — Phenobarbital can be used in two ways for patients with Crigler-Najjar syndrome type II:

- **Diagnostic trial** – For patients with suspected type II disease, a trial of phenobarbital should be performed to confirm the diagnosis. Phenobarbital is given for two weeks at a full dose (2 mg/kg/dose two to three times daily for children or 60 to 180 mg daily in divided doses in adults). Patients with type II disease display a significant reduction in serum bilirubin (>25 percent decrease) within two weeks, whereas patients with type I disease have little or no response. If type II disease is confirmed, the phenobarbital dose can be tapered over the next two weeks. (See 'Distinguishing type I from type II disease' above.)

- **Chronic treatment** – Chronic treatment with phenobarbital is appropriate for many patients with confirmed type II disease, in whom serum bilirubin is relatively high (between 15 mg/dL [255 micromol/L] and 20 mg/dL [340 micromol/L]), or in whom the quality of life is impaired because of cosmetic effects of marked jaundice. The dose is 2 mg/kg/dose two to three times per day in children or 60 to 180 mg daily in divided doses in adults; this typically reduces serum bilirubin levels by 25 percent or more [17]. A response should be expected within two to three weeks. If, at some point, it is decided to discontinue phenobarbital, the dose should be tapered over two weeks before stopping the drug to reduce the risk of withdrawal seizures.

Treatment of acute exacerbations — Neurologic complications of Crigler-Najjar syndrome type II are rare [17,24-26], and patients can be managed without any treatment. However, several confirmed cases of BIND have been reported during intercurrent illnesses that cause acute increase in serum bilirubin levels and reduction of serum albumin levels, leading to high B/A molar ratio [13].

If an acute hyperbilirubinemic crisis develops, treatment is similar to that described for type I disease and consists of phototherapy, albumin infusion, and plasmapheresis, with the target of keeping the B/A molar ratio at <0.7 (table 2). (See 'Treatment of acute exacerbations' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Inherited liver disease".)

SUMMARY AND RECOMMENDATIONS

- **Clinical manifestations and classification** – Crigler-Najjar syndrome, also referred to as congenital nonhemolytic jaundice with glucuronosyltransferase deficiency, is a rare autosomal recessive disorder of bilirubin metabolism. It has been divided into two forms (types I and II) based on the hepatic bilirubin-UGT1A1 activity, which correlates with disease severity and risk for neurologic sequelae (table 1) (see 'Classification' above):

  - **Type I** – Crigler-Najjar syndrome type I should be suspected in infants who develop jaundice with marked and persistent elevations of unconjugated bilirubin within the first few days after birth, with normal liver function tests and no evidence of hemolytic disease (eg, due to Rh or ABO incompatibility). If the hyperbilirubinemia is not treated promptly and effectively, the patient may develop bilirubin-induced neurologic dysfunction (BIND) or kernicterus. The diagnosis is confirmed by genetic testing. (See 'Type I disease' above and 'Diagnosis' above.)

  - **Type II** – In some cases, serum bilirubin concentrations do not reliably distinguish between Crigler-Najjar syndromes type I and II. Type II is generally associated with lower serum bilirubin concentrations, but values can overlap with type I, especially when there is underlying hemolysis (table 1). Some individuals develop acute exacerbations during fasting or intercurrent illness that can cause acute bilirubin encephalopathy and, occasionally, lead to BIND. Whenever possible, the diagnosis should be confirmed by genetic testing. In cases where daily phototherapy is needed to maintain serum bilirubin in the safe range, the patient should be treated as having Crigler-Najjar syndrome type I. (See 'Type II disease' above and 'Distinguishing type I from type II disease' above.)

- **Management of type I disease**

  - **Goals** – For Crigler-Najjar syndrome type I, the goal of treatment is to avoid BIND. Limited evidence suggests that this can be accomplished by maintaining serum bilirubin <20 mg/dL (340 micromol/L) and unconjugated bilirubin/albumin (B/A) molar ratio <0.7 mol:mol (table 2). (See 'Goals of treatment' above.)

- **Phototherapy** – For all patients, we recommend chronic phototherapy initiated at diagnosis (**Grade 1B**). Early diagnosis and initiation of phototherapy within the first one or two weeks of life effectively maintains chronic serum bilirubin concentrations and B/A ratios below thresholds that are associated with BIND and is associated with dramatic improvement in neurologic outcomes. Phototherapy should be used for 15 to 20 hours/day for neonates and 7 to 13 hours/day for children and adults. If optimally delivered, phototherapy effectively lowers serum bilirubin and reduces the risk for BIND. (See 'Phototherapy' above.)

