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Guideline

Guidelines for the Management of Cholestatic Liver Diseases (2021)

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Abstract

In 2015, the Chinese Society of Hepatology and the Chinese Society of Gastroenterology issued a consensus statement on the diagnosis and management of cholestatic liver diseases. More clinical data on this topic have appeared during recent years. The Autoimmune Liver Disease Group of the Chinese Society of Hepatology organized an expert group to review recent evidence and provide an update to these previous guidelines. Herein, we provide 22 recommendations as a working reference for the management of cholestatic liver diseases by clinical practitioners.

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Introduction

Cholestasis is a pathological condition in which various intrahepatic or extrahepatic factors impede bile formation, secretion, or excretion, leading to increased flow of bile into the duodenum and blood. The clinical characteristics of affected patients include pruritus, fatigue, darkened urine, and jaundice. During early-stage cholestasis, patients are usually asymptomatic and may only present with elevations of serum alkaline phosphatase (ALP) and gamma- glutamyl transferase (GGT). Hyperbilirubinemia may occur as disease progresses, and may lead to liver cirrhosis, liver failure, or even death.[1,2] Hepatobiliary diseases with cholestasis from various causes are called cholestatic liver diseases, and cholestasis itself further aggravates liver damage in these patients.

To help clinicians standardize the diagnosis and treatment of cholestatic liver diseases, the Chinese Society of Hepatology, Chinese Society of Gastroenterology, and Chinese Society of Infectious Diseases formulated the "Consensus on Diagnosis and Treatment of Cholestatic Liver Diseases" in 2015.[3] Because of the publication of additional clinical data regarding cholestatic liver diseases in China since then, we updated this guideline and revised the original consensus. The present guideline describes the etiology, classification, clinical manifestations, diagnostic criteria, treatment principles, diagnosis, and treatment of cholestatic liver diseases. The cholestasis induce by drugs, alcohol, hepatitis B virus, hepatitis C virus, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis, metabolic-related fatty liver disease and other liver diseases can be diagnosed and treated according to the corresponding guideline. We rated the evidence and recommendations in this guideline using the GRADE system for the evaluation of clinical guidelines (Table 1).

Etiology and classification

Hepatocytes and cholangiocytes produce bile, and the daily total flow of bile in a healthy adult is about 600 mL. Hepatocytes produce bile salt-dependent bile (about 225 mL/day) and bile salt-independent bile (about 225 mL/day), and cholangiocytes produce additional bile (about 150 mL/day). Cholestasis is a disorder caused by the reduced flow or formation of bile,[4] and the cause can be intrahepatic or extrahepatic. Intrahepatic cholestasis[4–7] is characterized by dysfunction of hepatocytes, bile canaliculus, canals of Hering, bile ductule (<15 μm,), or cholangiocytes of the interlobular bile duct (15 to 100 μm), without obvious manifestations of bile duct obstruction based on imaging examination. The main causes are use of drugs or alcohol, viral or bacterial infection, and immune system disorders, etc. (Fig. 1). Extrahepatic cholestasis is characterized by obstruction or injuries of the septal bile duct (>100 μm), regional bile duct (300 to 400 μm), segmental bile duct (400 to 800 μm), left or right hepatic ducts, or the common bile duct to the ampulla.[2,7] Although the main causes are outside the liver, biliary cancer growing into the intrahepatic bile duct and hilar bile duct is also a cause. Bile duct stones, a malignancy from the pancreas or bile duct

Keywords: Cholestatic liver disease; Diagnosis; Therapeutics; Practice guidelines.

Abbreviations: ALP, alkaline phosphatase; BRIC, benign recurrent intrahepatic cholestasis; CFLD, cystic fibrosis-associated liver disease; CFTR, cystic fibrosis transmembrane conductance regulator gene; CT, computed tomography; DEXA, dual energy X-ray absorptiometry; ERCP, endoscopic retrograde cholangiopancreatography; FIC, familial intrahepatic cholestasis; FXR, farnesoid X receptor; GGT, gamma glutamyl transferase; HELLP, hemolysis, elevated liver enzymes, and low platelet count syndrome; 5-HT, 5-hydroxytryptamine; IBAT, ileal bile acid transporter; ICP, intrahepatic cholestasis of pregnancy; MDR3, multidrug resistance protein 3; MRCP, magnetic resonance cholangiopancreatography; PBC, primary biliary cholangitis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; PT, prothrombin time; SAMe, S-adenosyl-L-methionine; TJP2, tight junction protein 2; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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Table 1. GRADE system used to evaluate all recommendations

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change confidence in the estimated effect.	A
Moderate quality	Further research is likely to have an important impact on confidence in the estimated effect and may change the estimated effect.	B
Low or very low quality	Further research is very likely to have an important impact on confidence in the estimated effect and may change the estimated effect. Any estimated effect is uncertain.	C

Grading of recommendations	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included quality of evidence, presumed patient-important outcomes, and cost.	1
Weaker recommendation	Variability in preferences and values, or more uncertainty; more likely a weak recommendation is warranted. Recommendation has less certainty; higher cost or resource consumption.	2

and ampulla, or a benign biliary stricture are the main causes of extrahepatic cholestasis, and these conditions usually cause acute cholestasis.[8] Cholestasis that persists more than 6 months is defined as chronic cholestasis.[5] It is important for clinicians to distinguish extrahepatic and intrahepatic cholestasis, but this could be difficult when only considering symptoms, signs, and biochemical parameters. Instead, a detailed diagnostic procedure is needed to distinguish these different conditions. PSC is a pathology that affects small and large intrahepatic bile ducts and/or extrahepatic bile ducts, and some patients with this condition can have intrahepatic or extrahepatic lesions (Fig. 1). According to the location of cytological damages, Cholestasis may be classified as hepatocellular or cholangiocytotic,[5] and injuries of both hepatocytes and cholangiocytes are known as mixed cholestasis.

Epidemiology

At present, there are no reliable data on the incidence of cholestatic liver diseases. Bortolini *et al*.[9] reported that cholestasis was present in 882 (35%) of 2,520 patients who were diagnosed with chronic liver diseases for the first time, and that cholestasis was more common in patients with PBC and PSC. A study of 1,000 patients with chronic viral hepatitis showed that 56% of them had elevated ALP or GGT at discharge, and that elevation of these enzymes

