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Guideline

Guidelines on the Diagnosis and Management of Primary Biliary Cholangitis (2021)

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Abstract

In 2015, the Chinese Society of Hepatology and the Chinese Society of Gastroenterology published a consensus on primary biliary cholangitis (PBC). In the past years, numerous clinical studies have been published in the field of PBC. To guide the clinical diagnosis and management of PBC patients, the Chinese Society of Hepatology invited a panel of experts to assess the new clinical evidence and formulate the current guidelines.

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Introduction

PBC, formerly known as primary biliary cirrhosis, is an autoimmune intrahepatic cholestatic disease. The etiology and pathogenesis have not been fully elucidated, but may involve complex interactions between genetic predisposition and environmental triggers that lead to immune-mediated injury of biliary epithelial cells.[1] PBC predominantly affects middle-aged women. Fatigue and pruritus are the most common symptoms. Laboratory characteristics include the elevation of serum alkaline phosphatase (ALP) and glutamyl transpeptidase (GGT), positive antimitochondrial antibodies (AMA), and increased immunoglobulin M (IgM). Histologic evidence includes non-suppurative destructive interlobular cholangitis. Ursodeoxycholic acids (UDCA) are the treatment of choice for PBC.[2]

In 2015, the Chinese Society of Hepatology and the Chinese Society of Gastroenterology published a consensus on the diagnosis and management of PBC. In the past years, additional clinical evidence has been reported in the field of PBC. To guide the clinical diagnosis and management of patients with PBC, the Chinese Society of Hepatology invited a panel of experts to assess the new clinical evidence and formulate the current guidelines. The recommendations follow the Grading of Recommendations Assessment Development and Evaluation (GRADE) system (Table 1).

Epidemiology

All races are affected, with a variable frequency worldwide. A recent meta-analysis reported an increasing incidence and prevalence of PBC, with North America being the highest, followed by Europe. Annual incidence and prevalence of PBC were estimated to be 0.23–5.31/100,000 and 1.91–40.2/100,000, respectively.[3] Population-based epidemiological data on PBC are lacking in China. A recent meta-analysis estimated the prevalence of PBC in China to be 20.5/100,000, the second-highest in the Asia-Pacific region after Japan.[4] Environmental factors, including exposure to toxins or chemicals,[5] poor environmental hygiene in child-

Keywords: Primary biliary cholangitis; Guidance; Diagnosis; Management; Chinese.

Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibodies; ANAs, Antinuclear antibodies; AST, aspartate aminotransferase; GGT, glutamyl transpeptidase; GRADE, Grading of Recommendations Assessment Development and Evaluation; IgM, increased immunoglobulin M; OCA, obeticholic acid; PBC, primary biliary cholangitis; RA, rheumatoid arthritis; RCTs, randomized controlled trials; TBIL, total bilirubin; UDCA, ursodeoxycholic acids; ULN, upper limit of normal.

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Table 1. Grading evidence and recommendations

Grade of evidence	
A	High quality: Further research is very unlikely to change our confidence in the estimate of effect.
B	Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
C	Low or very low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Grade of recommendation	
1	Strong recommendation: Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes and cost.
2	Weaker recommendation: Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

hood,[6] urinary infections,[7] and smoking[8] are potential risk factors for the development of PBC.

Natural history

In the pre-UDCA era, the natural history of PBC was divided into four phases.[9] (1) The preclinical stage included only AMA positivity. (2) The asymptomatic stage included elevated liver enzymes without clinical symptoms. (3) The symptomatic stage included symptoms of fatigue or pruritus. (4) The liver insufficiency stage included progressive jaundice, hepatic encephalopathy, and liver failure. Early diagnosis and UDCA treatment have significantly altered the natural history of PBC. Patients with biochemical responses to UDCA have a survival similar to the matched control population.[10] However, transplant-free survival of PBC patients with a suboptimal response to UDCA is significantly lower than that of healthy controls, although it is still higher than that of untreated PBC patients.[11]

Clinical manifestations

The early stages of PBC are generally asymptomatic.[12] About one-third of patients remain asymptomatic for many years, and some gradually develop symptoms including fatigue and pruritus.[13] Most untreated patients and patients with poor responses to treatment develop cholestasis and cirrhosis-related complications. PBC patients often have concomitant extrahepatic autoimmune (EHA) diseases, including Sjögren's syndrome (3.5–73%), systemic sclerosis (1.4–12.3%), rheumatoid arthritis (RA), and autoimmune thyroid disease.[14] A recent study found concomitant EHA diseases did not compromise the long-term outcomes of PBC patients.[15]

Laboratory, imaging, and histology studies

Liver biochemical tests

Most PBC patients have significantly increased ALP and/or GGT, mildly to moderately elevated aminotransferase (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) and increased immunoglobulins (mainly IgM). As the disease progresses, serum bilirubin (mainly direct bilirubin) gradually increases and serum albumin gradually decreases.

