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Consensus

Expert Consensus on the Diagnosis and Management of Inherited Hyperbilirubinemia (2025)

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Abstract

To support clinicians in making informed decisions regarding the diagnosis and management of inherited hyperbilirubinemia, including Gilbert syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome, and Rotor syndrome, the Inherited and Metabolic Liver Disease Collaboration Group of the Hepatology Branch of the Chinese Medical Association convened a panel of Chinese experts in this field. This multidisciplinary consortium developed the present expert consensus by integrating the latest advances in both clinical practice and basic research.

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Introduction

Hereditary hyperbilirubinemia refers to a group of genetic disorders characterized by abnormalities in bilirubin metabolism, including Gilbert syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome, and Rotor syndrome. Although these disorders are relatively prevalent in clinical practice, their diagnosis and management still lack globally standardized guidelines or expert consensus at present. In recent years, advancements in the understanding of these disorders, combined with the widespread application of gene sequencing technologies, have significantly increased diagnostic capabilities. To better support clinicians in diagnosing and treating hereditary hyperbilirubinemia, the Genetic Metabolic Liver Disease Collaborative Group of the Hepatology Branch of the Chinese Medical Association convened a multidisciplinary expert panel from China to develop the present consensus. This panel comprised specialists from hepatology, gastroenterology, pediatrics, infectious diseases, hematology, surgery, pathology, imaging, clinical methodology, and other related fields. It is important to note that hereditary hemolytic diseases and hyperbilirubinemia secondary to hereditary cholestatic liver diseases (refer to the Guidelines on the Management of Cholestasis Liver Diseases (2021)[1]) are excluded from the scope of this consensus.

This consensus document serves as a reference framework and does not claim to address all possible diagnostic and therapeutic scenarios associated with hereditary hyperbilirubinemia. In clinical practice, clinicians are advised to interpret and apply the recommendations in the context of individual patient circumstances, integrating a comprehensive understanding of the disorders, patient and family preferences, and available local healthcare resources to devise tailored and evidence-based management strategies.

The development of this consensus followed the internationally recognized the Participant, Intervention, Comparison, and Outcome framework and standard consensus development protocols. The strength of each recommendation was determined through structured voting by both the drafting and the consensus panel, employing five response categories: Full Agreement, Basic Agreement, Unclear Opinion,

Keywords: Inherited hyperbilirubinemia; Gilbert syndrome; Crigler-Najjar syndrome; Dubin-Johnson syndrome; Rotor syndrome; Expert consensus.

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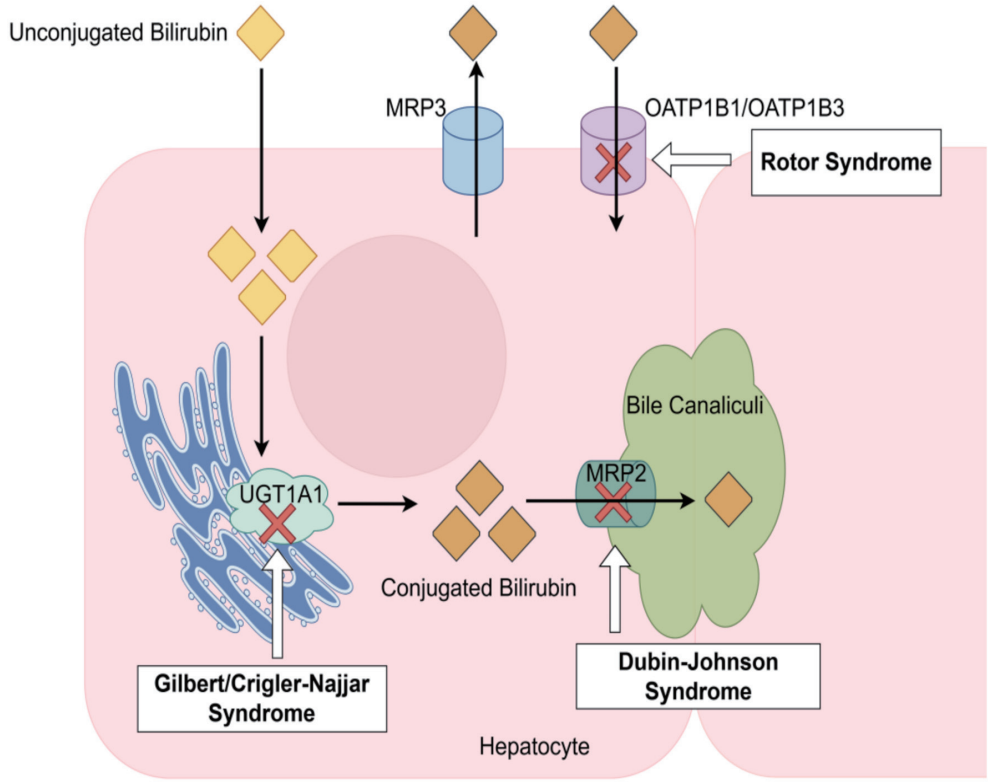

Fig. 1. The pathogenesis of hereditary hyperbilirubinemia. MRP3, multi-drug resistance protein 3; OATP1B1, organic anion transporting polypeptides B1; OATP1B3, organic anion transporting polypeptides B3; UGT1A1, uridine diphospho-glucuronosyl transferase 1A1; MRP2, multi-drug resistance protein 2.

Disagree with Minor Reservations, and Strong Disagreement. A recommendation was accepted as consensus if at least 75% of experts (combined Full Agreement and Basic Agreement) endorsed it. The final level of consensus is reported as the combined proportion of these two categories.

Pathogenesis

Bilirubin is produced by the degradation of heme, which primarily originates from the hemoglobin of senescent red blood cells. Heme is first converted to biliverdin by heme oxygenase, and then biliverdin is reduced to unconjugated bilirubin (UCB) by biliverdin reductase A. UCB binds to plasma albumin and is transported to the liver. In the smooth endoplasmic reticulum of hepatocytes, uridine diphospho-glucuronosyl transferase 1A1 (UGT1A1) catalyzes the conjugation of the lipophilic UCB with glucuronic acid to form hydrophilic conjugated bilirubin (CB), which is then excreted into the bile through multidrug resistance protein (MRP) 2 located on the canalicular membrane. When the secretion of CB into the bile canaliculi becomes saturated, hepatocytes can transport CB back into the hepatic sinusoids via MRP3 on the basolateral membrane, and CB can be reabsorbed into hepatocytes through organic anion transporting polypeptides (OATP), specifically OATP1B1 and OATP1B3.[2,3]

It is widely recognized that mutations in the *UGT1A1* gene are responsible for Gilbert syndrome and Crigler-Najjar syndrome. Mutations in the *ABCC2* gene, which encodes MRP2, are the cause of Dubin-Johnson syndrome. Meanwhile, solute carrier organic anion transporter (SLCO) family member 1B1 and 1B3, members of the SLCO family, encode OATP1B1 and OATP1B3, respectively, and are associated with Rotor syndrome. These inherited defects in bilirubin metabolism and transport underlie the major forms of hereditary hyperbilirubinemia (Fig. 1).