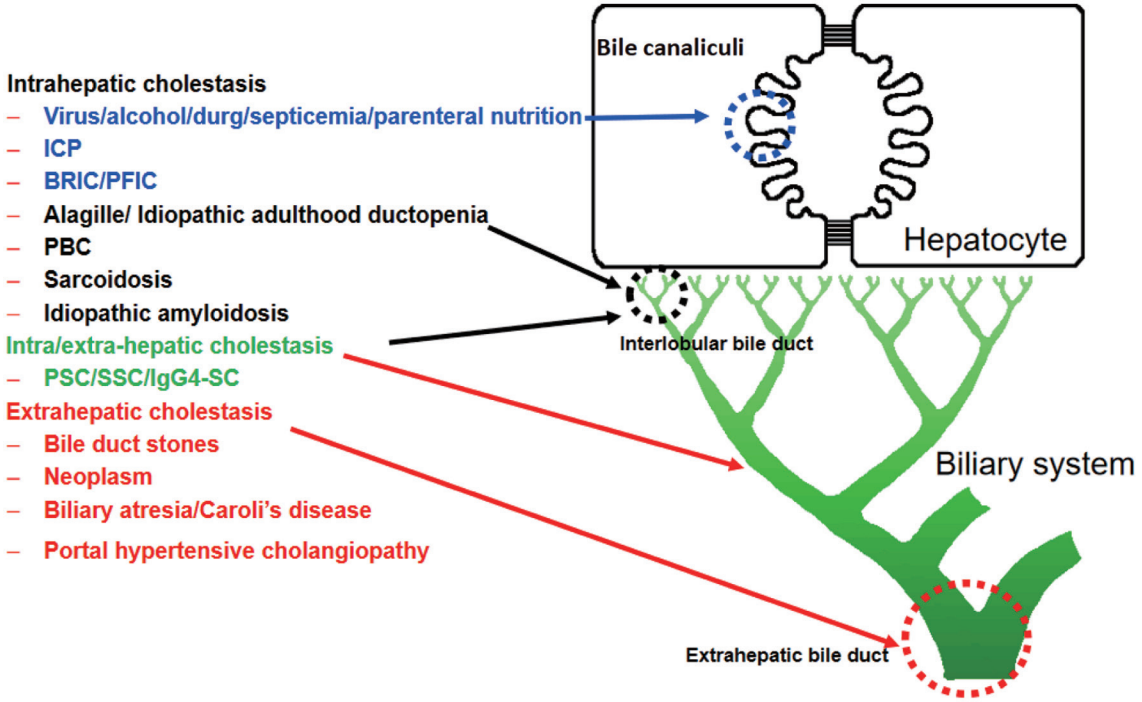

Fig. 1. Location of injuries that lead to cholestatic liver disease. BRIC, benign recurrent intra-hepatic cholestasis; ICP, intrahepatic cholestasis of pregnancy; IgG4-SC, IgG4-related sclerosing cholangitis; PBC, primary biliary cholangitis; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; SSC, secondary sclerosing cholangitis.

was associated with increased risk for and severity of liver fibrosis and cirrhosis.[10] Cao *et al*.[11] performed a survey of 4,660 patients who were hospitalized with chronic liver diseases in Shanghai and reported that the total incidence of cholestasis was 10.26%, and that the incidence increased with patient age.

Clinical manifestations

In addition to the clinical symptoms caused by the original disease, cholestasis itself can cause clinical symptoms, as well as secondary changes due to alterations in bile. Patients with early-stage disease may have no symptoms or nonspecific symptoms, such as fatigue, anorexia, nausea, and epigastric discomfort. The main clinical manifestations of cholestasis are jaundice, pruritus, fatigue, steatorrhea, xanthoma, and hepatic osteodystrophy.

Biomarkers

The most common biomarkers for cholestasis are ALP, GGT, bile acid, bilirubin, and several molecular markers.

ALP and GGT

Elevation of ALP and GGT are the most common manifestations of early cholestasis. It is generally thought that the retention of bile salts in cholestasis leads to the proliferating of small bile ductules with increase in ALP and GGT production. The mechanism by which ALP and GGT enters the blood and increases during cholestasis is still unclear. The internal pressure of the bile canaliculus and ductules leads to abnormally increased bile excretion and this increases ALP production. In addition, bile acid, because of its surface activity, dissolves ALP from lipid membranes, and this may also serum increased ALP.[12] Moreover, elevation of ALP can also occur during pregnancy, child growth, and in patients with bone diseases and certain tumors. Compared with other serum enzymes in these patients, GGT increases earlier and the increase remains longer. Among liver enzymes, GGT has the highest diagnostic sensitivity for cholestasis, but its specificity is low. The sensitivity and specificity of GGT in the diagnosis of cholestasis are noninferior or even better than those of ALP. If ALP and GGT are both elevated and other causes of liver injury are excluded (alcoholism, infection, etc.), this indicates damage of hepatocytes and cholangiocytes. If GGT is elevated but ALP is not, this indicates damage of bile canaliculus and cholangiocytes. If ALP is elevated but GGT is not, this indicates that liver injuries can often be excluded. However, in some specific cholestatic liver diseases, such as familial intrahepatic cholestasis (FIC type 1, 2, 4, 5, and 6), and USP53 deficiency disease, the levels of combined bilirubin or bile acid are increased, but GGT is normal or often reduced.[13,14]

Bile acids

Bile acid is more sensitive than bilirubin for the diagnosis of bile secretion disorder, but it is not as sensitive as ALP. Patients with many liver diseases, such as cirrhosis and acute and chronic hepatitis, have elevated serum bile acid. The normal range of fasting serum bile acid is 1.0 to 6.0 μmol/L, and the normal postprandial range (2 h after eating) is 6.0 to 9.0 μmol/L. This level of bile acid can be more than 10 μmol/L in patients with cholestasis, and there are standard ranges for defining mild elevation (10 to 20 μmol/L), moderate elevation (20 to 40 μmol/L), and severe elevation (>40 μmol/L).[1,4] Although bile acid and cholic acid are sensitive markers for cholestasis, these measurements have limited use in China and elsewhere due to the lack of reliable detection methodologies and standardization, the presence of various interfering factors, and poor diagnostic specificity. The elevation of bile acid is specific to hepatobiliary diseases, the sensitivity is low and cannot be increased by the additional measurement of bile acid at 2 h after a meal.[4]

Bilirubin

Cholestasis can cause elevated serum bilirubin, especially direct bilirubin. Hepatocellular damage can increase direct and indirect bilirubin due to abnormalities in bilirubin synthesis, conjugation, and excretion, but the increase of direct bilirubin is generally more obvious than that of indirect bilirubin. An increase of bilirubin without an increase of liver enzymes generally indicates hereditary diseases such as Gilbert's disease, or hemolysis diseases.

Molecular markers

Mutations of specific genes can cause hereditary cholestatic liver diseases. Traditional sequencing can directly detect mutations in specific genes whose alteration may be suggested by patient phenotype. Second-generation sequencing has also been applied in the clinic and has made it easier to identify certain hereditary cholestatic liver diseases, such as FIC. Table 2 summarizes specific hereditary cholestatic liver diseases and the genes with causative mutations.[15] However, mutations in individual genes account for only a small portion of liver diseases, and most hereditary liver diseases are caused by mutations of multiple genes or a combination of gene mutations and environmental factors.

Pathology

Patients with cholestasis have gross liver specimens that are yellow-green and liver biopsy specimens with scattered green or dark green spots. The basic pathological changes of intrahepatic cholestasis begin from zone 3 in the bile canaliculus and canals of Hering, and are characterized by feather degeneration of hepatocytes and plugs in the dilated bile ducts.[6,7,16] In severe cases, the hepatocytes are arranged in an acinar shape around the dilated bile canaliculus, and there are characteristic pathological changes indicative of intrahepatic cholestasis. There may also be hypertrophic Kupffer cells in the sinusoid bile and cholestasis of the interlobular bile duct in the portal area, with bile plug formation. Electron microscopy typically shows edematous and shortened microvilli of the capillary bile duct, and histopathology of extrahepatic obstructive cholestasis shows bile lakes in the liver around the portal area, with bile granulomas. Long-term extrahepatic obstruction can cause secondary intrahepatic cholestasis, and late-stage cholestasis can progress to portal fibrosis or even cirrhosis.