- **Calcium supplements** – For all patients, we suggest adjunctive treatment with oral calcium (as a mixture of calcium phosphate and calcium carbonate) (**Grade 2C**). When given in conjunction with phototherapy, oral calcium reduces serum bilirubin by approximately 18 percent. (See 'Oral calcium phosphate as an adjunct to phototherapy' above.)

- **Liver transplantation** – We suggest referral for liver transplantation early in the course of disease rather than waiting until late adolescence or adulthood (**Grade 2C**). Liver transplantation normalizes serum bilirubin and thus prevents BIND. The optimal timing of liver transplantation has not been established, but transplantation during infancy or childhood may be appropriate to minimize the risk for BIND. (See 'Early referral for liver transplantation' above.)

- **Acute exacerbations** – Acute exacerbations may be triggered by acute inflammatory illnesses, fasting, biliary obstruction, or general anesthesia. These events should be managed by hospital admission for continuous phototherapy, hydration, and correction of any underlying fluid and electrolyte abnormalities (table 2). If the B/A ratio rises into the danger zone, the patient should be treated with albumin infusion or plasmapheresis (or exchange transfusion in neonates). (See 'Treatment of acute exacerbations' above.)

- **Management of type II disease** – Patients with Crigler-Najjar syndrome type II are much less likely to develop neurologic consequences than those with type I disease. As a result, the main indication for treatment is to manage the jaundice if it has impaired the quality of life.

  - **Phenobarbital** – Patients who require treatment can be managed with phenobarbital, which reduces serum bilirubin levels by at least 25 percent. A response should be expected within two to three weeks. (See 'Phenobarbital' above.)

- **Acute exacerbations** – In rare cases, bilirubin levels may increase to dangerous levels during intercurrent illnesses. Acute hyperbilirubinemic crises are managed as described above for type I disease. (See 'Treatment of acute exacerbations' above.)

REFERENCES

1. Strauss KA, Ahlfors CE, Soltys K, et al. Crigler-Najjar Syndrome Type 1: Pathophysiology, Natural History, and Therapeutic Frontier. Hepatology 2020; 71:1923.
2. Ebrahimi A, Rahim F. Crigler-Najjar Syndrome: Current Perspectives and the Application of Clinical Genetics. Endocr Metab Immune Disord Drug Targets 2018; 18:201.
3. CHILDS B, SIDBURY JB, MIGEON CJ. Glucuronic acid conjugation by patients with familial nonhemolytic jaundice and their relatives. Pediatrics 1959; 23:903.
4. SZABO L, EBREY P. STUDIES ON THE INHERITANCE OF CRIGLER--NAJJAR'S SYNDROME BY THE MENTHOL TEST. Acta Paediatr Acad Sci Hung 1963; 4:153.
5. Bosma PJ, Seppen J, Goldhoorn B, et al. Bilirubin UDP-glucuronosyltransferase 1 is the only relevant bilirubin glucuronidating isoform in man. J Biol Chem 1994; 269:17960.
6. Seppen J, Bosma PJ, Goldhoorn BG, et al. Discrimination between Crigler-Najjar type I and II by expression of mutant bilirubin uridine diphosphate-glucuronosyltransferase. J Clin Invest 1994; 94:2385.
7. Kadakol A, Ghosh SS, Sappal BS, et al. Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. Hum Mutat 2000; 16:297.
8. Maruo Y, Verma IC, Matsui K, et al. Conformational change of UGT1A1 by a novel missense mutation (p.L131P) causing Crigler-Najjar syndrome type I. J Pediatr Gastroenterol Nutr 2008; 46:308.
9. Sneitz N, Bakker CT, de Knegt RJ, et al. Crigler-Najjar syndrome in The Netherlands: identification of four novel UGT1A1 alleles, genotype-phenotype correlation, and functional analysis of 10 missense mutants. Hum Mutat 2010; 31:52.
10. Jansen PL, Bosma PJ, Roy Chowdhury J. Molecular biology of bilirubin metabolism. In: Progress Liver Diseases, Boyer JL, Ockner RK (Eds), WB Saunders, 1995. p.125.
11. Erps LT, Ritter JK, Hersh JH, et al. Identification of two single base substitutions in the UGT1 gene locus which abolish bilirubin uridine diphosphate glucuronosyltransferase activity in vitro. J Clin Invest 1994; 93:564.