In current clinical practice, the terms "direct bilirubin" and "indirect bilirubin" are commonly used to refer to "conjugated bilirubin" and "unconjugated bilirubin," respectively. Therefore, this consensus document uses the terms "conjugated bilirubin" and "unconjugated bilirubin" when discussing bilirubin metabolism and pathogenesis, while "direct bilirubin" and "indirect bilirubin" are used when describing clinical features and laboratory test results.

Gilbert syndrome and Crigler-Najjar syndrome

Gilbert syndrome and Crigler–Najjar syndrome are typically regarded as autosomal recessive genetic disorders, primarily resulting from pathogenic variants in the *UGT1A1* gene. These variants lead to reduced or absent activity of the UGT1A1 enzyme, thereby impairing the conjugation of bilirubin and causing elevated serum levels of indirect bilirubin. In Gilbert syndrome, UGT1A1 enzyme activity is reduced to approximately 30% of normal levels, with serum total bilirubin (TBil) concentrations typically ranging from 17.1 to 102.6 μmol/L. Crigler–Najjar syndrome is further classified into Type I and Type II. Crigler–Najjar syndrome Type I represents a complete loss of UGT1A1 enzyme activity, with TBil levels ≥ 342.0 μmol/L. Crigler–Najjar Type II syndrome is characterized by UGT1A1 enzyme activity below 10% of normal, with TBil levels between 102.6 and 342.0 μmol/L. These three clinical subtypes can be considered a spectrum of *UGT1A1* gene diseases with varying degrees of enzymatic deficiency and clinical severity.[4]

Epidemiology

The prevalence of Gilbert syndrome in the general population is estimated to range from 3% to 12%, with significant racial and geographic variation. The highest prevalence has been reported in African populations (15% to 25%), followed by Caucasians (2% to 10%). In regions such as South Asia and the Middle East, prevalence rates can reach up to 20%, whereas a prevalence of 3.2% has been reported in Singapore.[4] To date, no large-scale epidemiological studies on Gilbert syndrome have been published from China. Clinically, Gilbert syndrome typically presents during adolescence, with a male-to-female ratio ranging from 1.5:1 to 10:1. Notably, certain studies have shown a higher prevalence of Gilbert syndrome among athletes compared to the general population.[5] In contrast, Crigler–Najjar syndrome is an extremely rare autosomal recessive disorder, with a global estimated prevalence of fewer than one in 0.75 million to one in 1.0 million live births,[6] and less than one in 0.1 million live births in Europe.[7] Data from two liver disease specialty hospitals in Beijing from 2002 to 2023 showed that Crigler-Najjar syndrome accounted for 1.077 per 100,000 of hospitalized patients during this period.[8]

Clinical manifestation

Gilbert syndrome may be associated with a positive family history of jaundice. It typically develops insidiously and is often discovered incidentally during routine health examinations or investigations for unrelated conditions due to elevated bilirubin levels. TBil concentrations usually range from 17.1 to 102.6 μmol/L, with the majority of cases remaining below 85.5 μmol/L, and the main symptom is elevated indirect bilirubin. The hallmark clinical manifestation is chronic, intermittent jaundice, characterized by yellowing of the skin and sclera. These episodes may be precipitated or exacerbated by factors such as puberty, fasting, dehydration, excessive fatigue, psychological stress, or menstrual cycles. A minority of patients may also report nonspecific symptoms, including fatigue, lethargy, and gastrointestinal discomfort.[9,10] Importantly, Gilbert syndrome is distinguished by the absence of hepatosplenomegaly and other clinical signs or biochemical markers of liver disease.

Patients with Crigler-Najjar Syndrome Type I typically present with neonatal jaundice, characterized by TBil concentrations ≥ 342.0 μmol/L and markedly elevated serum indirect (unconjugated) bilirubin. The UCB accumulates to neurotoxic levels and can cross the blood-brain barrier, leading to neurological dysfunction. Without timely and effective interventions, such as phototherapy or plasma exchange, the condition may rapidly progress to acute bilirubin encephalopathy, which carries a high risk of mortality. Early signs of acute bilirubin encephalopathy include hypotonia, lethargy, high-pitched crying, and a poor sucking reflex. As the condition advances, symptoms may progress to muscle rigidity, increased muscle tone, opisthotonos, irritability, fever, seizures, and apnea. In severe cases, the condition can result in death.[11] Chronic bilirubin encephalopathy, also known as kernicterus, often manifests as irreversible complications. These may include extrapyramidal motor dysfunction, sensorineural hearing loss, ocular motility disorders, and enamel hypoplasia.[12]

Crigler-Najjar syndrome Type II presents with milder clinical symptoms compared to Type I, with TBil concentrations ranging from 102.6 to 342.0 μmol/L. Most affected patients exhibit a favorable prognosis. However, isolated cases of adult-onset bilirubin encephalopathy have been documented, particularly in the context of precipitating factors such as trauma or surgical stress. The risk becomes clinically significant when the bilirubin-to-albumin molar ratio exceeds 0.8 (calculated using the formula: [bilirubin (mg/dL)×17.1] / [albumin(g/dL)×151]), warranting heightened clinical vigilance for potential bilirubin encephalopathy.[13] Emerging evidence suggests that *UGT1A1* gene mutations are associated with an increased risk of gallstone formation,[14] possibly due to impaired bilirubin conjugation via reduced UGT1A1 enzyme activity, UCB in bile can promote gallstone formation. Additionally, a few patients with Crigler-Najjar syndrome Type II may develop liver fibrosis and cirrhosis, even though the underlying mechanisms remain unclear. These outcomes may be linked to secondary chronic biliary obstruction caused by gallstones or the toxic effects of hemoglobin degradation products.[15–18]

Laboratory and imaging examinations

Liver biochemistry: Elevated serum bilirubin, mainly elevated indirect bilirubin, occurs without abnormalities in liver injury markers such as alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), or gamma-glutamyltransferase (GGT). However, a minority of Crigler-Najjar syndrome patients may exhibit progressive abnormalities in these liver function parameters during the later stages, possibly due to cholestasis, liver fibrosis, or other complications.

Hemolysis-related tests: *UGT1A1* gene diseases must be carefully differentiated from hemolytic diseases, given their overlapping presentations of unconjugated hyperbilirubinemia. In *UGT1A1* gene diseases, erythrocyte count, hemoglobin concentration, and hematocrit are typically normal or only mildly elevated. In the majority of patients with Gilbert syndrome, the reticulocyte percentage is below 1.5%. Peripheral blood smears reveal normal erythrocyte morphology. Additionally, laboratory assessments of hemolysis, including erythrocyte osmotic fragility, serum lactate dehydrogenase, and serum haptoglobin levels, generally fall within normal ranges. The direct antiglobulin (Coombs) test is consistently negative.

