Clinical Practice Guidelines

# Cholestatic liver disease: Practice guidelines from the Saudi Association for the Study of Liver diseases and Transplantation

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## Abstract

Cholestatic liver diseases (CLDs) are a group of diseases characterized by jaundice and cholestasis as the main presentation with different complications, which have considerable impact on the liver and can lead to end-stage liver disease, cirrhosis, and liver-related complications. In the last few years, tremendous progress has been made in understanding the pathophysiology, diagnosis, and treatment of patients with these conditions. However, several aspects related to the management of CLDs remain deficient and unclear. Due to the lack of recommendations that can help in the management, treatment of those conditions, the Saudi Association for the Study of Liver diseases and Transplantation (SASLT) has created a task force group to develop guidelines related to CLDs management in order to provide a standard of care for patients in need. These guidelines provide general guidance for health care professionals to optimize medical care for patients with CLDs for both adult and pediatric populations, in association with clinical judgments to be considered on a case-by-case basis. These guidelines describe common CLDs in Saudi Arabia, with recommendations on the best approach for diagnosis and management of different diseases based on the Grading of Recommendation Assessment (GRADE), combined with a level of evidence available in the literature.

**Keywords:** Cholestasis, cholestatic liver disease, jaundice

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## INTRODUCTION

Cholestatic liver diseases (CLDs) are a group of conditions characterized by jaundice and cholestasis as the main clinical presentation, with several other complications including cirrhosis, variceal bleeding, portal hypertension,

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etc. Cholestasis is characterized by an elevation in alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT), with a decrease in bile flow and increase in bilirubin, which can occur later. They have been reported in both adult and pediatric populations, with considerable impact on the liver tissues leading to end-stage liver disease for most patients. CLDs include a wide range of autoimmune diseases such as primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlap syndromes with different severity.

Considering the lack of universal consensus on the best management approach for CLDs, treatment modalities vary based on the clinicians' experience and the medical facility where treatment is offered. Therefore, a task force initiative under the Saudi Association for the Study of Liver diseases and Transplantation (SASLT) took place in order to provide CLDs management recommendations for daily clinical practice in Saudi Arabia. These recommendations are intended to guide health care practitioners, in association with clinical judgment, to optimize treatment and endure delivery of care. In addition, these guidelines will be updated on a regular basis following the international literature and guidelines as indicated. Published guidelines from the American Association of Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), were used as main references to provide the recommendations.

### Taskforce approach for CLDs management guidelines and recommendations

A panel of eight certified hepatologists with experience in the field of CLDs were asked to evaluate the current literature and develop management guidelines for patients in Saudi Arabia. In total, two pediatric hepatologists who were responsible for the section dealing with pediatric patients and six adult hepatologists, met in February 2020. The panel reviewed all current literature and guidelines of CLD's diagnosis and management, including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), overlap syndromes, IgG4 cholestatic disease, drug-induced liver cholestasis (DILI-C), and CLDs in pediatric patients. This included published guidelines from the AASLD and EASL.

The task force conducted the review in pairs, in which two hepatologists teamed up and were assigned a specific condition(s). The literature search was conducted independently and in duplicates. Eligible studies were reviewed and graded following the GRADE system [Table 1].[1] Any disagreement between reviewers was resolved by a group discussion to reach an agreement. Data were extracted from eligible studies and assessed for strength of evidence and inclusion in the CLDs management guidelines. The task force panel reviewed the developed guidelines for applicability in the Saudi population.