12. Bosma PJ, Chowdhury JR, Bakker C, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. N Engl J Med 1995; 333:1171.
13. Chalasani N, Chowdhury NR, Chowdhury JR, Boyer TD. Kernicterus in an adult who is heterozygous for Crigler-Najjar syndrome and homozygous for Gilbert-type genetic defect. Gastroenterology 1997; 112:2099.
14. Kadakol A, Sappal BS, Ghosh SS, et al. Interaction of coding region mutations and the Gilbert-type promoter abnormality of the UGT1A1 gene causes moderate degrees of unconjugated hyperbilirubinaemia and may lead to neonatal kernicterus. J Med Genet 2001; 38:244.
15. CRIGLER JF Jr, NAJJAR VA. Congenital familial nonhemolytic jaundice with kernicterus. Pediatrics 1952; 10:169.
16. Sleisenger MH. Nonhemolytic unconjugated hyperbilirubinemia with hepatic glucuronyl transferase deficiency: a genetic study in four generations. Trans Assoc Am Physicians 1967; 80:259.
17. Arias IM, Gartner LM, Cohen M, et al. Chronic nonhemolytic unconjugated hyperbilirubinemia with glucuronyl transferase deficiency. Clinical, biochemical, pharmacologic and genetic evidence for heterogeneity. Am J Med 1969; 47:395.
18. Berk PD, Martin JF, Blaschke TF, et al. Unconjugated hyperbilirubinemia. Physiologic evaluation and experimental approaches to therapy. Ann Intern Med 1975; 82:552.
19. Kapitulnik J, Kaufmann NA, Goitein K, et al. A pigment found in Crigler--Najjar syndrome and its similarity to an ultrafiltrable photoderivative of bilirubin. Clin Chim Acta 1974; 57:231.
20. Moscowitz A, Weimer M, Lightner DA, et al. The in vitro conversion of bile pigments to the urobilinoids by a rat clostridia species as compared with the human fecal flora. 3. Natural d-urobilin, synthetic i-urobilin, and synthetic i-urobilinogen. Biochem Med 1970; 4:149.
21. BILLING BH, GRAY CH, KULCZYCKA A, et al. THE METABOLISM OF (14C)-BILIRUBIN IN CONGENITAL NON-HAEMOLYTIC HYPERBILIRUBINAEMIA. Clin Sci 1964; 27:163.
22. Blaschke TF, Berk PD, Scharschmidt BF, et al. Crigler-Najjar syndrome: an unusual course with development of neurologic damage at age eighteen. Pediatr Res 1974; 8:573.
23. Mitchell E, Ranganathan S, McKiernan P, et al. Hepatic Parenchymal Injury in Crigler-Najjar Type I. J Pediatr Gastroenterol Nutr 2018; 66:588.
24. Van der Veere CN, Jansen PL, Sinaasappel M, et al. Oral calcium phosphate: a new therapy for Crigler-Najjar disease? Gastroenterology 1997; 112:455.

25. Li L, Deng G, Tang Y, Mao Q. Spectrum of UGT1A1 Variations in Chinese Patients with Crigler-Najjar Syndrome Type II. PLoS One 2015; 10:e0126263.
26. Takeuchi K, Kobayashi Y, Tamaki S, et al. Genetic polymorphisms of bilirubin uridine diphosphate-glucuronosyltransferase gene in Japanese patients with Crigler-Najjar syndrome or Gilbert's syndrome as well as in healthy Japanese subjects. J Gastroenterol Hepatol 2004; 19:1023.
27. Gollan JL, Huang SN, Billing B, Sherlock S. Prolonged survival in three brothers with severe type 2 Crigler-Najjar syndrome. Ultrastructural and metabolic studies. Gastroenterology 1975; 68:1543.
28. Gordon ER, Shaffer EA, Sass-Kortsak A. Bilirubin secretion and conjujation in the Crigler-Najjar syndrome type II. Gastroenterology 1976; 70:761.
29. Kadakol A, Deocharan B, Mukhopadhyay L, et al. Rapid prenatal diagnosis of Crigler-Najjar syndrome type 1 by genetic analysis of chorionic villus samples (abstract). Hepatology 1998; 28:316A.
30. van der Veere CN, Sinaasappel M, McDonagh AF, et al. Current therapy for Crigler-Najjar syndrome type 1: report of a world registry. Hepatology 1996; 24:311.
31. Fevery J, Blanckaert N, Heirwegh KP, et al. Unconjugated bilirubin and an increased proportion of bilirubin monoconjugates in the bile of patients with Gilbert's syndrome and Crigler-Najjar disease. J Clin Invest 1977; 60:970.
32. Supporting information for: Strauss KA, Ahlfors CE, Soltys K, et al. Crigler-Najjar Syndrome Type 1: Pathophysiology, Natural History, and Therapeutic Frontier. Hepatology 2020; 71:1923. Available at: https://aasldpubs-onlinelibrary-wiley-com.ezproxy.sastudents.uwi.tt/doi/full/10.1002/hep.30959#support-information-section (Accessed on June 15, 2020).
33. Itoh S, Onishi S. Kinetic study of the photochemical changes of (ZZ)-bilirubin IX alpha bound to human serum albumin. Demonstration of (EZ)-bilirubin IX alpha as an intermediate in photochemical changes from (ZZ)-bilirubin IX alpha to (EZ)-cyclobilirubin IX alpha. Biochem J 1985; 226:251.
34. Gajdos V, Petit F, Trioche P, et al. Successful pregnancy in a Crigler-Najjar type I patient treated by phototherapy and semimonthly albumin infusions. Gastroenterology 2006; 131:921.
35. Wilson JH, Sinaasappel M, Lotgering FK, Langendonk JG. Recommendations for pregnancies in patients with crigler-najjar syndrome. JIMD Rep 2013; 7:59.
36. Van Der Veere CN, Schoemaker B, Bakker C, et al. Influence of dietary calcium phosphate on the disposition of bilirubin in rats with unconjugated hyperbilirubinemia. Hepatology