Imaging examinations: In patients with Gilbert syndrome, the liver and spleen generally exhibit normal morphology, though some may show bile salt deposits or stones within the gallbladder. A minority of patients with Crigler-Najjar syndrome may develop signs of liver fibrosis or cirrhosis. In the context of acute bilirubin encephalopathy, brain magnetic resonance imaging may reveal symmetrical high signal intensity on T1-weighted imaging in the globus pallidus, thalamus, and basal ganglia, whereas T2-weighted imaging may show mild hyperintensity or isointensity in these regions. Chronic bilirubin encephalopathy may present with symmetrical high signals on T2-weighted imaging in the bilateral globus pallidus, thalamus, and basal ganglia.[19,20]

Genetic testing: In patients presenting with persistent hyperbilirubinemia primarily characterized by elevated indirect bilirubin levels and in whom Gilbert syndrome or Crigler-Najjar syndrome is clinically suspected, genetic testing for *UGT1A1* variants serves as a diagnostic tool.[21] For Crigler-Najjar syndrome in particular, genetic testing can be used as the first-line diagnostic method.

The *UGT1A1* gene is located on the long arm of chromosome 2 at band 37 and comprises an enhancer, promoter, and five exons. As of January 2025, the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk/ac/index.php) has documented at least 189 pathogenic variants of *UGT1A1*. Among these, several are associated with Gilbert syndrome. These include the TA insertion mutation in the TATA box of the promoter region [A(TA)$_7$TAA] (UGT1A1*28),

and the phenobarbital-responsive enhancer module variants c.-3152G>A and c.-3275T>G (formerly c.-3279T>G),[22] as well as the missense variant c.211G>A (p.Gly71Arg) in exon 1 (UGT1A1*6).[23] Other relatively common variants include c.686C>A (p.Pro229Gln), c.1091C>T (p.Pro364Leu), and c.1456T>G (p.Tyr486Asp). The distribution of *UGT1A1* variants demonstrates marked ethnic specificity.[21,24,25] In Caucasian populations, the $A(TA)_7TAA$ homozygous genotype is the predominant pathogenic variant associated with Gilbert syndrome. In the Chinese population, however, the most common variants are c.-3275T>G, $A(TA)_7TAA$, and c.211G>A.[23,26] Heterozygosity for the $A(TA)_7TAA$ variant reduces UGT1A1 enzyme activity by approximately 10–35%, while homozygosity decreases activity by about 70%. For the c.211G>A variant, UGT1A1 enzyme activity is reduced to 32.2% of normal levels in homozygous individuals and 60.2% in heterozygous individuals.

Patients with Crigler-Najjar syndrome Type II often carry homozygous or compound heterozygous missense variants in the *UGT1A1* exon regions. Among East Asian populations, the most common missense variants are c.211G>A in exon 1 and c.1456T>G in exon 5.[27] Functional analyses have shown that the c.1456T>G homozygous variant exhibits approximately 7.6% of normal UGT1A1 enzyme activity.

In contrast, patients with Crigler-Najjar syndrome Type I are characterized by the absence of UGT1A1 enzymatic function due to deleterious genetic alterations, including deletions, insertions, missense, nonsense, frameshift, and splicing variants.[7]

Liver pathology examination: Routine liver biopsy is not recommended for the diagnosis of Gilbert syndrome or Crigler-Najjar syndrome. However, when clinical findings suggest overlapping etiologies that require differential diagnosis, a liver biopsy should be considered. In Gilbert syndrome, liver tissue morphology typically appears normal, although fine lipofuscin deposits are often observed within the canalicular side of hepatocytes in the centrilobular zone. Ultrastructural examination reveals hyperplasia and hypertrophy of the smooth endoplasmic reticulum within hepatocytes. In contrast, Crigler-Najjar syndrome generally shows no significant histopathological abnormalities, with occasional bile pigment granules found in bile canaliculi, hepatocytes, or Kupffer cells. Emerging evidence indicates that a small number of patients with Crigler-Najjar syndrome may develop significant hepatic fibrosis.[28]

Diagnosis: The basic diagnostic approach for Gilbert syndrome is exclusion. In patients presenting with long-term or intermittent jaundice predominantly characterized by elevated indirect bilirubin, a clinical diagnosis can be established when at least two serum TBil measurements—each exceeding the upper normal limit (typically 17.1 to 102.6 μmol/L)—are recorded at intervals of more than six months, without concurrent elevations in liver enzymes such as ALT, AST, ALP, or GGT, and after excluding hemolytic and other related diseases.[29] Genetic testing serves as a valuable diagnostic tool for confirmation.[21,30] Crigler-Najjar syndrome is typically characterized by persistent jaundice with markedly elevated bilirubin levels. In patients with Crigler-Najjar syndrome Type II, TBil ranges from 102.6 to 342.0 μmol/L, whereas Type I patients generally present with TBil levels ≥ 342.0 μmol/L. Experimental treatment with phenobarbital is often effective for Type II Crigler-Najjar syndrome, with a reduction of approximately 25% to 30% in serum TBil levels,[7,31] but is ineffective in Type I cases. Diagnosis of Crigler-Najjar syndrome should be confirmed through *UGT1A1* gene testing.

It is important to recognize that Gilbert syndrome exhibits a high prevalence and may coexist with other etiological liver diseases.[32] This is particularly relevant in clinical scenarios where the primary hepatic disease is well controlled—for instance, in patients with chronic hepatitis B virus (HBV) infection who have undetectable serum HBV DNA and normal or mildly elevated ALT, AST, ALP, and GGT levels. In such cases, persistent chronic indirect hyperbilirubinemia warrants consideration of concurrent Gilbert syndrome after excluding hemolysis.

Differential diagnosis: It is essential to differentiate hereditary hyperbilirubinemia from other conditions characterized by increased production or decreased clearance of indirect bilirubin.

Diseases associated with increased indirect bilirubin production:

1. *UGT1A1* gene diseases should be differentiated from hemolytic diseases, especially chronic hemolytic conditions. Chronic hemolysis may manifest with anemia and gallstones, while extravascular hemolysis, such as hereditary spherocytosis and autoimmune hemolysis, is often accompanied by splenomegaly. Patients presenting with childhood-onset anemia or a clear family history should be evaluated for hereditary hemolytic disorders. The following tests assist in differentiating hemolytic diseases:
   a. Complete blood count and reticulocyte count: In hemolysis, reticulocytes typically increase, with the reticulocyte percentage exceeding 3–4%[33,34] or an absolute count above 120×10^9/L. Decreased hemoglobin and increased red cell distribution width also suggest hemolysis. Anemia may not occur when bone marrow hematopoiesis can compensate.
   b. Peripheral blood smear: May show immature erythrocytes, including late-stage erythrocytes, polychromatic erythrocytes, and basophilic stippling. Abnormal erythrocyte morphology may be observed in hereditary spherocytosis and elliptocytosis.
   c. Coombs test: Usually positive in autoimmune hemolysis.
   d. Lactate dehydrogenase: Elevated due to increased release from erythrocyte destruction.
   e. Plasma haptoglobin: Reduced during hemolysis.
   f. Plasma-free hemoglobin: Increased during hemolysis.
   g. Erythrocyte lifespan: Shortened in hemolytic conditions. It should be noted that some patients may have both Gilbert or Crigler-Najjar syndrome and hemolytic diseases.[35,36]
2. Hemorrhagic conditions such as gastrointestinal bleeding or large hematomas: the decomposition and absorption of hemoglobin may lead to increased indirect bilirubin.[37] Fecal occult blood testing, gastroscopy, and monitoring of decreased hemoglobin levels are useful for differential diagnosis.
3. Others: Patients with artificial heart valve implantation or those who have undergone a transjugular intrahepatic portosystemic shunt may exhibit elevated indirect bilirubin levels due to increased erythrocyte destruction.