Autoantibodies

AMA

Serum AMA is a specific marker for the diagnosis of PBC, especially the AMA-M2 subtype. There are three common methods for detecting AMA, indirect immunofluorescence (IIF), immunoblotting, and enzyme-linked immunosorbent assay. IIF is the preferred method for routine screening for AMA. However, each method has advantages and disadvantages.[16] The sensitivity and specificity of AMA for the diagnosis of PBC are 90% and 95%.[17] However, positive AMA can also be found in various intrahepatic and extrahepatic diseases, such as autoimmune hepatitis (AIH), chronic hepatitis C, acute liver failure caused by various etiologies, systemic lupus erythematosus, Sjögren's syndrome, and chronic bacterial infection, or even healthy people.[18]

Antinuclear antibodies (ANAs)

ANAs are also important diagnostic markers for PBC, and are present in approximately 50% of PBC patients. ANAs have unique immunofluorescence patterns such as nuclear dots or a nuclear ring-like pattern. PBC-specific nuclear antigens include a 210 kDa glycoprotein of the nuclear pore membrane (gp210), nuclear body speckled 100 kDa (sp100), and nucleoporin p62. A meta-analysis found that anti-gp210 and anti-sp100 had low sensitivity (23% and 25%, respectively), but high specificity (99% and 97%, respectively) for AMA-negative PBC patients.[19] Furthermore, the simultaneous positivity of both anti-sp100 and anti-gp210 had a 100% positive predictive value for PBC in a large study.[20] Anti-sp100 and anti-gp210 positivity was also reported to be associated with more advanced disease and worse outcomes.[21]

Imaging examinations

As biliary lesions are restricted to small intrahepatic ducts, imaging findings are usually normal in PBC patients. Imaging examinations are mainly used to exclude biliary obstruction and tumors. Ultrasonography is recommended as an initial diagnostic step for patients with cholestasis. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) are indicated for patients who are both AMA and PBC-specific ANAs negative, but with a rapid elevation of serum bilirubin, and suspicion of bile duct stricture or dilation on ultrasonography.

Transient elastography (TE) or magnetic resonance elastography is a reliable noninvasive means for assessing fibrosis and can be used to evaluate PBC staging.[22] A recent large international, retrospective study found that liver stiffness measurement by TE was an independent predictor of PBC with poor outcomes and could be a useful surrogate endpoint in PBC trials.[23]

Table 2. Histologic staging of PBC by the Ludwig system

Stage	Histological features
Stage I	Portal inflammation with bile duct damage with or without florid duct lesion
Stage II	Periportal inflammation, ductular reaction (periportal fibrosis often present)
Stage III	Bridging fibrosis (ductopenia usually present)
Stage IV	Biliary cirrhosis with regenerative nodules

PBC, primary biliary cholangitis.

Histological features

The histological feature of PBC is chronic, non-suppurative cholangitis that mainly affects interlobular and septal bile ducts. Lymphocyte infiltration and granuloma formation around the bile duct, known as florid duct lesion, is characteristic of PBC.[24] Duct paucity or ductopenia is usually defined as less than 50% of portal tracts containing bile ducts. Histologic lesions are classically divided into four stages by Ludwig's system (Table 2).

Diagnosis and differential diagnosis

Diagnosis

The diagnosis of PBC is based on a comprehensive assessment of clinical features, laboratory tests, imaging examinations, and histological findings. The diagnosis of PBC is based on the presence of two of the three criteria: (1) biochemical evidence of cholestasis (ALP and GGT elevation), and exclusion of extrahepatic cholestasis by imaging examinations; (2) presence of AMA/AMA-M2 or other PBC-specific autoantibodies (such as anti-spl00 or anti-gp210); and (3) histologic evidence of non-suppurative destructive cholangitis and destruction of the interlobular bile ducts.

Differential diagnosis

The differential diagnosis of PBC includes extrahepatic or intrahepatic cholestasis with various etiologies. Extrahepatic or intrahepatic biliary obstruction by stones, inflammatory stenosis, or tumors can be diagnosed by ultrasonography, CT, MRI, and other imaging modalities. The differential diagnosis of intrahepatic cholestasis requires detailed history taking and careful physical examination. If laboratory and imaging examinations are not diagnostic, then a liver biopsy is necessary. Disorders involving hepatocytes (such as alcoholic liver disease, and drug-induced liver injury), bile ducts (such as small-duct primary sclerosing cholangitis, IgG4-related cholangitis, or idiopathic adulthood ductopenia), intrahepatic vessels (such as sinusoidal obstruction syndrome, or Budd-Chiari syndrome), storage or infiltrative liver diseases (such as sarcoidosis, Langerhans cell histiocytosis, or hepatic amyloidosis) are all needed to distinguish PBC.

Recommendations

1. In patients with unexplained elevation of ALP and/or GGT, testing for AMA and/or AMA-M2 is recommended, and anti-sp100 or anti-gp210 should be tested, if negative for AMA or AMA-M2. (A1)
2. Liver biopsy is not required for the diagnosis of PBC in patients with cholestasis and PBC-specific autoantibodies (AMA, AMA-M2, anti-sp100, and anti-gp210), but histologic staging can provide prognostic information. (A1)
3. Liver biopsy is necessary for (1) patients with intrahepatic cholestasis but negative for PBC-specific autoantibodies; (2) PBC patients with unexplained elevation of transaminases AST or ALT ≥ 5 times the upper limit of normal (ULN), or with features of other liver diseases (such as AIH, nonalcoholic steatohepatitis or DILI); and (3) PBC patients with suboptimal biochemical response to UDCA. (C1)
4. The diagnosis of PBC is based on at least two of the following: (1) Elevation of ALP and GGT with the exclusion of extrahepatic cholestasis; (2) Presence of AMA/AMA-M2, or other PBC-specific autoantibodies such as anti-sp100 and anti-gp210 if AMA/AMA-M2 is negative; (3) Histological evidence of non-suppurative destructive cholangitis and interlobular bile ducts destruction. (A1)