Diagnosis

Diagnostic criteria

There are currently no unified diagnostic criteria or specific

Table 2. Genes related to cholestatic diseases[15]

Cholestatic disease	Gene(s) affected
Alagille syndrome	*JAG1, NOTCH2*
1-antitrypsin deficiency	*SERPINA1*
α-methylacyl-CoA racemase deficiency	*AMACR*
Arthrogryposis-renal dysfunction-cholestasis syndrome	*VIPAS39, VPS33B*
Autosomal recessive polycystic kidney disease	*PKHD1*
BA conjugation disorder	*SLC27A5*
BA reabsorption disorder	*SLC10A1, SLC10A2*
BA receptor defect	*GPBAR1*
BA synthesis disorders	*CYP7A1*
Biliary atresia	*SLC51B*
BRIC	*ABCB11, ATP8B1, SLC51A*
Cerebrotendinous xanthomatosis	*CYP27A1*
Cholesteryl ester storage disease	*LIPA*
Citrullinemia	*SLC25A13*
Congenital bile acid synthesis defect	*ACOX2, AKR1D1, AMACR, CYP7B1, HSD3B7*
Cystic fibrosis	*CFTR*
D-bifunctional protein deficiency	*HSD17B4*
Dubin–Johnson syndrome	*ABCC2*
Extrahepatic cholestasis	*SLC51B*
Familial hypercholanemia	*BAAT, TJP2*
Lucey–Driscoll syndrome	*UGT1A1*
Crigler–Najjar syndrome	*UGT1A1*
Fanconi renotubular syndrome 3	*EHHADH*
Gallbladder disease	*ABCB4, ABCG8*
Hereditary fructose intolerance	*ALDOB*
Ichthyosis, leukocyte vacuoles, alopecia and sclerosing cholangitis	*CLDN1*
ICP	*ABCB4, ATP8B1*
Joubert syndrome	*CC2D2A, MKS1, TMEM216, NPHP1*
Lipid storage disorder	*SCP2*
Transient infantile liver failure	*TRMU*
Meckel syndrome	*CC2D2A, MKS1, NPHP3, TMEM216*
Mitochondrial DNA depletion syndrome	*DGUOK, POLG, MPV17*
Neonatal sclerosing cholangitis	*DCDC2*
Nephronophthisis	*INVS, NPHP1, NPHP3, NPHP4*
Niemann–Pick disease	*NPC1, NPC2, SMPD1*
North American Indian childhood cirrhosis	*UTP4*
Peroxisomal disorders	*PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7*
PFIC	*ABCB11, ABCB4, SLC51A, TJP2, ATP8B1, NR1H4, MYO5B*
Renal cysts and diabetes syndrome	*HNF1B*
Renal-hepatic-pancreatic dysplasia 1	*NPHP3*
Sitosterolemia	*ABCG5, ABCG8*
Smith–Lemli–Opitz syndrome	*DHCR7*
Transaldolase deficiency	*TALDO1*
Tyrosinemia type I	*FAH*

indicators of cholestatic liver diseases, and the diagnostic value of ALP and GGT are uncertain. The European Association for the Study of the Liver, which presented guidelines for the management of cholestatic liver diseases in 2009, recommended diagnosis of cholestatic liver diseases using upper limit of normal (ULN) thresholds; in particular they considered an ALP exceeding 1.5×ULN and a GGT exceeding 3×ULN as pathological indicators.[5] In 2015, the Chinese Association of Hepatology supported the same recommendation.[3] However, it should be noted that GGT is not elevated in some specific cholestatic liver diseases, such as some progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC). Thus, in view recent progress and current understanding, the present guideline recommends a diagnosis of cholestasis when the ALP exceeds 1.5×ULN and the GGT exceeds 3×ULN, but that some specific cholestatic liver diseases (FIC 1, 2, 4, 5, and 6, and USP53 deficiency) are characterized by increased conjugated bilirubin or bile acid, but normal or nearly normal GGT. GGT may be elevated in FIC type 3, Alagille syndrome, Citrin deficiency, biliary duct plate dysplasia (Caroli disease, congenital and cystic fibrosis), and Niemann-ck disease (C1/C2 type).

Diagnostic steps

First, the presence of cholestasis should be determined by serological measurements. Second, imaging and endoscopy should be used to distinguish intrahepatic from extrahepatic cholestasis. Finally, the diagnosis should be obtained using a comprehensive analysis of medical history, symptoms, and signs, blood biochemistry, imaging, endoscopy, liver biopsy, and gene detection (Fig. 2).

Difference and connection with jaundice

Cholestasis has some similarities to jaundice, a condition due to the accumulation of all bile components, including bilirubin.[1] However, jaundice is characterized by increased serum bilirubin with yellow skin and sclera. Patients with early-stage cholestasis typically have only elevated ALP and GGT, but no signs of jaundice, which appears only when the serum bilirubin exceeds 34.2 μmol/L. Some diseases, such as hereditary hyperbilirubinemia (Gilbert syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome, and Rotor syndrome) are characterized by disruption of bilirubin metabolism, and affected patients have increased serum bilirubin; however, patients with these diseases have normal levels of the other components of bile, and normal levels of ALP and GGT, and are not considered cholestatic disorders. Jaundice may also occur in some hemolytic diseases, such as hereditary spherocytosis, thalassemia, paroxysmal nocturnal hemoglobinuria, acquired hemolytic anemia, and newborn hemolytic disease, but these patients usually have normal levels of liver enzymes. Therefore, genetic factors and hemolytic diseases should first be excluded when a patient presents with jaundice.

Recommendations

1. We recommend a diagnosis of cholestatic liver diseases when ALP exceeds 1.5×ULN and GGT exceeds 3×ULN (B1), although some familial intrahepatic cholestastic diseases are characterized by elevated conjugated bilirubin and/or bile acids, but normal or nearly normal GGT (B2).
2. We recommend computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), and/or ultrasound imaging as the main approach to distinguish intrahepatic and extrahepatic cholestasis (C1).
3. We recommend endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasonography when a routine imaging examination cannot provide a definite diagnosis, and when extrahepatic biliary obstruction or cholangitis is highly suspected (B1).
4. When the tests are negative for AMA, AMA2, anti-SP100, and anti-GP210, we recommend additional autoantibody tests to exclude systemic or autoimmune diseases for unexplained intrahepatic cholestasis. We recommend a liver biopsy when the cause of cholestasis remains uncertain (C1). We recommend detection of gene variants for patients with suspected hereditary cholestasis (B1).
5. We recommend exclusion of hemolytic disease in patients who present with jaundice, although jaundice may be absent in patients with early-stage cholestatic liver diseases or hereditary hyperbilirubinemia (B1).

Treatment

Treatment principle

The main treatment principle is to etiological treatment and management of symptoms. Etiological treatment, such as removal of stones or surgical resection of tumors to relieve obstruction, is often the most effective treatment. Ursodeoxycholic acid (UDCA) can also be used for PBC and PSC. Cessation in the use of drugs or alcohol is the most important intervention for patients with drug- or alcohol-induced liver diseases. Patients with hepatitis B or C should receive antiviral treatment, those with autoimmune hepatitis should be considered for glucocorticoid and/or immunosuppressant treatment, and those with metabolic-related fatty liver diseases should be encouraged to change their lifestyles, especially diet and exercise.