1996; 24:620.

37. Hafkamp AM, Nelisse-Haak R, Sinaasappel M, et al. Orlistat treatment of unconjugated hyperbilirubinemia in Crigler-Najjar disease: a randomized controlled trial. Pediatr Res 2007; 62:725.
38. Squires RH, Ng V, Romero R, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the American Association for the Study of Liver Diseases, American Society of Transplantation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Hepatology 2014; 60:362.
39. Sokal EM, Silva ES, Hermans D, et al. Orthotopic liver transplantation for Crigler-Najjar type I disease in six children. Transplantation 1995; 60:1095.
40. Ozçay F, Alehan F, Sevmiş S, et al. Living related liver transplantation in Crigler-Najjar syndrome type 1. Transplant Proc 2009; 41:2875.
41. Elisofon SA, Magee JC, Ng VL, et al. Society of pediatric liver transplantation: Current registry status 2011-2018. Pediatr Transplant 2020; 24:e13605.
42. Dhawan A, Lawlor MW, Mazariegos GV, et al. Disease burden of Crigler-Najjar syndrome: Systematic review and future perspectives. J Gastroenterol Hepatol 2020; 35:530.
43. Jansen PL. Diagnosis and management of Crigler-Najjar syndrome. Eur J Pediatr 1999; 158 Suppl 2:S89.
44. Shanmugam NP, Valamparampil JJ, Reddy MS, et al. Auxiliary Partial Orthotopic Liver Transplantation for Monogenic Metabolic Liver Diseases: Single-Centre Experience. JIMD Rep 2019; 45:29.
45. Rela M, Muiesan P, Vilca-Melendez H, et al. Auxiliary partial orthotopic liver transplantation for Crigler-Najjar syndrome type I. Ann Surg 1999; 229:565.
46. Sood V, Squires JE, Mazariegos GV, et al. Living Related Liver Transplantation for Metabolic Liver Diseases in Children. J Pediatr Gastroenterol Nutr 2021; 72:11.
47. Sze YK, Dhawan A, Taylor RM, et al. Pediatric liver transplantation for metabolic liver disease: experience at King's College Hospital. Transplantation 2009; 87:87.
48. Govil S, Shanmugam NP, Reddy MS, et al. A metabolic chimera: Two defective genotypes make a normal phenotype. Liver Transpl 2015; 21:1453.
49. D'Antiga L, Beuers U, Ronzitti G, et al. Gene Therapy in Patients with the Crigler-Najjar Syndrome. N Engl J Med 2023; 389:620.
50. George LA. Hemophilia A Gene Therapy - Some Answers, More Questions. N Engl J Med 2023; 388:761.