Diseases related to reduced clearance of indirect bilirubin:

1. Neonatal jaundice: Newborns have a short erythrocyte lifespan, immature liver function, low UGT1A1 enzyme activity, and underdeveloped intestinal flora, all of which contribute to increased bilirubin reabsorption into the bloodstream via enterohepatic circulation. In the majority of cases, neonatal jaundice is physiological in nature, typically resolving within 14 days in full-term infants. In preterm infants, jaundice usually improves within 21 days after birth.
2. Breast milk jaundice: Breast milk contains components

such as pregnane-3,20-diol, certain unsaturated fatty acids, and excess lipoprotein lipase, which may inhibit UGT1A1 enzyme activity and contribute to neonatal jaundice. Breast milk jaundice typically manifests within two to three days postpartum, with the majority of cases resolving spontaneously within three to twelve weeks.

Treatment: Gilbert syndrome generally has a good long-term prognosis and often requires no medical intervention. Crigler-Najjar syndrome, in contrast, necessitates prompt management to reduce indirect bilirubin levels and prevent bilirubin encephalopathy. Crigler-Najjar syndrome Type II typically exhibits a good prognosis. In pediatric patients with TBil levels exceeding 200.0 μmol/L, phototherapy or phenobarbital treatment should be considered based on the clinical presentation. Adults generally do not require specific treatment, but phenobarbital may be administered during bilirubin surges caused by comorbidities, stress, or when jaundice affects quality of life. Patients with Crigler-Najjar syndrome Type I should receive plasma exchange or phototherapy within the first week of life to rapidly reduce bilirubin levels and prevent the development of bilirubin encephalopathy. Without timely treatment, the risk of irreversible neurological damage increases substantially. Currently, liver transplantation remains the only curative treatment for Crigler-Najjar syndrome Type I and should be performed before the onset of permanent neurological injury.

Medication: The mechanism of phenobarbital involves activating residual UGT1A1 enzyme activity in the body.[7] For children with Crigler-Najjar syndrome Type II, the standard dosage is 2 mg/(kg·day), administered in two to three divided doses. Adults typically receive 60–180 mg/day in two divided doses,[7] with therapeutic effects usually observed within two to three weeks. At present, there is no established consensus regarding the optimal duration of treatment, and the available literature remains limited. Reported treatment durations range from two weeks to one month in adults, and from two to three weeks to several months or even years in pediatric patients.[38,39] In Crigler-Najjar syndrome Type II, phenobarbital can reduce serum bilirubin levels by approximately 25–30%. However, in patients with Crigler-Najjar syndrome Type I, it is ineffective. For patients with Gilbert syndrome whose jaundice significantly impacts quality of life, phenobarbital therapy at a dose of 30–60 mg/day could also be considered on an individualized basis. Administering the drug at bedtime usually yields favorable outcomes.

Phototherapy: Phototherapy involves irradiating the skin of patients with special blue fluorescent lamps or high-intensity light-emitting diodes,[14] which convert UCB in the blood into water-soluble isomers. These isomers are then excreted via bile and urine without undergoing hepatic conjugation, thereby leading to a reduction in serum bilirubin levels. With increasing age of patients, the efficacy of phototherapy declines due to increased skin thickness, pigmentation, and body surface area. In addition, patients may also experience adverse effects such as dry skin, hyperpigmentation, rashes, or lichenification.[6,14,40] In individuals with Crigler-Najjar syndrome Type I, early initiation of long-term phototherapy is critical to reduce the risk of kernicterus. In contrast, in children with Crigler-Najjar syndrome Type II, phototherapy should be considered when TBil levels exceed 200.0 μmol/L, as shorter treatment durations can enhance quality of life.

Plasma exchange: Plasma exchange can effectively and rapidly reduce bilirubin levels, helping patients manage hyperbilirubinemia crises. In pregnant patients, it may also prevent bilirubin from crossing the placenta and entering the fetal circulation, thereby protecting the fetal central nervous system. However, this treatment often requires multiple sessions, involves large volumes of fresh plasma, and may lead to adverse effects such as allergic reactions.

Liver transplantation: Liver transplantation can fully restore UGT1A1 function and effectively reduce serum bilirubin levels to normal. It should be considered for patients with Crigler-Najjar syndrome Type I. Indications for liver transplantation include: (1) Inadequate response to phototherapy (inability to maintain indirect bilirubin < 300 μmol/L) or intolerance to phototherapy due to complications such as severe photosensitive dermatitis or retinal damage; (2) Early neurological symptoms (e.g., abnormal muscle tone, seizures)—even if bilirubin levels are well controlled with phototherapy, liver transplantation should still be considered; (3) Long-term phototherapy leading to sleep deprivation, psychological disorders, or social isolation that negatively impacts quality of life or mental health.

Treatment of pregnancy and lactation in patients with Crigler-Najjar syndrome Type II: The management of Crigler-Najjar syndrome Type II during pregnancy is mainly reported in case studies. Elevated maternal bilirubin levels may increase the risk of neonatal kernicterus.[6] Therapeutic strategies aimed at optimizing perinatal outcomes include phenobarbital therapy, phototherapy, and albumin infusion. It is suggested that sequential phototherapy be used during early pregnancy, followed by phenobarbital treatment in the later stages.[41] In early pregnancy, taking phenobarbital at doses exceeding 750–1,000 mg/day may lead to fetal facial malformations and intellectual disability.[42] It is recommended that the dosage during pregnancy be kept below 50–60 mg/day.[43] However, dynamic monitoring of maternal bilirubin levels is essential during treatment, with target levels of TBil < 200 μmol/L and a bilirubin-to-albumin molar ratio < 0.5.[44] Phenobarbital carries a risk of affecting infants through maternal breastfeeding.[45] If the neonate exhibits excessive drowsiness or inadequate weight gain, discontinuation of maternal phenobarbital therapy may be warranted, with close monitoring of neonatal clinical status.

Health education: Gilbert syndrome can lead to anxiety and concern about jaundice, potentially affecting patients' social functioning and quality of life.[29] Patients should be advised to avoid known factors such as fasting, dehydration, and infections. Effective patient education is essential. Clinicians should provide clear and evidence-based information emphasizing the benign nature of the disorder, its favorable prognosis, and the lack of need for specific treatment. Proper education can alleviate anxiety, enhance self-management, and reduce unnecessary medical investigations.

Precautions for combined medication: UGT1A1 is a phase II metabolic enzyme involved in the metabolism of various endogenous and exogenous substances. Genetic variations in *UGT1A1* represent a potential risk factor for drug toxicity. Furthermore, inhibition of UGT1A1 activity may result in elevated bilirubin levels.