Treatment of PBC

First-line therapy

UDCA is the first-line therapy for PBC. Several randomized controlled trials (RCTs) have demonstrated that UDCA (13–15 mg/kg/d) significantly improved liver biochemistry, delayed the progression of the disease to death, and reduced the need for transplantation.[11,25] A low dose of UDCA (≤10 mg/kg/d) had inadequate efficacy. High-dose UDCA (28–30 mg/kg/d) did not have more benefits and was associated with serious adverse reactions, as demonstrated in primary sclerosing cholangitis (PSC) patients.[26] UDCA at a dose of 13–15 mg/kg/d is recommended by all the major practice guidelines of PBC. UDCA should be continued indefinitely and can be given one, two, or three times per day, as per the patient's choice. In addition, it is necessary to monitor the change in body weight and adjust the UDCA dose accordingly. Cholestyramine may interfere with the absorption of UDCA, therefore, they should be taken 4-6 hours apart. UDCA is well tolerated. The side effects are limited to diarrhea, abdominal distension, weight gain, and aggravation of pruritus, which usually does not need UDCA withdrawal. Very few patients are intolerant or allergic to UDCA.

Second-line therapy

Patients with suboptimal response to UDCA are at risk of disease progression, so a second-line treatment should be considered. Biochemical response to UDCA is usually assessed after 1 year of treatment in most criteria, but some studies have shown that the biochemical response at 6 months has similar predictability to that at 12 months.[27] Several biochemical response criteria have been established for PBC (Table 3).[28] Paris I[29] and Paris II[30] criteria are widely used for patients with advanced PBC (stage III-IV) and early PBC (stage I-II), respectively. In the clinical trial of new agents for PBC, ALP ≥1.67 ULN is an important criterion for patient enrollment.[31,32] GLOBE score and UK-PBC score are also suitable for assessing response to treatment.[33] For patients with an insufficient response to UDCA, adding a second-line therapy such as obeticholic acid, fibrates, and budesonide can be considered.

Obeticholic acid (OCA): OCA is the only second-line therapy approved by the US Food and Drug Administration

Table 3. Criteria for evaluation of response to UDCA therapy in patients with PBC

Response criteria	Time (months)	Definition of response
Barcelona	12	>40% decrease or normalization of ALP
Mayo	6	ALP < 2 × ULN
Paris I	12	ALP ≤ 3.0 × ULN and AST ≤ 2.0 × ULN and normalization of bilirubin
Paris II	12	ALP and AST ≤ 1.5 × ULN and normalization of bilirubin
Toronto	24	ALP < 1.67 × ULN
Rotterdam	12	Normalization of abnormal bilirubin and/or albumin
UK-PBC score	12	Baseline albumin and platelet count, ALP, bilirubin and AST (or ALT) at 12 months
GLOBE score	12	Age at diagnosis. ALP, bilirubin, albumin and platelet count at 12 month

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN upper limit of normal; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acids.

(FDA). As a semisynthetic hydrophobic bile acid analog that is highly selective for farnesol X receptor (FXR), OCA inhibits the expression of genes for rate-limiting enzymes for bile acid synthesis, thereby regulating the metabolism of bile acids and affecting inflammation, and liver fibrosis.[34] Several phase II and phase III clinical trials have demonstrated that adding or switching to OCA (10 mg or 5–10 mg dose titration) significantly improved serum ALP and total bilirubin (TBIL) levels in patients with a suboptimal biochemical response or intolerant to UDCA.[31] An open-label extension study[35] and a randomized, double-blind phase III clinical trial also reported that OCA significantly reduced ALP, TBIL, direct bilirubin, GLOBE score, and UK-PBC score in PBC patients with UDCA intolerance or poor response.[36] A subanalysis of data from a phase III clinical trial found 3 years of OCA treatment in PBC patients (n=17) was associated with improvement or stabilization of fibrosis and ductular injury.[37]

OCA is generally well tolerated, with pruritus (77%) and fatigue (33%) being the most common side effects.[35] The incidence and severity of pruritus were dose-dependent.[38] OCA treatment results in a reduction of high-density cholesterol, but whether that increases the risk of cardiovascular events is unclear.[31,38] Another safety concern is that OCA can cause serious liver decompensation events.[39] Therefore, the FDA issued a new warning regarding OCA use in patients with advanced liver cirrhosis (e.g. decompensation events such as hepatic encephalopathy, ascites, esophageal and gastric varices, or persistent thrombocytopenia).[40] Thus, the use of OCA in patients with decompensated cirrhosis is not recommended. In addition, clinicians should be cautious about using OCA even in patients with well-compensated cirrhosis.