51. Chandler RJ, Sands MS, Venditti CP. Recombinant Adeno-Associated Viral Integration and Genotoxicity: Insights from Animal Models. Hum Gene Ther 2017; 28:314.
52. Nault JC, Datta S, Imbeaud S, et al. Recurrent AAV2-related insertional mutagenesis in human hepatocellular carcinomas. Nat Genet 2015; 47:1187.
53. Vroemen JP, Blanckaert N, Buurman WA, et al. Treatment of enzyme deficiency by hepatocyte transplantation in rats. J Surg Res 1985; 39:267.
54. Ilan Y, Roy-Chowdhury N, Prakash R, et al. Massive repopulation of rat liver by transplantation of hepatocytes into specific lobes of the liver and ligation of portal vein branches to other lobes. Transplantation 1997; 64:8.
55. Fox IJ, Chowdhury JR, Kaufman SS, et al. Treatment of the Crigler-Najjar syndrome type I with hepatocyte transplantation. N Engl J Med 1998; 338:1422.
56. Ambrosino G, Varotto S, Strom SC, et al. Isolated hepatocyte transplantation for Crigler-Najjar syndrome type 1. Cell Transplant 2005; 14:151.
57. Dhawan A, Mitry RR, Hughes RD. Hepatocyte transplantation for liver-based metabolic disorders. J Inherit Metab Dis 2006; 29:431.
58. Jorns C, Nowak G, Nemeth A, et al. De Novo Donor-Specific HLA Antibody Formation in Two Patients With Crigler-Najjar Syndrome Type I Following Human Hepatocyte Transplantation With Partial Hepatectomy Preconditioning. Am J Transplant 2016; 16:1021.
59. Soltys KA, Setoyama K, Tafaleng EN, et al. Host conditioning and rejection monitoring in hepatocyte transplantation in humans. J Hepatol 2017; 66:987.
60. Wolkoff AW, Chowdhury JR, Gartner LA, et al. Clinical conference. Crigler-Najjar syndrome (type I) in an adult male. Gastroenterology 1979; 76:840.
61. BERENDSOHN S, LOWMAN J, SUNDBERG D, WATSON CJ. IDIOPATHIC DYSERYTHROPOIETIC JAUNDICE. Blood 1964; 24:1.
62. Passuello V, Puhl AG, Wirth S, et al. Pregnancy outcome in maternal Crigler-Najjar syndrome type II: a case report and systematic review of the literature. Fetal Diagn Ther 2009; 26:121.

Topic 3569 Version 30.0

GRAPHICS

Principal differential characteristics of inherited unconjugated hyperbilirubinemia

	Crigler-Najjar syndrome type I	Crigler-Najjar syndrome type II	Gilbert syndrome
Epidemiology and natural history			
Mode of inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive
Prevalence	Rare	Rare	Common (approximately 9% of White people are homozygous for a variant TATAA box; 4 to 5% have hyperbilirubinemia)
Prognosis	Kernicterus, unless vigorously treated	Usually benign, kernicterus occurs rarely	Benign
Routine clinical evaluation			
Serum bilirubin concentration*	20 to 50 mg/dL (340 to 850 micromol/L)	Usually 8 to 20 mg/dL (136 to 340 micromol/L)	Usually <3 mg/dL (<51 micromol/L)
Routine liver function tests	Normal	Normal	Normal
Effect of phenobarbital on serum bilirubin	None	Reduction	Reduction
Tests not routinely performed			
Bilirubin glucuronides¶	Usually pale; contains small amounts of unconjugated bilirubin	Bilirubin glucuronides present: Increased proportion of bilirubin monoglucuronide	Bilirubin glucuronides present: Increased proportion of bilirubin monoglucuronide
Liver histology	Normal, but fibrosis is present in approximately 40% of cases[1]	Normal	Normal

Hepatic bilirubin UGT activity	Absent	Markedly reduced (10% of normal)	Reduced (30% of normal)
45-minute plasma BSP retention[Δ]	Normal	Normal	Usually normal; may be prolonged

UGT: uridine diphosphate glucuronosyltransferase; BSP: bromosulfophthalein.

* Serum bilirubin concentrations depend on age and optimal medical management. In each of these disorders, further acute elevations may occur, triggered by fasting or intercurrent illnesses. The risk of severe acute exacerbations (eg, bilirubin >20 mg/dL) and resulting kernicterus is high for Crigler-Najjar syndrome type I, low for Crigler-Najjar syndrome type II, and absent for Gilbert syndrome.

¶ Bilirubin glucuronides are measured by high-pressure liquid chromatography of bile collected from the duodenum.