Irinotecan is commonly used to treat advanced colorectal and pancreatic cancers. Its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), is primarily metabolized by the enzyme UGT1A1. Accumulation of SN-38 in the body can lead to severe diarrhea and bone marrow suppression. To improve treatment safety, several guidelines and regulatory agencies—including the Dutch Pharmacogenetics Working Group, the Pan-Asian adapted ESMO consensus guidelines for the management of metastatic colorectal cancer, the U.S. Food and Drug Administration, and the European Medicines Agency—recommend adjusting the irinotecan dose based on the *UGT1A1* genotype. For patients carrying *UGT1A1* risk alleles such as *28/*28, *6/*6, *6/*28, or *28/*37 [A(TA)7TAA/A(TA)8TAA], dose reductions are advised.[46–50]

The Dutch Pharmacogenetics Working Group specifically recommends genotyping UGT1A1 before initiating irinotecan therapy,[46] as this approach enhances drug safety and has been shown to be cost-effective.[46,49]

Atazanavir is an HIV protease inhibitor that inhibits the activity of the UGT1A1 enzyme. In patients carrying *UGT1A1* variants such as *28/*28, *28/*37 [A(TA)7TAA/A(TA)8TAA], *37/*37, *80/*80 (c.-364C>T/c.-364C>T), and *6/*6, approximately 20% to 60% may develop jaundice, leading to treatment discontinuation. In such cases, alternative antiretroviral agents should be considered.[51]

Belinostat, a histone deacetylase inhibitor targeting histone proteins, is indicated for the treatment of relapsed or refractory peripheral T-cell lymphoma. The UGT1A1 enzyme is involved in its metabolism. The U.S. Food and Drug Administration recommends reducing the initial dose of belinostat to 750 mg/m^2 in patients homozygous for the UGT1A1*28 variant to minimize the risk of adverse reactions.[48,50]

In addition, several commonly used drugs, such as acetaminophen, statins, estradiol formate, and lamotrigine, are metabolized via the UGT1A1 enzyme. Reduced UGT1A1 enzyme activity may potentially impact the safety profile of these medications. Sorafenib and lenvatinib can inhibit UGT1A1 activity and may lead to elevated bilirubin levels.[52,53] In the absence of other biochemical indicators of liver injury, such as elevated ALT, AST, or GGT, careful assessment and close monitoring are recommended to help avoid unnecessary drug discontinuation. Conversely, phenobarbital and rifampicin can induce UGT1A1 activity, potentially accelerating the inactivation of other drugs metabolized by this enzyme and thereby reducing their efficacy. However, the precise clinical efficacy and potential toxic effects of these drugs in patients with *UGT1A1* genetic diseases remain unclear and require further investigation. For more information about the potential effects of *UGT1A1* gene variation on drug efficacy and safety, please consult the Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) database (https://www.pharmgkb.org/page).

Recommendations

Recommendation 1: For patients presenting with long-term or intermittent jaundice as the main clinical symptom, a clinical diagnosis of Gilbert syndrome can be made if there are two serum TBil elevations spaced more than six months apart (>1 times the upper limit of normal, typically 17.1–102.6 μmol/L), predominantly with indirect bilirubin elevation, no concurrent increases in liver enzymes such as ALT, AST, ALP, or GGT, and hemolytic diseases have been excluded. If TBil remains persistently elevated above 102.6 μmol/L or 342.0 μmol/L, a diagnosis of Crigler-Najjar syndrome Type II or Type I should be considered, respectively. Genetic testing aids in making definitive diagnosis and differential diagnosis. (Consensus level: 98.2%).

Recommendation 2: Gilbert syndrome generally has a favorable prognosis and typically does not require treatment. However, if jaundice significantly impacts quality of life, phenobarbital therapy can be administered based on patient preference. (Consensus level: 100%).

Recommendation 3: Crigler-Najjar syndrome Type II generally has a favorable prognosis. In pediatric patients with TBil levels exceeding 200.0 μmol/L, phototherapy or phenobarbital treatment may be considered based on individual clinical circumstances. In adult patients, therapeutic intervention is typically unnecessary. However, phenobarbital therapy can be administered in the presence of exacerbating factors such as comorbidities, stress, or when jaundice significantly impacts quality of life. (Consensus level: 99.1%).

Recommendation 4: In patients with Crigler-Najjar syndrome Type I, liver transplantation should be considered prior to the elevation of indirect bilirubin levels above 300.0 μmol/L or the onset of irreversible brain injury, despite phototherapy. (Consensus level: 99.1%).

Recommendation 5: Genetic testing for UGT1A1 polymorphisms is recommended prior to the initiation of treatment with Irinotecan, Atazanavir, and Belinostat to assess the risk of drug-related adverse effects. (Consensus level: 95.5%).

Dubin-Johnson syndrome

Dubin-Johnson syndrome is a rare autosomal recessive genetic disorder caused by mutations in the *ABCC2* gene located on chromosome 10q24. These mutations impair the function of MRP2, leading to defective excretion of CB and other organic anions from hepatocytes into the bile canaliculi. Due to the accumulation of bilirubin in hepatocytes and its subsequent reflux into the bloodstream, CB levels in the blood become elevated.

Epidemiology

Dubin-Johnson syndrome is a rare disorder with a low overall incidence and no apparent sex predilection. It has been reported across all ethnic groups but is more prevalent among Hispanic and Iranian Jewish populations, with an estimated prevalence of approximately one in 1,300 individuals.[54] Comprehensive epidemiological data for the Chinese population remain unavailable. Nonetheless, institutional data from two specialized liver disease hospitals in Beijing indicate that Dubin-Johnson syndrome accounts for 0.45 cases per 10,000 hospitalized patients during the same period.[8]

Clinical manifestations

Most cases of Dubin-Johnson syndrome manifest during adolescence or young adulthood. Patients are often asymptomatic, with hyperbilirubinemia typically discovered incidentally during routine physical exams or evaluations for other medical issues. Elevated direct bilirubin is the primary laboratory finding. Clinically, patients may present with mild jaundice and dark-colored urine. The jaundice is intermittent and can be triggered by factors such as pregnancy, surgery, or oral contraceptive use. Some patients may also experience mild fatigue, weakness, or abdominal discomfort. Physical examinations are generally unremarkable, though occasional hepatosplenomegaly may be observed. Pruritus or hemolysis are absent, and serum total bile acid levels remain within normal limits. In contrast to adult-onset presentations, neonatal Dubin-Johnson syndrome can present with transient or severe cholestasis and hepatomegaly.[31,55]

Laboratory and imaging examinations

Liver biochemistry and blood routine tests: Serum TBil in most patients with Dubin-Johnson syndrome ranges from 34.0 to 85.0 μmol/L. However, fluctuations are common, with levels occasionally returning to normal or rising as high as 300.0 to 400.0 μmol/L, with elevated direct bilirubin as

the predominant feature.[56] Other liver function parameters, including ALT, AST, ALP, GGT, and total bile acids, are usually within normal reference ranges. Similarly, coagulation profiles, such as prothrombin time and activated partial thromboplastin time, as well as complete blood counts, are generally within normal limits.[57] It is noteworthy that ALP elevation may be observed in pediatric or adolescent patients. There is no laboratory or clinical evidence of hemolysis.