Fibrates: Fibrates, including fenofibrate and bezafibrate, regulate bile acid synthesis by activating the peroxisome proliferator-activated receptor pathway. A recent meta-analysis showed that the combination therapy of UDCA and fenofibrate was superior to UDCA monotherapy in reducing ALP, GGT, IgM, and triglyceride, but not pruritus.[41] Bezafibrate improved the liver chemistries of patients with a suboptimal response to UDCA. A recent phase III trial confirmed that patients on a combination of UDCA and bezafibrate had substantial remission in ALP and other biochemical markers.[42] Furthermore, an RCT showed bezafibrate led to a ≥ 50% reduction of severe or moderate pruritus in 45% of patients compared with 11 % of the those in the placebo group. Bezafibrate also reduced the intensity of pruritus in the morning and evening and improved responses to the validated 5D-Itch Questionnaire.[43] In addition, a large retrospective cohort study in Japan found that bezafibrate significantly reduced all-cause and liver-related mortality or liver transplantation rates in PBC patients with suboptimal responses to UDCA.[44]

Fibrates appear to be safe and well tolerated in PBC patients. The most commonly reported side effects were gastrointestinal and musculoskeletal abnormalities. In addition, the use of fibrates can lead to the elevation of transaminases and serum creatinine.[45] A single-center study reported that both fenofibrate and bezafibrate induced significant biochemical improvement, but that the former could better reduce the low-density lipoprotein cholesterol and uric acid.[46] However, fenofibrate treatment was associated higher rates of side effects and withdrawal events than bezafibrate.[47]

Budesonide: Budesonide is a second-generation glucocorticoid with high first-pass elimination in the liver and with relatively few systemic side effects. Budesonide regulates bile acid synthesis, transport, and metabolism through the glucocorticoid receptor/pregnane X receptor pathway. Two multicenter prospective RCTs showed that combination therapy of budesonide (6–9 mg/d) and UDCA (15 mg/kg/d) was superior to UDCA monotherapy in improving the liver chemistries and histological progress.[48] Another placebo-controlled, double-blind trial found that budesonide (9 mg/d) combined with UDCA (12–16 mg/kg/d) was associated with improved biochemical markers, but not liver histology.[31] Therefore, further studies are warranted to explore the effect of budesonide on improving mortality and liver transplantation in PBC patients. In advanced PBC patients, the plasma concentration of budesonide increases significantly, and serious adverse events such as portal vein thrombosis may occur. Therefore, budesonide is not recommended for patients with cirrhosis or portal hypertension.[49]

Liver transplantation: Indications for liver transplantation for PBC patients include decompensated cirrhosis (e.g. ascites, variceal hemorrhage, and hepatic encephalopathy), a Model for End-stage Liver Disease (MELD) score >15, or a Mayo risk score of PBC of at least 7.8.[50] Intractable severe pruritus is an additional indication for liver transplantation specific to PBC patients.

The outcome of liver transplantation for patients with PBC is generally good, but the recurrence of PBC exists, which is associated with graft loss. The incidence of recurrent PBC (rPBC) after a liver transplant is 22% at 5 years, 21–37% at 10 years, and 40% at 15 years.[51] Clinical and biochemical features are often absent, and AMA alone cannot be used for the diagnosis of rPBC since it could be persistently positive in both patients with or without rPBC. Therefore, the diagnosis of rPBC depends on the histological features, including granulomatous cholangitis and/or florid duct lesions.[52] Risk

factors of PBC recurrence include younger age at liver transplantation, use of tacrolimus, and occurrence of cholestasis.[51] The association between the immunosuppressive regimen and recurrent PBC remains controversial. Some studies found tacrolimus was associated with an increased risk of rPBC when compared with cyclosporine.[51] In contrast, one study suggested that tacrolimus and cyclosporine had no significant influence on the rate of rPBC. Meanwhile, tacrolimus showed fewer side effects than that cyclosporine.[53] Studies showed that the conventional use of UDCA after liver transplant could effectively decrease the rate of rPBC.[54]

Recommendations

5. UDCA at 13–15 mg/kg/d for life-long is a standard therapy for all PBC patients, which can be taken in single or divided doses. It is necessary to monitor the change in body weight and adjust the dose of UDCA in time. (A1)
6. Biochemical response to UDCA should be assessed 6–12 months after treatment initiation. Paris II criteria are suitable for patients with early-stage (I-II) PBC with ALP and AST ≤1.5 times the ULN, normalization of TBIL after 1 year of UDCA treatment. Paris I criteria are suitable for advanced stage (III-IV) PBC with ALP ≤3 times the ULN, AST ≤2 times the ULN, normalization of TBIL after 1 year of UDCA treatment. (B2)
7. OCA at a dose of 5–10 mg/d is recommended for patients with suboptimal biochemical response to UDCA. OCA should not be used in patients with current or previous evidence of decompensation (e.g, ascites, encephalopathy, gastroesophageal varices bleeding), abnormal coagulation function, and persistent thrombocytopenia. Patients with compensated cirrhosis need to be closely monitored during the use of OCA. (A1)
8. Bezafibrate (400 mg/d) or fenofibrate (200 mg/d) are off-label therapies for patients with a suboptimal biochemical response to UDCA. Fibrates are contraindicated for patients with decompensated cirrhosis. It is necessary to monitor drug-induced liver injury (especially the elevation of bilirubin) and other related side effects during fibrate therapy. (B1)
9. Decompensated PBC patients with MELD score >15 or Mayo score >7.8, or patients with severe intractable pruritus, should be evaluated for liver transplantation. (C1)
10. UDCA is recommended for post-transplant patients to prevent and reduce the recurrence of PBC. (A1)
11. The available data are not sufficient to recommend the best immunosuppressive drugs and regimens for liver transplantation patients. (C2)