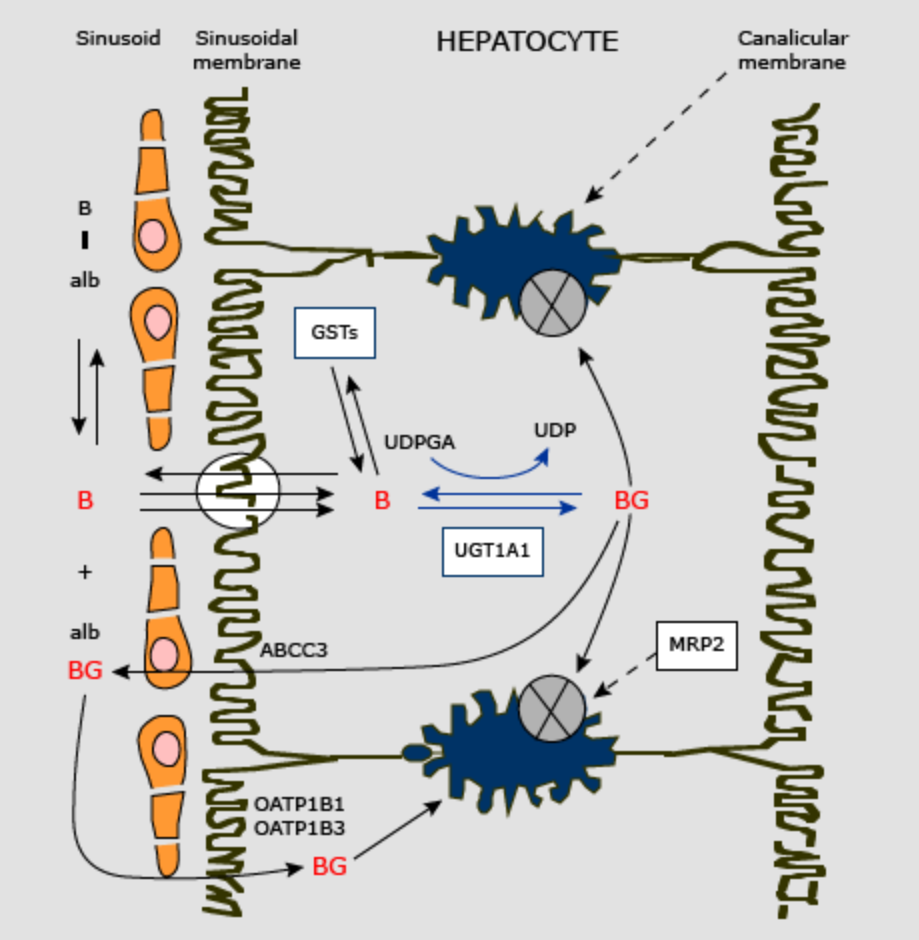
Δ Plasma BSP retention is prolonged in Dubin-Johnson and Rotor syndromes and in hepatobiliary cholestatic disorders.

Reference:

1. *Mitchell E, Ranganathan S, McKiernan P, et al. Hepatic Parenchymal Injury in Crigler-Najjar Type I. J Pediatr Gastroenterol Nutr 2018; 66:588.*

Graphic 80818 Version 6.0

Bilirubin throughput in hepatocytes



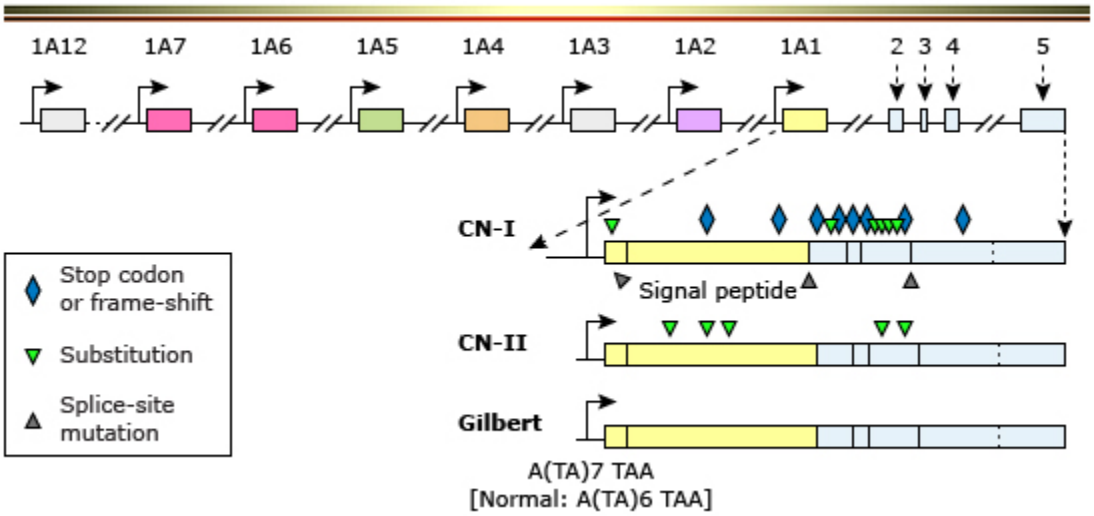
Schematic representation of the steps involved in bilirubin (B) throughput in hepatocytes: transport to the liver (primarily as albumin-bound bilirubin), uptake at the sinusoidal membrane, intracellular binding, conjugation (glucuronidation), and canalicular excretion. Sinusoidal bilirubin uptake requires inorganic anions such as chloride and is thought to be mediated by carrier proteins. Within the hepatocyte, bilirubin binds to glutathione S-transferases (GSTs). GST-binding reduces the efflux of the internalized bilirubin, thereby increasing the net uptake. GSTs also bind bilirubin glucuronides (BG) prior to excretion. Bilirubin also enters hepatocytes by passive diffusion. Glucuronidation of bilirubin is mediated by a family of enzymes, termed uridine diphosphoglucuronosyltransferase (UGT), the most important of which is bilirubin-UGT-1 (UGT1A1). Conjugated bilirubin is secreted actively across the bile canalicular membrane of the hepatocyte against a concentration gradient that may reach 1:1000. The canalicular multidrug resistance protein 2 (MRP2) appears to be the most important for the canalicular secretion of bilirubin. A portion of the conjugated bilirubin is transported into the sinusoidal blood via the ATP hydrolysis-couple pump, ABCC3, to undergo