Bromosulfophthalein (BSP) removal rate test: BSP is administered intravenously at a dose of 5 mg/kg. In healthy individuals, most of the drug is eliminated within 45 m, with serum levels remaining below 5% of the total injected dose. Patients with Dubin-Johnson syndrome initially show normal plasma clearance rates following BSP administration. At 45 m, retention levels are either normal or slightly elevated. However, by 90 m, a second (biphasic) peak appears due to BSP reflux into the bloodstream, indicating impaired excretion. Despite this, the BSP clearance test has poor specificity and carries the risk of serious adverse effects, including occasional anaphylactic shock, which has led to its rare use in the diagnosis of Dubin-Johnson syndrome.

Urinary coproporphyrins: An abnormal distribution of coproporphyrin isomers I and III in urine is characteristic of Dubin-Johnson syndrome. Normally, coproporphyrin III accounts for about 75% of total urinary coproporphyrins. However, in patients with Dubin-Johnson syndrome, while the total urinary coproporphyrin levels remain normal, over 80% of the total is coproporphyrin I. This test is not performed in most hospitals in China, and with the application of genetic testing, it is now rarely used.

Imaging studies: Ultrasound and magnetic resonance imaging examinations in patients with Dubin-Johnson syndrome typically show no significant abnormalities. However, case reports have noted increased liver density on CT scans in affected infants.[58] Oral cholecystography may reveal delayed visualization of the gallbladder and bile ducts, though this technique is now rarely employed for diagnosis.

Genetic testing

Genetic testing can serve as a first-line diagnostic method for Dubin-Johnson syndrome. To date, nearly 100 variants of the *ABCC2* gene have been reported, encompassing diverse types and multiple loci. The most common variants include c.1177C>T (p.Arg393Trp), c.2125T>C (p.Trp709Arg), c.2302C>T (p.Arg768Trp), c.3196C>T (p.Arg1066Ter), and c.3825C>G (p.Tyr1275Ter). Current literature indicates that the predominant pathogenic variants in China are c.1177C>T (p.Arg393Trp) and c.2078G>A (p.Gly693Glu).[59,60] Notably, Gilbert syndrome has also been documented in China alongside Dubin-Johnson syndrome.[61]

Liver pathological examination

Routine liver biopsy and pathological examination are not recommended for the diagnosis of Dubin-Johnson syndrome. The liver often appears "black". Histologically, the liver lobule structure is normal, and coarse brown granules are diffusely distributed in the hepatocytes around the central vein, which are more prominent on the pericanalicular site and can also extend to the hepatocytes around the portal area. The pigment granules have characteristics of lipofuscin and melanin, and Fontana staining is black. Immunohistochemical staining of the bile duct capillary MRP2 may be negative. Under transmission electron microscopy, electron-dense material wrapped in a single layer of membrane in the hepatocytes can be seen, mainly distributed around the bile canaliculus.

Diagnosis

Dubin-Johnson syndrome should be considered in patients presenting with long-term, fluctuating hyperbilirubinemia predominantly involving direct bilirubin (direct bilirubin/TBil > 50%),[56] while other liver function indicators (serum ALT, AST, ALP, GGT) and coagulation indicators are normal. Liver biopsy shows abundant coarse brown granules, which stain black with Fontana stain, providing supportive histological evidence. Confirmation of the diagnosis requires the identification of pathogenic variants in two alleles of *ABCC2* through genetic testing, which serves as a definitive diagnostic criterion.

Differential diagnosis

Dubin-Johnson syndrome should be differentiated from other hepatobiliary diseases with elevated direct bilirubin, such as Rotor syndrome and intrahepatic cholestasis.

Treatment

Dubin-Johnson syndrome is generally associated with a favorable prognosis. Most cases do not progress to fibrosis or cirrhosis and typically require no treatment. However, early diagnosis is essential to exclude other hepatobiliary diseases that may cause liver damage. Patients should try to avoid adverse factors such as oral contraceptives that may aggravate jaundice.[2] In newborns with severe cholestasis, phenobarbital and ursodeoxycholic acid therapy may be considered.[54]

Precautions for combined medication

MRP2 protein is involved in the transport of various endogenous and exogenous substances. Estrogen acts both as an endogenous substrate of MRP2 and influences its transport function. Pregnancy and oral contraceptive use may elevate bilirubin levels in patients with Dubin-Johnson syndrome.[62] Exogenous substrates of MRP2 include certain anticancer drugs (methotrexate, tamoxifen, docetaxel, vincristine, irinotecan[63]), antiepileptic medications (carbamazepine, valproic acid), antibiotics (amoxicillin, ceftriaxone, rifampicin), nonsteroidal anti-inflammatory drugs (salicylates, ibuprofen, naproxen[64]), HBV antiviral drugs (tenofovir), and HIV antiviral drugs (saquinavir[65]). Dysfunction of MRP2 may alter the pharmacokinetics of these drugs, potentially increasing toxicity. However, the clinical efficacy and toxic effects of these medications in patients with Dubin-Johnson syndrome remain unclear and warrant further study. For detailed information on specific drugs, please refer to the PharmGKB database.

Rotor syndrome

Rotor syndrome is a rare autosomal recessive genetic disease.[56] Its pathogenesis involves homozygous or compound heterozygous mutations in the *SLCO1B1* and *SLCO1B3* genes, which are located adjacent to each other on chromosome 12, resulting in simultaneous functional defects of the OATP1B1/1B3 proteins encoded by them. OATP1B1 and OATP1B3 are both expressed on the hepatocyte membrane and are members of the organic anion transporter polypeptide superfamily of solute carriers. They primarily mediate the uptake of various endogenous and exogenous compounds from the blood into hepatocytes. Bilirubin and its glucuronide conjugates are substrates of OATP1B1 and OATP1B3. Functional defects in these two genes impair bilirubin uptake by hepatocytes, leading to increases in both UCB and CB in the serum, with CB predominating.

Epidemiology

Rotor syndrome is an exceedingly rare disorder, with an estimated prevalence of approximately one in 1,000,000 individuals.[56] There is currently no epidemiological data for specific regions or countries, and research is mainly based on case reports. Data from two liver disease specialist hospitals in Beijing showed that Rotor syndrome accounted for 0.15 per 10,000 hospitalized patients during the same period.[8]

Clinical manifestations

Rotor syndrome typically manifests during adolescence or young adulthood, though cases of onset shortly after birth or during childhood have also been reported. Its primary clinical features include chronic, persistent, or intermittent jaundice, with no apparent sex predilection. Approximately half of affected individuals remain asymptomatic, while some patients may experience fatigue, upper abdominal or liver pain, and general discomfort. Jaundice can be long-lasting and may be exacerbated by factors such as fatigue, infection, pregnancy, or surgery. Hepatosplenomegaly is generally absent in Rotor syndrome.[66]

Laboratory and imaging examinations

Liver biochemistry and blood routine tests: Blood TBil levels typically range from 34.0 to 85.0 μmol/L, though they can occasionally rise as high as 300.0 to 400.0 μmol/L. Direct bilirubin often accounts for more than 50% of TBil. Other liver function tests—including ALT, AST, ALP, and GGT—generally remain within normal limits, although ALP may be elevated in children or adolescents. Coagulation parameters, such as prothrombin time and activated partial thromboplastin time, as well as complete blood counts, typically show normal results. No evidence of hemolysis has been observed.