Treatment of symptoms and comorbidities

Fatigue

Fatigue is the most common symptom of PBC. It is necessary to exclude the alternate causes of fatigue (such as anemia, thyroid disorder, sleep disorders, and depression), and provide appropriate treatment. To date, there is no effective therapy for fatigue caused by PBC. A meta-analysis has shown that UDCA, OCA, fluoxetine, colchicine, methotrexate, and cyclosporine did not improve fatigue. A prospective study found that liver transplantation was associated with an improvement in the fatigue score of PBC patients.[55] Whether modafinil improves fatigue in PBC patients is still under debate.[56]

Recommendations

12. No specific therapeutic agent is recommended for fatigue in PBC patients. Other factors associated with fatigue such as anemia, extrahepatic autoimmune diseases, sleep disorders, and depression should be evaluated and treated as appropriate. (C1)

Pruritus

About 70% of PBC patients suffer from pruritus, which decreases the quality of life.[57] Cholestyramine, rifampicin, and opioid receptor blockers are the main drugs used to relieve pruritus. Intractable pruritus is also a specific indication for liver transplantation. Some studies have suggested that bezafibrate may help alleviate pruritus in PBC patients.[43] Cholestyramine, a bile acid chelator, is the first-line therapy for pruritus. The recommended dose is 4–16 g per day,[58] given 4–6 h apart from other medications to avoid inhibiting their absorption. Cholestyramine is not well tolerated and the side effects such as nausea, abdominal distension, and constipation often occur. Rifampicin is the second-line therapy for those who are ineffective or intolerant to cholestyramine. A Meta-analysis found that rifampicin effectively alleviated the pruritus caused by cholestasis.[59] The recommended dose is 150–300 mg twice a day. However, rifampicin can cause severe liver injury, hemolytic anemia, renal injury, and interaction with other medications.[60] So, it is necessary to start with a low dose (100–300 mg/d) and closely monitor the side effects.

Opioid antagonists are also effective for pruritus, but their withdrawal-like reactions limit their use. Two RCTs and follow-up studies have shown that intravenous or oral naloxone is effective for intractable pruritus,[61] which needs to start with a low dose and titrate to the appropriate dose to reduce adverse reactions. Nafuranfen hydrochloride is a selective opioid receptor agonist approved in Japan to treat intractable pruritus in PBC patients.[61] Drugs that antagonize the effects of serotonin, such as ondansetron and sertraline, are also used to treat pruritus. Sertraline and rifampicin are equally effective in improving pruritus, but sertraline is safer because of its lower liver toxicity.[60] In addition, many new agents targeting ileal bile acid transporters and reducing enterohepatic circulation, like linerixibat, are effective for cholestasis-associated pruritus.[62]

Recommendations

13. Cholestyramine (4–16 g/d) is the first-line therapy for pruritus. It should be taken 4–6 h apart from other medications, especially UDCA, to avoid affecting the absorption of other medicines. (B2)
14. Rifampicin (100–300 mg/day) is recommended for those who do not respond or are intolerant to cholestyramine. Liver biochemical tests are needed to routinely monitor drug-induced liver injury. (C2)

Dry eyes and dry mouth

Artificial tears are preferred for patients with dry eyes. Cyclosporine or lifitegrast is suitable for those for whom artificial tears alone are ineffective.[63] For patients with dry mouth and dysphagia, it is recommended to try over-the-counter saliva substitutes such as moisturizing mouthwashes and mouth spray. If the symptoms worsen, cholinergic agents such as pilocarpine or cevimeline are recommended to increase saliva secretion. RCTs have confirmed that cholinergic agents alleviate the symptoms of dry mouth and dry eyes but may have side effects such as nausea, sweating, flushing, frequent urination, dizziness, or diarrhea.[64]

Recommendations

15. Artificial tears are the treatment of choice for patients with

dry eyes. Those with poor responses to artificial tears can try pilocarpine or cevimeline. Cyclosporine or lifitegrast can be used for those being refractory to other agents. (C1)

16. Patients with dry mouth and dysphagia can be treated with over-the-counter saliva substitutes; pilocarpine or cevimeline can be used to increase saliva secretion in patients with moderate to severe symptoms. (C1)

Osteoporosis

Metabolic bone disease is a common complication in PBC patients, including osteopenia and osteoporosis. Osteoporosis occurs in about 20–45% of patients with PBC and is more common in liver transplant and postmenopausal patients.[65,66] Bisphosphonates, vitamin D, and calcium can be used to treat osteoporosis in patients with PBC, with particular care in patients with femur T-scores lower than −1.5.[66,67] The efficacy of bisphosphonates in PBC patients remains controversial.[68] A meta-analysis found that first-generation bisphosphonates did not reduce fracture incidence in patients with PBC.[69] However, a recent RCT showed that third-generation bisphosphonates (e.g. alendronate 70 mg/week or ibandronate 150 mg/month) significantly increased lumbar bone mineral density and were safe in patients with PBC.[70] As bisphosphonates may cause side effects such as variceal bleeding, gastroesophageal reaction, and atrial fibrillation, they should be used with caution in patients with esophageal varices. Bleeding risk should be monitored.