Drug treatment

The purpose of treatment is to reduce the clinical symptoms and liver damage caused by cholestasis. The main drugs are UDCA, S-adenosyl-L-methionine (SAMe), cholestyramine, obeticholic acid, and fibrates.[17–19]

UDCA

UDCA is used to treat cholestasis because of its hydrophilic, cytoprotective, and non-cytotoxic properties. UDCA functions as a replacement for lipophilic, detergent-like toxic bile acids, and it promotes of secretion of bile and immune regulation. It can successfully manage symptoms in patients with PBC, PSC, intrahepatic cholestasis of pregnancy (ICP), cystic fibrosis, cholestasis after liver transplantation, drug-induced cholestasis, FIC, and Alagille syndrome. The typical dose is 10 to 15 mg/kg/day, but it can be increased 20 to 25 mg/kg/day for cystic fibrosis and 45 mg/kg/ day for Byler's disease and Alagille syndrome.

SAMe

SAMe functions as an *in vivo* as a methyl donor in transmethylation and a precursor of sulfhydryl compounds (cysteine, taurine, glutathione, and coenzyme A). SAMe can be used to treat hepatocellular cholestasis, ICP, and drug-induced

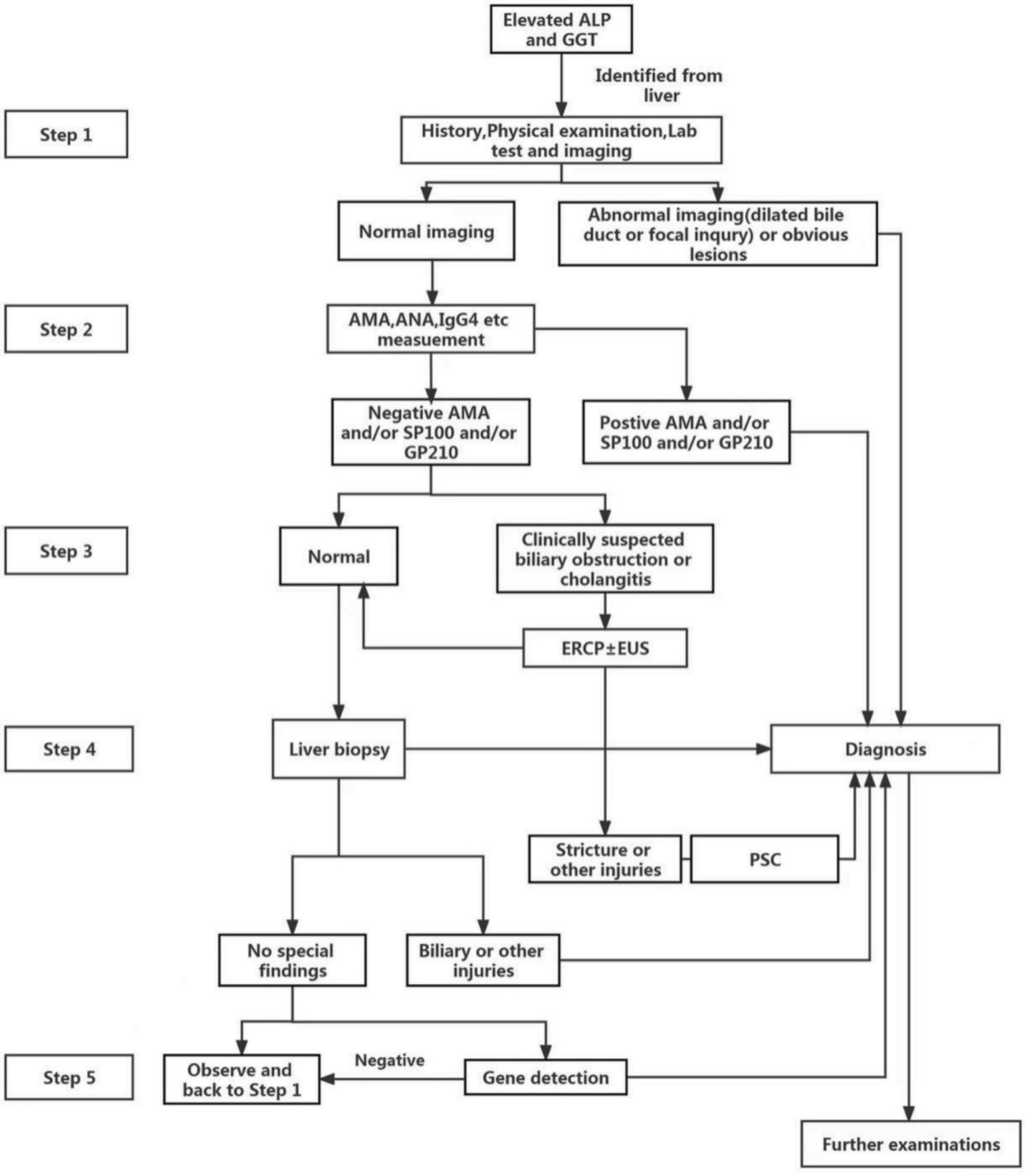

Fig. 2. Recommended procedures for diagnosis of cholestatic liver diseases. ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; GGT, gamma-glutamyl transferase; IgG4, immunoglobulin G4; PSC, primary sclerosing cholangitis.

cholestasis. Intravenous SAMe (0.5 to 1.0 g/day) is recommended for initial treatment, and oral SAMe tablets (1.0 to 2.0 g/day) is recommended for maintenance treatment.

Cholestyramine

Cholestyramine is an anion exchange resin that combines with bile acids in the intestine, and then increases the excretion of bile acids by 3 to 4-fold above the normal level. Oral cholestyramine (12 to 16 g/day, *t.i.d.*) can be taken with water or another drink ~20 minutes before meals and before bed. There should be an interval of at least 4 h between taking cholestyramine, UDCA, or other drugs.

Obeticholic acid

Obeticholic acid is a farnesoid X receptor (FXR) agonist that indirectly inhibits the expression of cytochrome 7A1 (CYP7A1) and the synthesis of bile acid. It is mainly used to treat patients with PBC who had poor responses to UDCA,

and the recommended oral dose is 5 to 10 mg/day. Obeticolic acid should be avoided in advanced and decompensated liver disease.

Fibrates

Fibrates are peroxisome proliferator-activated receptor agonists that reduce bile acid synthesis by inhibiting the expression of a bile acid synthase (CYP7A1). Fibrates can also increase bile excretion by up-regulating the expression of a bile acid transporter and multidrug resistance protein 3 (MDR3). The recommended dose for oral fenofibrate is 160 to 200 mg/day and for oral bezafibrate is 400 mg/day.