BSP removal rate test: The retention rate of BSP in patients with Rotor syndrome can be as high as 50–60% at 45 m post-injection, without a biphasic peak at 90 m. However, with the application of genetic testing, this test is now rarely used.

Urinary coproporphyrins: In patients with Rotor syndrome, total 24-h urinary coproporphyrin excretion increases by two to five times, of which coproporphyrin I usually accounts for less than 65%.[66] This test helps differentiate Rotor syndrome from Dubin-Johnson syndrome. However, due to limited availability in most clinical laboratories and the increasing reliance on genetic testing for definitive diagnosis, this test is now infrequently performed.

Imaging studies: Imaging studies can help exclude other causes of hyperbilirubinemia, such as obstructive jaundice.

Genetic testing

Genetic testing can serve as the first-line diagnostic tool for Rotor syndrome. As of January 2025, the Human Gene Mutation Database has documented 39 pathogenic variants in the *SLCO1B*1 gene, primarily missense and nonsense mutations. A Japanese study identified c.1738C>T (p.Arg580Ter) and c.757C>T (p.Arg253Ter) as the most common *SLCO1B1* variants.[67] In addition, 42 pathogenic variants have been reported in the *SLCO1B3* gene, with splicing mutations such as c.1747+1G>A being more prevalent. Other *SLCO1B3* variants are predominantly structural alterations, including copy number variations, inversions, and large insertions. In East Asian populations, long interspersed nuclear element-1 insertions have been detected in intronic regions, which can lead to aberrant splicing, exon inversion, or skipping, thereby impairing SLCO1B3 function.[68–70] Notably, structural variants are often undetectable through conventional sequencing methods such as first-generation Sanger sequencing and whole-exome sequencing, significantly complicating genetic diagnosis of Rotor syndrome.

Liver pathological examination

Liver biopsy is not recommended as a routine diagnostic method for Rotor syndrome. However, it may be considered in cases where comorbid conditions are present or differential diagnosis is required. Liver histology in Rotor syndrome is typically normal, with no pigment deposition in hepatocytes. Histopathological examination can help distinguish Rotor syndrome from Dubin-Johnson syndrome.

Diagnosis

Rotor syndrome should be considered when patients have long-term, fluctuating hyperbilirubinemia, with elevated direct bilirubin as the main symptom, and liver indices (ALT, AST, GGT, and ALP) are normal or only slightly elevated. The diagnosis depends on genetic testing to identify homozygous or compound heterozygous pathogenic variants in both *SLCO1B1* and *SLCO1B3* genes.

Differential diagnosis

It is important to distinguish Rotor syndrome from Dubin-Johnson syndrome (Table 1). In addition, it should be differentiated from cholestatic liver diseases, which are typically characterized by marked elevations in cholestatic enzymes such as GGT and ALP. Imaging studies in cases of obstructive jaundice often reveal bile duct dilation.

Treatment

Rotor syndrome has a good prognosis, generally does not progress to liver fibrosis or cirrhosis, and does not require treatment. The value of a clear diagnosis lies mainly in differentiating it from other hepatobiliary diseases and avoiding overtreatment.

Precautions for combined medication

In addition to bilirubin, steroid conjugates are also endogenous substrates of OATP1B1 and OATP1B3, which may affect their transport function. Administration of such agents may aggravate jaundice. OATP1B1 and OATP1B3 also transport exogenous substrates, such as some anti-tumor drugs (cyclosporine A, methotrexate), statins, and antibacterial drugs (rifampicin).[66] Functional defects in OATP1B1 and OATP1B3 may cause these drugs to accumulate in the body, increasing their toxicity. However, the clinical efficacy and toxicity of these drugs in Rotor syndrome remain unclear, and further research is needed. For more specific medication references, please consult the PharmGKB database.

Recommendation

Recommendation 6: In patients with simple hyperbilirubinemia, mainly with elevated direct bilirubin, after excluding other causes such as cholestasis, viruses, drugs, and alcohol, a diagnostic consideration of Dubin-Johnson syndrome or Rotor syndrome should be made. Genetic testing can be used as the first-line test to help clarify the diagnosis. (Consensus level: 99.1%).

Recommendation 7: Liver biopsy is not recommended as a routine method for diagnosing Dubin-Johnson syndrome or Rotor syndrome. Liver pathological examination can be considered when clinical manifesta-

Table 1. Differential diagnosis of hereditary hyperbilirubinemia

Category	Gilbert/Crigler-Najjar syndrome	Dubin-Johnson syndrome	Rotor syndrome
Gene	*UGT1A1*	*ABCC2*	*SLCO1B1/ SLCO1B3*
Chromosome Location	2q37	10q24	12p12
Encoded Protein	Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1)	Multidrug resistance-associated protein 2 (MRP2)	Organic anion transporting polypeptides 1B1/3 (OATP1B1/3)
Pathogenic Mechanism	Decreased UGT1A1 activity leading to impaired glucuronidation of unconjugated bilirubin	Defective transport of conjugated bilirubin and other non-bile acid organic anions to bile canaliculi	Impaired hepatic uptake of conjugated bilirubin
Inheritance Pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive with digenic involvement
Type of Hyperbilirubinemia	Predominantly indirect bilirubin elevation	Predominantly direct bilirubin elevation	Predominantly direct bilirubin elevation
TBil Levels	Gilbert: 17.1–102.6 μmol/L; CN Type II: 102.6–342.0 μmol/L; CN Type I: ≥342.0 μmol/L	Typically 34.0–85.0 μmol/L, may reach up to 400.0 μmol/L	Typically 34.0–85.0 μmol/L, may reach up to 400.0 μmol/L
ALT	Normal	Normal	Normal
Urinary Coproporphyrins	Normal; ~75% Coproporphyrin III	Normal total coproporphyrin; >80% are coproporphyrin I	Total coproporphyrin increased by 2–5 times; coproporphyrin I <65%
Pathological Features	Generally normal	"Black liver" appearance; coarse brown granules in hepatocytes near bile canaliculi; positive Fontana stain	Generally normal
Prognosis	Benign for Gilbert and most CN Type II; Poor for CN Type I without liver transplantation	Benign	Benign
Inducing Factors	Drugs inhibiting UGT1A1 (e.g., atazanavir), fatigue, fasting	Oral contraceptives, pregnancy	Unclear
Treatment Strategy	Gilbert: No treatment; CN Type II: Phenobarbital, phototherapy; CN Type I: Phototherapy, liver transplant	Usually not required	Usually not required

UGT1A1 refers to the gene encoding uridine diphosphate glucuronosyltransferase 1A1. *ABCC2* denotes the gene encoding ATP-binding cassette subfamily C member 2. *SLCO1B1* and *SLCO1B3* refer to solute carrier organic anion transporters B1 and B3, respectively. TBil represents total bilirubin, and ALT denotes alanine aminotransferase.

tions are atypical and differentiation from other liver diseases is required. (Consensus level: 99.1%).