Vitamin D deficiency is common in PBC patients.[66,71] EASL nutritional guidelines recommend oral supplement vitamin D in cirrhotic patients with vitamin D levels of <20 ng/mL, to reach serum vitamin D (25-hydroxyvitamin D) >30 ng/ml.[72] For patients over 50 years of age, a daily dietary intake of 800–1,000 mg is recommended. For patients with osteoporosis, supplementation with 500–1,200 mg of calcium and 400–800 IU vitamin D per day is recommended. In addition, vitamin D is recommended at a dose of 800–1,200 IU/d to prevent osteoporosis.[73] A 3-year study found significant attenuation in the loss of bone mineral density in PBC patients treated with vitamin D, calcium, and calcitonin.[74]

Recommendations

17. All PBC patients, especially postmenopausal women, should be monitored because of osteoporosis risk. (C2)
18. For PBC patients without a history of kidney stones, 800–1,200 mg of calcium and 800–1,000 IU of vitamin D should be taken daily in the diet or supplements to prevent or treat osteoporosis. (C2)
19. Patients with osteoporosis can be treated with bisphosphonates (e.g. alendronate 70 mg/week, ibandronate 150 mg/month, or other similar agents). However, they should be used with caution in patients with esophageal varices, and they should be monitored because of the risk of bleeding. (C2)

Special considerations

AMA-negative PBC

Generally, 5–10% of PBC patients are AMA-negative,[16,17] but a higher rate of AMA-negative PBC patients (about 15%) has been reported in China.[75] Most studies demonstrated that AMA-negative and AMA-positive PBC patients had similar clinical manifestations, pathological features, natural history, and prognosis.[75,76] However, AMA-negative PBC had worse scores in itch and social/emotional domains of questionnaires.[77] They were also more likely to have concomitant extrahepatic autoimmune diseases;[78] lower IgM levels and higher positive rates of PBC-specific ANA antibodies (anti-gp210 and anti-sp100).[76,78–80] Histologically, AMA-negative patients had more severe bile duct damage around the portal areas.[81] In addition, liver-related complication-free survival was significantly lower in AMA-negative PBC patients.[80] Therefore, timely liver biopsies are recommended for cholestatic patients with unknown causes and negative PBC antibodies (AMA, anti-gp210, and anti-sp100) to confirm the diagnosis and avoid delayed treatment.

Preclinical PBC or AMA positivity alone

Preclinical PBC refers to patients with positive AMA, normal serum cholestatic markers (ALP, GGT), and no histological evidence of PBC but eventually developed PBC during follow-up. A recent single-center study in China found that up to 80% of patients with positive AMA and normal ALP were histologically diagnosed with PBC,[82] similar to a multicenter study in Switzerland.[83] Higher AMA titers, elevated IgM, and ALP approaching the upper limit of normal (ULN) were predictors of the histological findings of PBC.[82,83] Furthermore, although ALP was normal in these two studies, most patients had an elevated GGT, which may explain the high rates of PBC development. A prospective, multicenter study in France found a 5-year PBC incidence of 16% in a cohort of positive AMA and normal ALP.[84] In line with this, a recent single-center Austrian study reported that only six of 59 patients with AMA positivity alone progressed to PBC after a mean follow-up of 5.8 years.[85] An earlier study followed 26 AMA-positive first-degree relatives of PBC patients. The relatives had normal ALP values for up to 8.9 years, and only one developed PBC.[86] All these studies showed that among patients with positive AMA but normal ALP and GGT and no other evidence of chronic liver injury, only a minority progressed to PBC over long-term follow-up. All of these pieces of evidence demonstrate that AMA positivity alone was not enough to diagnose PBC; for AMA-positive patients with normal ALP and GGT and no evidence of chronic liver injury, the prevalence of developing PBC is low.[87] Therefore, for such patients, it is reasonable to monitor liver biochemistry annually. For patients with any clinical evidence of chronic liver injury, elevated GGT, or elevated IgM, a liver biopsy may be considered to rule in or rule out PBC. Patients with biochemical or histological evidence of PBC that emerged during follow-up should be treated with UDCA promptly. Currently, there is no sufficient clinical evidence to recommend the prophylactic use of UDCA for those with AMA positivity alone.

Recommendations

20. AMA or AMA-M2 positivity alone is not enough to diagnose PBC. Liver biochemistry should be monitored yearly. If clinical or biochemical evidence of liver injury such as elevated IgM or elevated GGT emerges, a liver biopsy may be a reasonable choice to confirm the existence of PBC. (C2)

PBC with features of AIH

PBC and AIH that coexist in a patient simultaneously or sequentially are considered PBC with AIH features or PBC-AIH overlap syndrome. Some investigators believe that PBC with features of AIH may develop in PBC patients with genetic susceptibility to AIH.[88] Recent studies have found that the histological immunophenotype of PBC with features of AIH was similar to that of PBC, suggesting that the overlap syndrome may be a variant form of PBC.[89]

Diagnosis of PBC with features of AIH: There are no unanimously accepted diagnostic criteria for PBC with fea-