Other treatments

After fully weighing the risks and benefits, patients with immune-mediated cholestasis may be considered for glucocorticoid or immunosuppressant treatment. Other treatments, such as ultraviolet irradiation, albumin dialysis, and nasobiliary drainage may also be considered. Patients with cholestatic liver diseases who have poor responses to active treatment and have a risk of death within 6 to 12 months or a MELD score of more than 15 should be evaluated for liver transplantation. Traditional Chinese medicines, such as Yinzhihuang and Kuhuang, may provide some benefit for cholestatic liver diseases, but further investigations are needed. There are many new drugs under development, including FGF19 analogues, nor-UDCA, simtuzumab, infliximab, and fecal transplantation, that may provide new alternatives in the future.

Recommendations

6. We recommend etiological treatment and management of cholestasis as the treatment principle for cholestatic liver diseases. We recommend UDCA (A1), SAMe (B1), cholestyramine (B1), fibrates (B1), and obeticholic acid (B1), alone or in combination, as the main therapeutic drugs.
7. We recommend a glucocorticoid and/or immunosuppressant, ultraviolet irradiation, albumin dialysis, and nasobiliary drainage (as appropriate) for patients who fail to respond to the above treatments (C2).
8. We recommend evaluation of patients for liver transplantation if the active medical treatments for cholestatic liver disease were unsuccessful, or if death within 6 to 12 months seems likely, or if the MELD score is 15 or more (B1).

Hereditary cholestatic liver diseases

Cystic fibrosis-associated liver disease (CFLD)

CFLD is an autosomal recessive disease caused by a mutation of a cystic fibrosis transmembrane conductance regulator gene (*CFTR*) on the long arm of chromosome 7, and it affects 27% of patients with cystic fibrosis. It is characterized by hepatomegaly, abnormal liver biochemistry and ultrasound results, and may be accompanied by congenital cholestasis, hepatic steatosis, and focal or multilobular cirrhosis.[20,21] There is no clear diagnostic standard for CFLD. About one-third of these patients have hepatomegaly, and this can be caused by the CFLD itself or by liver congestion or *cor pulmonale*. If the levels of ALP, ALT, AST, bilirubin, and GGT are more than 1.5×ULN, further examinations should assess liver injury (prothrombin time and albumin) and exclude other causes. Ultrasonography can find signs of CFLD, such as hepatomegaly, abnormal bile duct, or echoless lesions in the liver. An abdominal CT can show the size of a cyst and the amount of remaining normal liver tissue. Because many patients have focal or multilobular fibrosis and cirrhosis, a liver biopsy provides little benefit. No therapy of proven benefit for the long-term prognosis of CFLD exists. There are only limited drugs used for management of CFLD. UDCA (20 to 30 mg/kg/day) can improve liver biochemical indexes, stimulate bile secretion from a damaged bile duct, improve histology (after more than 2 years), and improve nutritional status. Patients generally live long lives, and prognosis depends on the severity of CFLD, and cancerization is seldom. This disease rarely needs surgical treatment, but puncture and aspiration with ultrasound guidance can be used when there are acute symptoms, while fluids regenerate. Liver transplantation[20–22] should be considered when a patient's daily life is severely restricted or the patient has progressed to the terminal stage.

Recommendations

9. We recommend a diagnosis of CFLD based on the presence of cystic fibrosis, hepatomegaly, abnormal biochemical indexes, and the numbers and sizes of cystic lesions from imaging (C2). We recommend UDCA (20 to 30 mg/kg/day) to improve liver biochemical and histological indexes (C1). We recommend liver transplantation when a patient's daily life is severely restricted or when a patient has progressed to the terminal stage (B1).

FIC

FIC is a family of autosomal recessive diseases caused by mutations of the *ATP8B1*, *ABCB11*, *ABCB4*, *TJP2*, *NR1H4*, *MYO5b*, or *USO53* genes. These mutations directly or indirectly lead to abnormal function of bile canaliculus transporters in hepatocytes. The incidence is similar in males and females.[8,13,14] The most common manifestation is intrahepatic cholestatic jaundice with severe pruritus, conditions that can seriously affect quality-of-life. A physical examination shows obvious skin scratches, and cholangiography indicates normal intrahepatic or extrahepatic bile ducts. The disease exists on a spectrum that ranges from benign BRIC to severe PFIC. Bile duct hyperplasia is not common, but liver fibrosis can eventually develop and progress into cirrhosis or liver failure. Some patients may experience recurrent and self-limited severe pruritus and cholestasis, in which an attack lasting weeks or months is followed by no symptoms for months or years, leading to the name BRIC. At the onset of BRIC, the liver histology shows cholestasis in the hepatocytes or cholangiocytes, with no obvious fibrosis; the liver histology and function are normal during the interictal period. It was initially thought that although each individual BRIC attack was serious, progressive liver injury and cirrhosis would not occur. However, there was also evidence that some so-called BRIC cases were recurrent and progressed to end-stage liver disease, and that the word "benign" should not be used.[4] There is also evidence that some patients only had cholestasis during infancy without recurrence, a condition called "transient infantile cholestasis".[23] FIC 1,2,4,5,6 are characterized by low GGT, and usually begins during the neonatal period. The serum bilirubin and bile acid levels are significantly increased, but there is no significant increase of GGT, and the level is often less than 100 U/L.[13,14] ATP8B1

deficiency includes PFIC1, but the pathogenetic mechanism is still unclear. Patients with PFIC1 (also known as Byler's disease) present with cholestasis, and may also have diarrhea, pancreatitis, developmental disorders, hearing loss, hypothyroidism, and other extrahepatic manifestations. Electron microscopy can be used to identify coarse particles of bile in the bile canaliculus (Byler bile). The phenotype of ATP8B1 deficiency appears unrelated to the genotype.[24] ABCB11 defect includes PFIC2 (formerly Byler's syndrome) and BRIC2. The *ABCB11* gene encodes a bile salt export pump (BSEP), the only transporter of bile salt in the bile canaliculus. A defective gene causes bile acid accumulation in hepatocytes, leading to portal inflammation and giant cell hepatitis. Patients with PFIC2 have an increased risk of liver cancer and gallstones.[25,26], and there is a close relationship between the genotype and phenotype. The tight junction protein 2 (TJP2) occurs in the junctions between epithelial cells and endothelial cells and interacts with several other proteins. Patients with TJP2 deficiency, also known as FIC4, have loss of TJP2 protein expression in severe cases (based on immunohistochemistry), often leading to death or the need for liver transplantation. Recent studies found a significant relationship between genotype and phenotype, with a continuous spectrum of clinical severity.[27] The synthesis, secretion, and metabolism of bile acids are finely regulated by nuclear receptor proteins. FXR (encoded by *NR1H4*, also called *FIC5*) is activated by bile acid, functions in feedback regulation, and is the most important protein in bile acid homeostasis. Patients with FIC5 can experience severe neonatal cholestasis, early onset of non-vitamin K-dependent coagulation disorders, rapid development to end-stage liver disease, and often need early liver transplantation for survival. MYO5b functions in intracellular transport and has an important role in the formation of microvilli on the surfaces of intestinal epithelial cells and hepatocytes in the bile canaliculus. There is a close relationship between genotype and phenotype in patients with defective *MYO5b* genes. In particular, complete loss of the gene causes microvilli inclusion body disease; a partial loss of this gene causes wrong location of BSEP through a special toxic negative effect, and is also called FIC 6.[28] *USP53* encodes ubiquitin specific peptidase 53, a protein that interacts with TJP2. USP53 deficiency leads to cholestasis, and may be accompanied by hearing impairment or hearing loss in severe cases. Electron microscopy shows an elongation of the tight junction structure between hepatocytes.[29] FIC 3 is caused by a mutation of the *ABCB4* gene, which encodes MDR3, a phosphatidylcholine translocation enzyme in the canaliculi bile that transfers phosphatidylcholine from hepatocytes to the canaliculi bile. In contrast to other FICs, patients with FIC 3 usually have significantly elevated GGT. Histopathology shows diffuse bile duct hyperplasia with portal inflammation and fibrosis or cirrhosis. FIC3 may be associated with intrahepatic cholelithiasis. A recent study reported that a novel type of PFIC could be induced by a homozygous R148W mutation of the *SEMA7A* gene.[30] At present, there no curative drugs for FIC, but UDCA and bile acid blocking agents are generally recommended. A dietary supplement of medium-chain triglycerides and fat-soluble vitamins are also generally recommended. UDCA may improve biochemical indexes and prolong survival of some patients with mild FIC3. Rifampicin can be used to relieve itching. Liver transplantation is recommended for patients with advanced FIC.