Recommendation 8: Dubin-Johnson syndrome and Rotor syndrome generally have a good prognosis and typically do not require treatment. (Consensus level: 99.1%)

Diagnostic approach and differential diagnosis

Hereditary hyperbilirubinemia can be diagnosed step by step. Patients with long-term, intermittent, or persistent hyperbilirubinemia who are in good general condition, especially those with onset during adolescence or young adulthood, should be alert to this type of disease. When liver enzymes (ALT, AST) are normal and there is no obvious liver damage, the condition is divided into hereditary hyperbilirubinemia with predominantly elevated indirect bilirubin or direct bilirubin. When indirect bilirubin is mainly elevated, after excluding hemolytic diseases and other conditions, a UGT1A1 gene disorder can be considered; when direct bilirubin is mainly elevated, after excluding cholestatic liver disease, Dubin-Johnson syndrome and Rotor syndrome should be considered. The diagnostic roadmap and differential diagnosis of hereditary hyperbilirubinemia are shown in Figure 2 and Table 1.

Problems that remain to be studied and solved

1. Epidemiological data on hereditary hyperbilirubinemia in the Chinese population remain limited. The gene variation spectrum and the correlation between genotype and clinical phenotype require further clarification.
2. The pathogenic genes and gene variation spectrum of Gilbert syndrome, especially genetic factors other than the *UGT1A1* gene,[71] need further study.
3. The natural history and influencing factors of Crigler-Najjar syndrome type II, Dubin-Johnson syndrome, and Rotor syndrome remain unclear and need further elucidation.
4. Gene therapy and cell therapy represent promising directions for treating hereditary hyperbilirubinemia. Recent progress, such as the AAV8-UGT1A1 gene therapy trial (NCT03466463), provides encouraging early evidence. In this phase 1–2 study, a single infusion of the vector showed an acceptable safety profile in five patients, and those receiving the higher dose achieved sustained re-

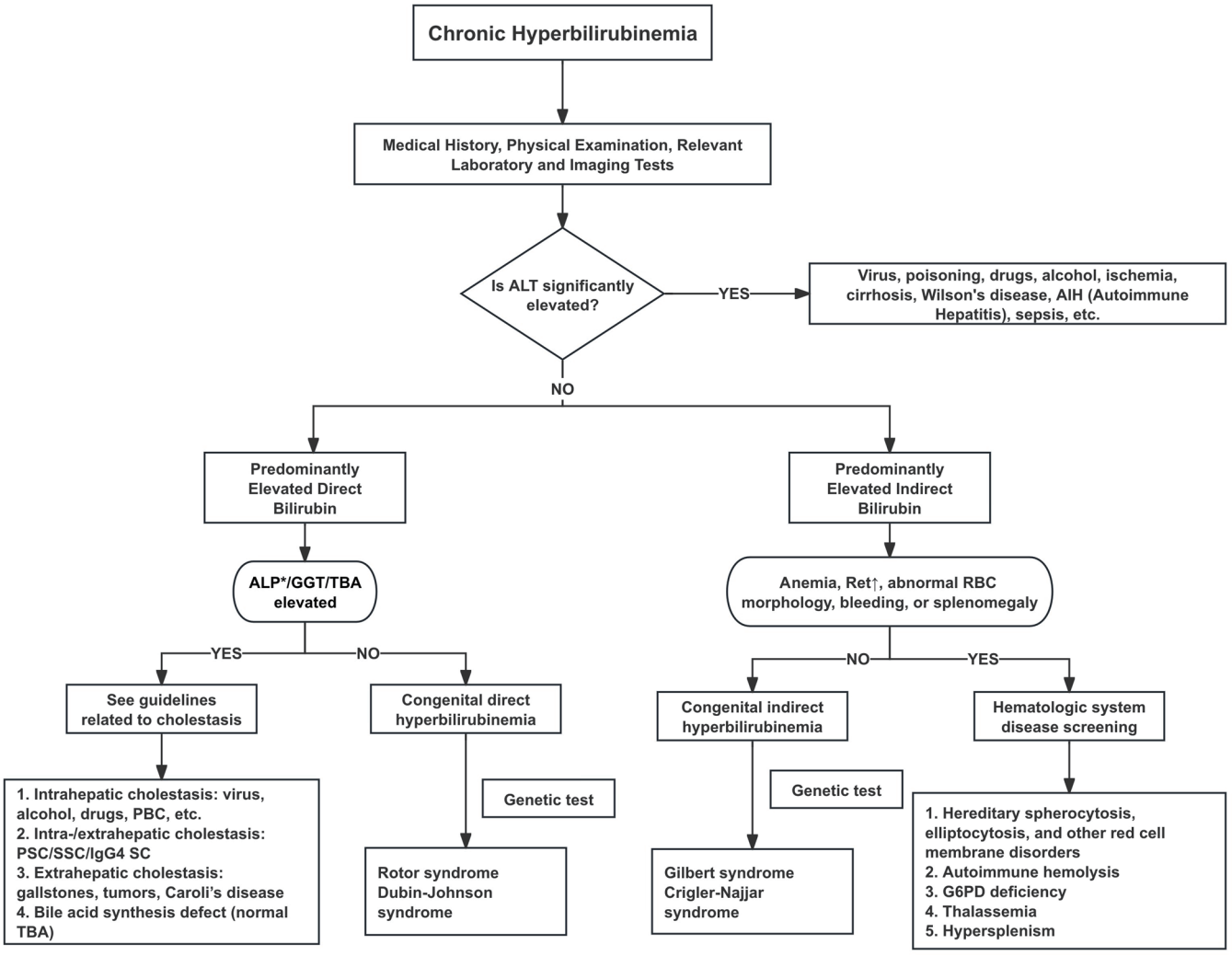

Fig. 2. Diagnostic approach for hereditary hyperbilirubinemia. *ALP may be elevated in children or adolescents. AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; TBA, total bile acid; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis; IgG-4 SC, IgG-4-related sclerosing cholangitis; Ret, reticulocyte; RBC, red blood cell; G6PD, glucose-6-phosphate dehydrogenase.

ductions in serum bilirubin and remained free from phototherapy for at least 78 weeks.[72] Despite these promising findings, the technology remains at an early stage. Corresponding treatment technologies and protocols must still be developed and optimized. Comprehensive preclinical and clinical studies are required to rigorously evaluate their efficacy and safety.

5. As a novel signaling molecule, the role of bilirubin deserves increased attention. The association between mild hyperbilirubinemia in Gilbert syndrome and risks of metabolic-related steatohepatitis, obesity, metabolic syndrome, diabetes, and overall cancer remains controversial.[73,74]
6. The interplay between genetic variation and drug response in hereditary hyperbilirubinemia is not fully understood. Urgent basic and clinical research is needed to enable individualized precision treatment, improve efficacy, and reduce drug-related adverse reactions.

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Conflict of interest

YN and XZ have been Editorial Board Members of *Journal of Clinical and Translational Hepatology* since 2022 and 2013, LW and JJ have been Executive Associate Editors of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

The Consensus Committee and Methodology Experts were

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