tures of AIH. The most commonly used Paris criteria include the presence of at least two of the three items for each disease.[90] The diagnostic criteria for PBC are (1) serum ALP ≥ 2 × ULN or serum GGT ≥ 5 × ULN, (2) positive serum AMA/AMA-M2, (3) florid bile duct lesion on histology. The diagnostic criteria for AIH are (1) serum ALT ≥ 5 × ULN, (2) serum IgG ≥ 2 × ULN or positive anti-smooth muscle antibody (ASMA), and (3) liver histology (mandatory) showing moderate/severe interface hepatitis. The presence of ASMA or IgG ≥ 2 × ULN is a critical Paris diagnostic criterion. However, whether it is suitable for Chinese patients is still an issue of discussion.[91] A prospective study in China found that an IgG ≥ 1.3 × ULN had a sensitivity of 60% and specificity of 97% for identifying patients who had a complete response to corticosteroids, but the sensitivity and specificity of the Paris IgG ≥ 2 × ULN criterion were 10% and 100%, respectively.[92] Therefore, 1.3 × ULN IgG is a more appropriate threshold for Chinese patients. In addition, studies have shown that the simultaneous positivity of ds-DNA and AMA have 98% specificity for the diagnosis of PBC with features of AIH,[93] but its diagnostic value needs further verification. Most hepatologists and pathologists agree that the revised original scoring system and the simplified AIH score developed by the International Autoimmune Hepatitis Group (IAIHG) are not for diagnosing PBC with features of AIH.[94] First, the two scoring systems are designed for AIH but not for PBC with features of AIH. Second, the presence of AMA is a subtraction item in the revised original scoring system, which may lead to the underdiagnosis of overlap syndrome. Third, the simplified AIH score may lead to the over-diagnosis of overlap syndrome, resulting in unnecessary corticosteroid exposure.

Treatment of PBC with features of AIH: PBC with features of AIH has a worse prognosis than PBC or AIH alone.[95] At present, there is no consensus on the treatment protocol for PBC with features of AIH. Studies have shown that treatment with glucocorticoids alone or combined with azathioprine or second-line immunosuppressive agents like mycophenolate mofetil, tacrolimus, or cyclosporine A, can improve the biochemical response and prognosis of patients.[96] A multicenter retrospective study showed that severe interface hepatitis is an independent risk factor for incomplete response to UDCA monotherapy in patients with PBC with features of AIH,[97] supporting the use of UDCA combined with immunosuppressants treatment as the treatment of choice for patients with severe interface hepatitis.

Recommendations

21. A diagnosis of PBC with features of AIH can be made in PBC patients who also meet two of the three diagnostic criteria AIH (1+2, or 1+3): (1) moderate/severe interface hepatitis; (2) AST or ALT≥5×ULN; (3) IgG ≥ 1.3 × ULN or the presence of ASMA. (C2)
22. Patients with moderate interface hepatitis can be treated with UDCA and immunosuppressants, or initially treated with UDCA monotherapy and added immunosuppressants if not responding to UDCA. (C2)
23. Patients with severe interface hepatitis should be treated with UDCA and immunosuppressants (glucocorticoid alone, or combined with azathioprine 50 mg/d or mycophenolate mofetil 0.5–1.0 g/d). (C2)

PBC-PSC overlap syndrome

PBC-PSC overlap is defined as the presence of PBC and PSC simultaneously or sequentially in the same patient. A recent review summarized 12 cases of PBC-PSC overlap syndrome from 10 case reports, with most cases successively diagnosed with PSC after 3 months to 18 years of PBC diagnosis.[98] At present, there are no well-accepted diagnostic criteria or standardized dosage of UDCA treatment for PBC-PSC overlap syndrome. The diagnosis is mainly based on the establishment of both PBC and PSC. Although most patients can achieve biochemical remission after UDCA therapy, the long-term prognosis is not clear.[98]

Pregnancy of PBC patients

Retrospective studies showed that most PBC patients were stable during pregnancy. Only a few patients experienced newly developed or worsened pruritus. Liver biochemistry often deteriorates after giving birth. Maternal and infant outcomes are usually favorable, but patients with cirrhosis have an increased risk of maternal and infant complications.[99,100] Therefore, female PBC patients of childbearing age need individualized counseling before pregnancy. For those with portal hypertension, upper gastrointestinal endoscopy can be performed in the second trimester, and endoscopic intervention can be performed as appropriate to reduce the risk of variceal bleeding. There are few reports on use of UDCA by PBC patients during pregnancy. No significant fetal adverse effects were observed with daily administration of UDCA up to 2,000 mg/kg, which is equivalent to approximately 100 times the clinical dose, in rats during pregnancy.[101] There is much experience in the use of UDCA in patients with intrahepatic cholestasis of pregnancy (ICP) in the second and third trimesters. A recent meta-analysis showed that UDCA treatment did not increase the stillbirth rate in patients with ICP.[102] There are few safety data on UDCA in the first trimester of pregnancy. In a recent study, no fetal side effects were observed in 16 PBC patients who continued to take UDCA during the first trimester.[100] Several earlier studies included 4, 8, and 12 PBC patients who continued using UDCA during pregnancy, respectively, none of whom reported fetal side effects.[99] These data suggested that UDCA use during pregnancy appears safe and well tolerated. Therefore, most researchers support the continued use of UDCA throughout pregnancy to prevent the disease progression of PBC. Safety data on UDCA use during breastfeeding are limited. German investigators could not detect UDCA in the breast milk of a patient taking 750 mg/d UDCA using high-pressure liquid chromatography.[103] A recent case report also showed that an increased UDCA dose of up to 1,500 mg/d had no effect on the bile acid content of breast milk, and the children grew normally.[104] Additional studies have shown that the total bile acid concentration in the colostrum of ICP patients was higher than that in normal controls, and UDCA treatment reduced endogenous bile acid levels in colostrum.[105] Therefore, UDCA treatment during breastfeeding may be safe for PBC patients.