Recommendation

10. We recommend a diagnosis of FIC (a group of autosomal recessive hereditary diseases) when the main symptoms are pruritus and jaundice, manifesting in varying degrees (B1). We recommend genetic analysis for detection as the gold standard for diagnosis of FIC (B1). We recommend a diagnosis of FIC 1, 2, 4, 5, or 6 when the GGT is normal or nearly normal, and there is severe pruritus and different extrahepatic manifestations; we recommend a diagnosis of FIC3 when the GGT is elevated. Although there are no curative treatments for FIC (C2), we recommend UDCA to improve liver function in some patients with FIC3 (C2). We recommend a bile shunt to improve some liver biochemical indexes for suitable patients with FIC (C2). We recommend assessment of the suitability for liver transplantation in patients with advanced disease (B1).

Alagille syndrome

Alagille syndrome has an autosomal dominant inheritance and is caused by mutations of the *JAG1* gene (94%) or *NOTCH2* gene (2.5%), both of which function in the Notch signaling pathway. The incidence of this disease is higher in children and adolescents. The disease is characterized by elevated GGT and involvement of various extrahepatic organs, including the cardiovascular system, bones, kidneys, eyes, and face. The estimated incidence is 1/30,000 to 1/70,000. There is no significant relationship between genotype and phenotype in this disease.[31,32] The most important feature of Alagille disease is a decrease or total lack of the interlobular bile ducts as indicated by liver biopsy, but some patients lack this manifestation or have bile ductule or interlobular hyperplasia in the early stage. The diagnostic criteria are: (1) reduced or absent interlobular bile ducts based on histology, with at least three characteristic clinical features (chronic cholestasis, heart murmur, butterfly vertebrae, eye abnormalities, kidney abnormalities, and characteristic facial features); (2) at least four of the above clinical features in the absence of hepatic histologic interlobular bile duct decrease or lack of evidence; (3) at least two of the above clinical features with clear family history of the disease, or identification of the gene mutation. There are no satisfactory treatments for Alagille syndrome, but symptoms can be managed using UDCA, drugs blocking bile acid enterohepatic circulation, and a dietary supplement of fat-soluble vitamins. The US Federal Drug Administration recently approved oral miracidia chloride (Livmarli) for treatment of cholestatic pruritus in patients with Alagille syndrome who are aged 1 year and older.[33] Ileal bile acid transporter (IBAT) inhibitors have also been approved for PFIC1 and 2 in Europe. The drug inhibits IBAT and blocks the intestinal hepatic circulation of bile acids.

Recommendation

11. We recommend considering Alagille syndrome when children or adolescents present with cholestasis. We recommend confirmation of mutations in *JAG1* or *NOTCH2*, which lead to a decrease of interlobular bile ducts, cholestasis with pruritus, and multiple system damage (especially disorders of the cardiovascular system, eyes, and bones, and facial abnormalities) to confirm the diagnosis. We recommend symptomatic and supportive management as the main treatments (C2).

ICP

Genetic, hormonal, and environmental factors can contribute to the pathogenesis of ICP. Affected patients experience increased flow of bile acid from the mother to the fetus,

and increased bile acid in the amniotic fluid, umbilical cord blood, and meconium.[34,35] The incidence of ICP is higher in twin pregnancies. Use of high-dose contraceptives and progesterone might induce ICP, suggesting that hormones function in the pathogenesis. An increased incidence among family members and differences among races suggest a role of genetic factors. Recent genetic studies identified mutations of canaliculi bile transporter genes (*ABCB4*, *ABCB11*, *ABCC2*, and *ATP8B1*) and *NR1H4* in some ICP patients. During pregnancy, when hormones and other substrates exceed the transport capacity of the bile canaliculi transporter, a mild dysfunction of bile transportation can apparently induce cholestasis. Therefore, if cholestasis with elevated GGT level persists after delivery, an *ABCB4* mutation should be considered.

Diagnosis: These patients experience cholestasis during late pregnancy, with rapid and spontaneous recovery after delivery. The three main characteristics in pregnant women are: (1) severe pruritus, typically during the second or third trimester; (2) increased levels of ALT, fasting bile acid, and glycocholic acid; (3) spontaneous remission of symptoms and signs after delivery, typically within 4 to 6 weeks.[34–36] Pruritus can cause significant discomfort and distress in pregnant women, and ICP increases the risk of premature delivery and sudden fetal death. Patients usually have good prognoses, but if the jaundice is persistent then massive hemorrhage may occur during labor due to a deficiency of vitamin K-dependent coagulation factors II, VII, and X. The risks of fetal distress, premature delivery, and stillbirth are relatively high. ICP can be diagnosed according to clinical manifestations of elevated serum glycocholic acid (≥10.75 μmol/L) and total bile acid (≥10 μmol/L). A diagnosis can be confirmed when these liver biochemical indexes return to normal after delivery. ICP patients who have the *ABCB4* mutation have an elevated GGT, but are otherwise normal. About 10 to 15% of these patients have only a moderate increase of serum conjugated bilirubin and mild jaundice. ICP diagnosis requires the exclusion of other diseases, and the final diagnosis is made by postpartum recovery. A liver biopsy is usually not necessary.

In addition to ICP, preeclampsia, Hemolysis, Elevated Liver enzymes, and Low Platelet count (HELLP) syndrome, and acute fatty liver of pregnancy.[4] should be considered when abnormal biochemical parameters occur during pregnancy. Preeclampsia, the rapid elevation of blood pressure during pregnancy, can lead to organ damage. Organ damage is multifaceted and kidney damage during preeclampsia manifests as increased urine protein. Preeclampsia can also cause abnormal liver biochemical parameters, thrombocytopenia, and hemolysis.

HELLP syndrome is characterized by hemolysis, elevated liver enzymes, and thrombocytopenia ($<50\times10^9$ platelets/L), and is a serious complication from hypertension disorders during pregnancy. HELLP mostly occurs during the prenatal period, and these patients have bilirubin below 85 μmol/L, liver necrosis, hemangioma, and evidence of hepatic rupture based on imaging. Acute fatty liver of pregnancy is a kind of acute hepatic steatosis that can occur during late pregnancy, mostly in young primiparas. It usually occurs during the last three months of pregnancy or early postpartum. The onset is sudden and the prognosis is poor without aggressive and rapid treatment. The clinical manifestations are similar to those of acute severe hepatitis, and it is characterized by acute liver failure, often accompanied by renal failure. Liver steatosis can be identified by imaging.