reuptake via OATP1B1 and OATP1B3 by hepatocytes downstream to the sinusoidal blood flow.

UDP: uridine diphosphate; UDPGA: uridine 5'-diphosphoglucuronic acid; ABCC3: ATP-binding cassette subfamily C number 3; OATP1B1: organic anion-transporting polypeptide 1B1; OATP1B3: organic anion-transporting polypeptide 1B3.

Graphic 52393 Version 5.0

Genetic lesions in bilirubin-UGT deficiency syndromes



Organization of the *UGT1A* gene. The organization of the UGT1A locus is depicted in the top panel. Four common exons (exons 2, 3, 4, and 5) are used in several UGT isoforms expressed from this locus. Upstream from these exons are a series of "unique" exons, only 1 of which is used in a given isoform. Each unique exon is preceded by a separate promoter (solid arrows). Splicing of exon 1A1 to the common region exons (2 to 5) generates the mRNA for bilirubin UGT (also termed UGT1A1). Genetic lesions in any of the 5 exons constituting the bilirubin UGT mRNA can abolish (Crigler-Najjar type I) or reduce (Crigler-Najjar type II) bilirubin-UGT activity. With type I, the genetic lesions may result in a premature stop codon or a single amino acid substitution. The sequence abnormalities can be located in the region encoding the signal peptide or other domains of the enzyme, or even in the introns at the splice donor or splice acceptor sites. Type II is caused by point mutations that result in substitution of a single amino acid. In contrast with Crigler-Najjar syndrome types I or II, Gilbert syndrome is caused by a promoter abnormality. Normally, the TATAA element within the promoter upstream to exon 1A1 consists of A(TA)6TAA. In Gilbert syndrome, 2 additional nucleotide residues (TA) are present in this element. Alleles containing the Gilbert-type promoter are termed UGT1A1*28. In addition, Japanese investigators have reported sequence abnormalities in the coding region of the gene that cause mild elevations of serum bilirubin concentrations, consistent with Gilbert syndrome.

UGT: uridine diphosphate glucuronosyltransferase; mRNA: messenger ribonucleic acid.

Graphic 73505 Version 2.0

Management of Crigler-Najjar syndrome

Principles of effective phototherapy

- *Light source:* High-intensity LED, BB fluorescent tubes, or energetic equivalent (eg, TL52); maximum emission of 400 to 525 (peak 450 to 460) nm
- *Source distance from skin:* 30 to 45 cm for infants, 45 to 60 cm for children and adults
- *Skin exposure:* Body surface area exposure 60 to 70% for neonates, 35 to 50% for children and adults
- *Exposure duration:* 15 to 20 hours per day for neonates, 7 to 13 hours per day for children and adults
- *Surroundings:* White bedsheets; reflective surfaces