Recommendations

24. Pregnancy is acceptable in female PBC patients of childbearing age, but patients with cirrhosis have an increased risk of maternal and infant complications. Limited data suggest that UDCA use appears safe during pregnancy, including the first trimester. Therefore, UDCA can be used with fully informed consent after carefully weighing the benefits and risks. (C2)

Male PBC

As reported by previous international studies, the female-to-male ratio in PBC patients was about 10:1, but two large studies in China reported a lower ratio (6.2–6.9:1).[75,106] Compared with female PBC patients, the incidence of PBC-related clinical symptoms and the proportion of patients con-

comitant with Sjögren's syndrome was significantly lower in male patients. The long-term outcomes of male PBC patients are still controversial. Studies in China[75] and Canada[107] reported that the prognosis was worse in male than in female patients. In the Global PBC Study, Male PBC patients had a treatment response and outcome similar to those in female patients.[108] Male sex was also found to be an independent risk factor for HCC in PBC patients,[109] which supports close monitoring of HCC in male PBC patients.

Recommendations

25. Male sex and cirrhosis are independent risk factors for HCC in PBC patients, therefore, abdominal ultrasonography and/or AFP should be monitored every 6 months for those patients. (B1)

Young PBC patients

PBC patients less than 45 years of age were shown to have significantly higher baseline serum levels of transaminases and ALP than older patients.[108] Young patients also had higher rates of symptoms including pruritus and fatigue, lower response rates to UDCA, and increased risk of liver transplant or death compared with older PBC patients.[108,110] Therefore, regular follow-up is essential for this group of people.

PBC with bile duct loss

Bile duct loss involves partial or complete disappearance of intrahepatic small bile ducts, and has many causes. Vanishing bile duct syndrome is defined as less than 50% of portal areas having bile ducts. Bile duct loss is a risk factor for biochemical nonresponse in PBC patients.[111] Regular administration of sufficient UDCA dosage may not improve the degree of bile duct loss.[112] In view of the association of bile duct loss with persistent cholestasis and refractory jaundice,[113] the degree of bile duct loss has been identified as one of the markers of disease staging in patients with PBC.[114]

Prognosis

The overall prognosis of PBC patients has been improved significantly by UDCA therapy. In China, the 5-year and 10-year transplantation-free survival rates of PBC patients treated with UDCA are estimated as 78.0–86.7% and 71.1–74.3%, respectively, and the 5-year incidence of HCC and decompensation as 1.62% and 3.81–4.31%, respectively.[4,75] Not surprisingly, the prognosis of PBC patients with cirrhosis is poor. The 5-year transplantation-free survival rates for PBC patients with compensated and decompensated cirrhosis were reported to be 77.1% and 35.9%, respectively.[75] The GLOBE score[33] and UK-PBC[115] score are based on data from multi-center large cohorts. The scores accurately predict the 5-, 10-, and 15-year transplantation-free survival rates of PBC patients, which have been verified in cohorts in many countries, including China. Generally, they are more predictive than other models.[116] The calculation of the GLOBE (www.globalpbc.com/globe) and UK-PBC (www.uk-pbc.com) scores can be performed with online tools.

Recommendations

26. Prognostic models, such as GLOBE and UK-PBC scores, can assess the clinical outcome of patients with PBC after treatment with UDCA. (C2)

Screening and follow-up

Screening of first-degree relatives: Family members of PBC patients have an increased risk of PBC development that mainly includes first-degree female relatives, especially sisters, mothers, and daughters. The AMA positivity in first-degree relatives of PBC patients is as high as 13.1%, and as high as 20.7% in sisters.[117] Co-incidence cases in mother and child, and siblings have also been reported. Although the evidence for screening first-degree relatives of PBC patients is insufficient, the screening of AMA and ALP in first-degree female relatives over 30 years of age is recommended. Further studies to optimize the diagnosis, treatment and follow-up strategies for PBC relatives are justified.

Follow-up: PBC patients require long-term UDCA treatment. Monitoring with liver biochemical tests every 3–6 months is recommended to evaluate the biochemical response and identify patients who may develop PBC with features of AIH. Liver ultrasonography and alpha-fetoprotein should be assessed every 6 months to monitor HCC in cirrhotic and male patients. All patients should be screened for thyroid function annually. Upper gastrointestinal endoscopy should be performed to assess gastroesophageal varices in cirrhotic patients. Endoscopy should be repeated every 1–3 years based on endoscopy and evaluation of liver function reserve. According to the baseline bone mineral density and the severity of cholestasis, bone mineral density should be assessed by dual-energy X-ray absorptiometry (DEXA) every 2–3 years. For patients with jaundice, the level of fat-soluble vitamins can be monitored every year if it is feasible.

Gaps and future research directions

1. There is still a lack of population-based epidemiological data on PBC in China.
2. There is still a lack of evidence-based diagnostic criteria and treatment options for special conditions such as AIH and preclinical PBC.
3. Safe and effective second-line therapy is strongly recommended for patients with suboptimal biochemical response to UDCA, especially for those with compensated and decompensation cirrhosis.
4. The etiology and pathogenesis of PBC, especially the initiating factors that trigger the autoimmune response to intrahepatic bile duct epithelium, need to be explored and clarified.
5. Novel therapeutic agents targeting the key pathogenesis of PBC are urgently needed for new drug development.

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Conflict of interest

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, YN has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2023, LL has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2013, LW and JJ have been executive associate editor of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

Author contributions

Designed, revised, and finalized the manuscript (HY, JJ, YH, XX), searched the literature and drafted the manuscript (WD,

SL, TL, SC), critically reviewed and revised the recommendations (all other authors), read and approved the final manuscript (all authors).

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