Treatment: UDCA can be used as a first-line drug for treatment of ICP. This treatment can reduce pruritus and improve liver biochemical parameters in 67% to 80% of patients.[34–36] The effect of SAMe is inferior to UDCA, but it may provide additional benefit. If pruritus does not decrease after several days of standard UDCA treatment, SAMe or rifampicin should be considered. There is also a need for increased fetal monitoring during treatment, and birth induction should be considered to reduce perinatal mortality. In particular, birth induction should be considered after 35 weeks of pregnancy if there is evidence of disease progression, no inhibition of uterine contraction, abnormal fetal movement, fetal heart rate variability or no response to a stress test, or contamination of the amniotic fluid with meconium.[4]

Recommendations

12. We recommend the following diagnostic criteria for IPC: (1) pruritus during pregnancy; (2) increased levels of serum ALT, fasting bile acid, and glycocholic acid; and (3) exclusion of other causes of liver dysfunction or pruritus. Diagnosis is confirmed if the liver biochemical parameters return to normal after delivery (B2).
13. We recommend UDCA and SAMe for symptomatic patients who have cholestasis during the second or third trimesters of pregnancy to relieve pruritus and improve liver biochemistry (B1). Other than supportive care, we are unable to recommend a treatment to protect the fetus and reduce fetal complications (C2).

Extrahepatic manifestations and management

Pruritus

Pruritus is the sensation of skin irritation in the absence of primary skin damage that leads to excessive scratching. It differs from the senses of touch and pain in nature, persistence, and location. The existence of pruritus itself has no prognostic value and does not reflect disease severity. The pathogenesis of pruritus is not clear, but it may be related to increased activity of an autocrine movement factor (autotaxin) and the formation of lysophosphatidic acid.[37,38] In addition, bile acid salt, endogenous opioid peptide, 5-hydroxytryptamine (5-HT), hyperactivity of sensory neurons, estrogen and progesterone, hepato-intestinal pruritus changes, and genetic factors may contribute to pruritis. The relationship between pruritus and cholestasis suggests that the substances causing pruritus are normally excreted in bile. The resolution of pruritus during hepatocyte failure indicates that these substances are produced by hepatocytes, but serum bile acid remains very high in this situation.[4] Pruritus can be divided into three categories based on severity.[38,39] First, a visual analog scale classifies the severity of pruritus as scratch, plaque, nodule, and/or scar according to the characteristics of skin scratches, and the degrade is 0–3 according to the light, moderate, and severe degree, and the total score ranges from 0 to 10. Second, an Itch Severity Scale considers the frequency of itching, sleep, mood, sexual desire, sexual function, and uses a Likert scale to assess the intensity of pruritus and the total surface area of the body that is affected; the total score ranges from 0 to 21, with 21 indicating the most severe itching. Third, a semiquantitative evaluation of pruritus can be performed by recording the frequency of pruritus, with division into four stages: occasional, daily intermittent without clinical symptoms, daily intermittent with clinical symptoms, and persistent.

Several drugs can be used alone or in combination to reduce pruritus, including cholestyramine, antihistamines, pregnane X receptor agonists, opioid receptor antagonists, and 5-HT receptor antagonists. Oral cholestyramine is a first-line treatment for cholestatic pruritus.[5,40], with a recommended dose of 4 g/day and a maximum dose of 16

g/day. When administered with other drugs (especially UDCA), cholestyramine should be taken at intervals of 4 to 6 h to prevent interactions. Rifampicin, a pregnane X receptor agonist, is a second-line treatment for pruritus. Rifampicin down-regulates ATX and reduces the formation of lysophosphatidic acid, especially in patients who are intolerant or nonresponsive to cholestyramine.[41] The recommended oral dose is 150 mg/day initially, and this dose can be maintained if it is effective. If necessary, the dose can be increased to 600 mg/day every other week. When rifampicin is used to treat methadone addicts, it can cause opioid withdrawal reactions. Therefore, rifampicin might relieve cholestatic pruritus due to its opioid antagonistic effects. Red urine, toxic kidney damage, liver toxicity, and hemolysis (rarely) may occur after use of rifampicin. Due to the potential of rifampicin to cause liver damage, it is necessary to closely monitor biochemical parameters during treatment. Oral naltrexone, an opioid receptor antagonist, can be given at a dose of 25 to 50 mg/day as a third-line treatment for pruritus. Some patients have nausea, vomiting, mild pain, and other side effects due to this treatment. The metabolites of naltrexone can accumulate in patients with decompensated liver disease, so caution should be used when treating these patients. Treatment should begin with a low dose, and the dose can then be gradually increased to avoid withdrawal effects, similar to the recommendations for anesthetics.[40]

If the above drugs are ineffective, sertraline (a selective 5-HT reuptake inhibitor) can be used as a fourth-line treatment. The initial dose of 50 mg/day can be increased to 100 mg/day after a few weeks. In recent years, ultraviolet radiation, albumin dialysis, and nasobiliary drainage have been used to manage cholestatic pruritus, and favorable curative effects were reported. Liver transplantation should be considered for patients with intractable pruritus who have poor responses to drugs or other approaches.

Recommendations

14. We recommend cholestyramine as a first-line drug for treatment of pruritis, with an initial dose of 4 g/day and a maximum dose of 16 g/day. We recommend doses taken at intervals of 4 to 6 h when using other drugs (especially UDCA) so as not to affect their absorption (B2).
15. We recommend oral rifampicin as a second-line drug for treatment of pruritus, with an initial dose of 150 mg/day, and continuation at this dose if effective. If necessary, the dose can be increased to 300 mg/day every other week. We recommend close monitoring of liver biochemical parameters should during treatment (C2).
16. We recommend oral naltrexone, an opioid receptor antagonist, as a third-line drug for treatment of pruritus, beginning with a dose of 25 mg/day, and gradually increasing the dose to 50 mg/day to prevent withdrawal effects, similar to anesthetics (C1).
17. We recommend sertraline, a selective 5-HT reuptake inhibitor, as a fourth-line drug for treatment of pruritus, with an initial dose of 50 mg/day, and increasing the dose to 100 mg/day after a few weeks if necessary (C2).
18. We recommend ultraviolet irradiation, albumin dialysis, or nasobiliary drainage if the other treatments for pruritus are ineffective (C2). We recommend consideration of liver transplantation in patients with severe pruritus who have poor responses to drugs and other approaches (C2).