Treatment goals

- *Phototherapy with irradiance at skin surface:* 40 to 100 microW/cm^2 per nm*
- *Maintain unconjugated bilirubin (serum or plasma):* <20 mg/dL (340 micromol/L)
- *Maintain unconjugated bilirubin/albumin (B/A) ratio in safe range:*
  - <0.7 mol:mol (molar ratio)
  - <6.15 mg/g (mass ratio)
  - 1 g of albumin binds approximately 9 mg total bilirubin
- *Avoid:* Drugs and drug vehicles that displace bilirubin from the albumin-binding site

Inpatient management for severe hyperbilirubinemia

- *Reverse and/or prevent concomitant neurologic threats, such as:*
  - Hypovolemia, hypotension
  - Hypercarbia, acidosis
  - Hypoglycemia, hyperglycemia
  - Hypernatremia, hyperosmolarity
  - Hyperthermia
- *Rule out concomitant conditions that exacerbate hyperbilirubinemia, such as:*
  - Hemolytic disease¶
  - Internally sequestered or ingested blood$^{\Delta}$
  - Cholelithiasis or biliary obstruction$^{\diamond}$
  - Constipation
- *Provide continuous high-intensity phototherapy:*
  - Position the light source at minimal tolerated distance from skin
  - Maximize the proportion of skin surface exposed
  - Provide light exposure for about 24 hours per day
- *Restore and maintain intravascular hydration:*
  - Intravenous normal saline (10 to 20 mL/kg bolus infusions) to establish euvolemia
  - Intravenous dextrose in normal saline at 1 to 1.5 times maintenance rate$^{\diamond}$

- *Prevent bilirubin displacement from albumin:*
  - Avoid drugs and drug vehicles that displace bilirubin from the albumin-binding site
  - Avoid drug combinations when possible
  - Use special caution with intravenous bolus dosing of drugs or contrast agents
- *Optimize enterohepatic lumirubin excretion:*
  - Enteral feeding: Milk-based formula in infants, lipid-rich foods in children and adults
  - Enteral calcium salts (mixture of calcium phosphate and calcium carbonate)§
  - For cholelithiasis and/or biliary sludging: Consider emergency cholecystectomy
- *Prepare for emergency measures, based on B/A ratio:*
  - For B/A ≥0.7 mol:mol: Give intravenous albumin 1 to 2 g/kg per dose, every 6 to 12 hours as needed
  - For B/A ≥0.9 mol:mol: Plasmapheresis (or exchange transfusion in neonates)

LED: light-emitting diode; W: watts; B: total bilirubin; A: albumin.

* Different light meters produce variable measurements from the same source. We use the BiliBlanket Meter II (GE Healthcare, Chicago, IL).

¶ Hemolytic conditions should be sought and treated. Consider (1) immunologic/autoimmune, (2) red blood cell enzymopathies, (3) ineffective erythropoiesis, and (4) physical destruction.

Δ Internal hemorrhage, occult tissue hematoma, peripartum blood ingestion by neonates.

◇ 10% dextrose solution for infants and toddlers, 5% dextrose for older children and adults.

§ Equimolar doses of calcium carbonate and calcium phosphate are better tolerated and more effective than calcium carbonate alone. We use the following **total** daily doses for oral calcium salts:

- Adults and children >40 kg body weight: 100 mmol calcium, which may be delivered as[1]:
  - Four 1250 mg calcium carbonate tablets (or 20 mLs of 1250 mg/5 mL oral suspension), providing 50 mmol (2 g) elemental calcium **plus**
  - Two rounded teaspoonfuls of dicalcium phosphate (4 g salt/teaspoon) bulk powder supplement[2] providing approximately 50 mmol (2 g) elemental calcium
- Children <40 kg body weight:
  - 2.5 mmol calcium/kg body weight (up to 100 mmol per day), as equal calcium mmols as carbonate and phosphate salts.
  - The following conversions may be used[3]:
    - 1 gram calcium carbonate = 400 mg elemental calcium = 10 mmol calcium
    - 1 gram dicalcium phosphate = 233 mg elemental calcium = 5.8 mmol calcium

The above total daily doses for adults and children are given in 3 to 4 divided doses per day (eg, with meals and at bedtime).

References:

1. *Van der Veere CN, Jansen PL, Sinaasappel M. Oral calcium phosphate: a new therapy for Crigler-Najjar disease? Gastroenterology 1997; 112:455.*
2. *National Institutes of Health; Dietary Supplement Label Database: Dicalcium Phosphate (DCP) bulk powder. Available at https://dsld.od.nih.gov/dsld/prdLabel.jsp?id=23078 (accessed November 26, 2020).*
3. *Lexicomp online. Copyright © 1978-2023 Lexicomp, Inc. All Rights Reserved.*

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Contributor Disclosures

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