Fatigue

Patients with cholestasis, especially those with PBC, often experience fatigue, and fatigue occurs in 70 to 80% of patients with chronic cholestasis.[4] Fatigue is a complex symptom that includes persistent feelings of exhaustion, loss of normal working ability, and decline of psychological and physiological functions. Because it is a non-specific symptom, the Fatigue Impact Score or the Primary Biliary Cirrhosis 40 scale (PBC-40) may be used to assess symptoms and severity.[42,43] The pathogenesis of fatigue is still not clear, and there is no effective treatment. Anemia, diabetes, hypothyroidism, renal and adrenal insufficiency, and depression should be excluded before treatment. At present, the possible therapeutic methods and drugs are selective 5-HT3 receptor antagonists such as ondansetron, opioid receptor antagonists, and the central nervous stimulant modafinil. The initial dose of modafinil is 100 mg/day, and it may be gradually increased to 200 mg/day according to tolerance and responsiveness, but further studies of its efficacy are needed. Although UDCA is an effective treatment for PBC, it apparently has no significant effect on the accompanying symptoms of fatigue. Even 1 year after liver transplantation, fatigue may remain a persistent symptom for these patients, although the degree of fatigue may be less. A healthy lifestyle, including adequate sleep, regular exercise, abstinence from alcohol, and avoidance of coffee at night are beneficial. Antidepressants may partly reduce the fatigue of patients with depression.

Xanthoma

Xanthomas are common in patients with chronic cholestasis. This condition is characterized by flat or slightly raised fat deposits on the skin surface that are yellow and soft and often occur around the eyes. They may also occur in the palmar fold, breast, neck, chest, and back. Their occurrence is related to an elevated level of blood lipids, with serum cholesterol usually more than 4.5 g/L. When jaundice subsides or liver failure occurs, the level of cholesterol drops and these manifestations might disappear. Xanthomas require no special treatment.

Dyslipidemia

Cholestasis inhibits the metabolism of cholesterol due to the increase of bile acid, and this often leads to lipid metabolic disorder. Thus, patients with cholestasis often have elevated levels of cholesterol and triglycerides, although there is no evidence that this increases their risk of atherosclerosis. Statins and fibrates are safe treatments for patients who have cholestatic liver disease with lipid metabolic disorders.[44] Cholestyramine can also reduce the level of blood lipids.

Steatorrhea

Steatorrhea is characterized by large stools that are soft, excessively oily, gray, and with a peculiar smell. This may occur in patients with cholestasis because the intestinal tract lacks sufficient bile salt, leading to impaired digestion and absorption of fats and fat-soluble vitamins (A, D, E, and K). Thus, steatorrhea is positively correlated to the degree of jaundice.

Recommendations

19. We recommend exclusion of anemia, diabetes melli-

tus, hypothyroidism, renal and adrenal insufficiency, and depression when a patient presents with cholestatic fatigue. We recommend adequate sleep, regular exercise, and abstaining from alcohol and coffee for management of fatigue (C2). We recommend selective 5-HT3 receptor antagonists, such as ondansetron, an opioid receptor antagonist, or the central nervous stimulant modafinil as drug treatments (C2). We recommend antidepressants to assist in reducing fatigue in patients with depression. We do not recommend liver transplantation for management of fatigue (C2).

20. We recommend no special treatment for xanthoma (B2). We recommend statins and fibrates for patients with dyslipidemia, and cholestyramine to help resolve dyslipidemia (B2).

Hepatic osteodystrophy

Bone complications may occur in patients with chronic liver disease due to osteoporosis and osteomalacia, and these can manifest as bone pain and fracture. Osteoporosis is characterized by bone matrix or mineral loss and osteomalacia as osteoid mineralization defects. Dual energy X-ray absorptiometry (DEXA) is used to diagnose osteoporosis based on bone mineral density (BMD).[4,5,45] According to the diagnostic criteria of the World Health Organization, BMD measured by DEXA is defined by T-score, which indicates the number of standard deviations above or below the mean (normal: T-score ≥ −1.0; osteopenia: −2.5 < T-score < −1.0; osteoporosis: T-score ≤ −2.5). The treatments for osteoporosis include following a healthy diet and lifestyle with exercise, use of calcium and vitamin D supplements, and drug interventions. The Chinese Nutrition Association recommends 800 mg calcium per day for adults and a 1,000 mg calcium per day for postmenopausal women and the elderly. The recommended dose of vitamin D for adults is 200 IU/day, and the dose for the elderly is 400 to 800 IU/day, especially when there is a lack of exposure to sunshine and/or impaired intake or absorption. The dose of vitamin D should be 800 to 1,200 IU/day for treatment of osteoporosis. Epidemiological data support the use of calcium supplements (1,000 to 1,200 mg/day) and vitamin D (400 to 800 IU/day) for reducing or reversing the rate of bone loss. Hormone replacement therapy is effective in postmenopausal women. To decrease the risk of hepatocellular carcinoma, males should avoid testosterone. Research supports the use of diphosphonates (alendronate at 70 mg/week, ibandronate at 150 mg/month, or other similar drugs) to treat and prevent osteoporosis. Annual BMD measurements should be performed during follow-up to assess treatment efficacy.

Deficiency of fat-soluble vitamins

Cholestasis leads to disruption in the secretion of bile from the liver to the small intestine, and this decreases bile salt in the intestine and can cause a deficiency of fat-soluble vitamins and steatorrhea. Therefore, fat-soluble vitamins should be administered as dietary supplements.[45] If the prothrombin time(PT) is prolonged, intramuscular vitamin K1 (10 mg/day) can be given until it returns to normal. Oral vitamin A at a dose of 25,000 to 50,000 IU/day can be used to treat night blindness. Vitamin E deficiency is rare, but children with cerebellar ataxia, posterior funicular dysfunction, peripheral neuropathy and retinal degeneration, might benefit from oral supplements. Measuring the blood levels of fat-soluble vitamins can help guide their administration, but these measurements are not common.

Recommendations

21. We recommend calcium and vitamin D supplements for prevention of osteoporosis. For calcium, adults should take 800 mg/day and postmenopausal women and the elderly should take 1,000 mg/day. For vitamin D, adults should take 200 IU/day, and the elderly should take 400 to 800 IU/day (C1). We recommend diphosphonates (alendronate, 70 mg/week; ibandronate, 150 mg/month; and others) for treatment and prevention of osteoporosis (C2). We recommend annual BMD measurements during the treatment and follow-up of patients with osteoporosis (C2).
22. We recommend monitoring and supplementation of fat-soluble vitamins. We recommend intramuscular vitamin K1 (10 mg/day) for patients with prolonged PT (B1) and oral vitamin A (25,000 to 50,000 IU/day) for night blindness due to vitamin A deficiency (C1). Although vitamin E deficiency is rare, if present we recommend an oral dose of 10 to 100 mg/day (C2).

Problems to be Solved

Although there has been significant progress in the diagnosis and treatment of cholestatic liver diseases during recent years, many problems and challenges remain. In terms of basic research, there is a need for more studies that examine the mechanisms of these diseases (especially at the molecular level), the effect of heritable risk factors and alterations of different bile acid transporters on the occurrence and development of disease, and the influence of bile acid composition on the liver and the whole body. PBC and PSC are the major cholestatic liver diseases, and their etiologies are not yet fully clear. UDCA is the main treatment for PBC, but some patients have poor responses to this drug. In addition, there is no effective drug for PSC. The epidemiology, diagnostic markers, and diagnostic criteria for cholestatic liver diseases require further studies for verification. There is also an urgent need to identify additional drugs and treatments for the different cholestatic liver diseases.

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Conflict of interest

LL has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2013. HY has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. YH has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2013. LW and JJ have been an executive associate editor of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

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