**Table 1: Evidence grading (Adapted from GRADE system)**

| Grade | Evidence |
|---|---|
| I | Randomized controlled trials |
| II-1 | Controlled trials without randomization |
| II-2 | Cohort or case-control studies |
| II-3 | Multiple time series, dramatic uncontrolled experiments |
| III | Opinions of respected authorities, descriptive epidemiology |
| Evidence quality | |
| High | Further research is very unlikely to change our confidence in the estimate of effect (A) |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (B) |
| Low | 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 (C) |

Estimate. Any estimation change is uncertain

## PRIMARY BILIARY CHOLANGITIS

### Background

Primary biliary cholangitis is a chronic inflammatory, autoimmune disease that is characterized by cholestatic elevation of liver enzymes associated with positive antimitochondrial antibody (AMA). The disease is associated with several clinical manifestations and complications which can progress to cirrhosis. The clinical practice guidelines will provide an evidence-based approach to patients with PBC disease, with the main objective to prevent liver disease progression as well as management of potential complications.

### Pathophysiology

PBC is an autoimmune disease that is characterized by positive AMA with bile duct pathology.[2,3] The disease is associated with multiple environmental as well as genetic factors.[4-6] AMA can be described as a disease-specified autoantibody which aims at the lipoic acid presented at the 2-OXO dehydrogenase complex in the inner membrane of the mitochondria.[7,8] The majority of AMA produced by plasma blasts is mainly IgA, which goes through transcytosis at the biliary epithelium as well as affects the liver cell mitochondria. The disease is related to deficiency of humoral tolerance in addition to autoreactive differentiation of clusters of CD4+/CD8+ pyruvate dehydrogenase complex (PDC-E2)–specific T-cells in the liver.[9,10]

Several environmental factors have been attributed to the disease in large case-control studies, including smoking,

hormone replacement, nail polish, and urinary tract infection. No definite association was confirmed, and studies are currently ongoing to define the interactions between genetic and environmental factors.[11-13]

## Epidemiology

Presently, there is no literature about the current prevalence of PBC in Saudi Arabia due to its rarity. The current overall prevalence of the disease worldwide is between 19 and 402 cases per million.[3] In general, the overall prevalence of this disease is increasing, with a women to men ratio of 9:1.[14,15] The prevalence of positive AMA is unknown worldwide. Several studies from Italy and Japan estimated a prevalence of 0.5% and 0.64%, respectively.[16,17] PBC is characterized by higher concordance in monozygotic twins than dizygotic twins.[4] Overall, 15% of the disease variability is accounted by genetic factors.[18]

Positive AMA can be present with normal liver function tests and no clinical manifestations.[19] In one study, 5-year occurrence of PBC in these patients was observed to be 16% after 7 years of follow-up.[20] The positive AMA prevalence in PBC patient's first-degree relative (FDR) was higher than in control (13.1% vs. 1%).[21]

## Natural History

The survival of patients with PBC is correlated with the histological progression of the disease.[22,23] Three large studies estimated a median time of 2 years to develop (advanced fibrosis (F3, Metavir) or more in patients without treatment.[23-25] In a large community-dependent study in the UK, 15% of patients decompensated during 5 years follow-up, where 50% patients at entry had cirrhosis.[26] The esophageal varices' development impacts the survival, with an estimated 3-year survival of 59%.[27] Liver transplantation (LT) work-up should be considered in patients with total bilirubin >6 mg/dL (103 μmol/L) or Model for End-stage Liver Disease (MELD) score >12. One- and five-year survival is estimated to be 90% and 80%–85%, respectively, in patients who achieve a biochemical response. The risk of disease recurrence is estimated to be 18%.[28,29]Several factors were associated with recurrent PBC after LT, including young age at the time of transplantation, tacrolimus use, and biochemical markers of cholestasis after transplantation, as was demonstrated in the longest published experience of LT for PBC[30]

## Prognostic Models For PBC

Different models have been studied to be used for prognostication for PBC patients. The Yale model was the 1st PBC-specific model which includes serum bilirubin, age, hepatomegaly, and evidence of cirrhosis or fibrosis, which were all independent risk factors for poor prognosis.[22] The major limitation of this model is the requirement of the liver biopsy. The Mayo model was introduced in 1989.[31] Recently, two prognostic models for PBC, the UK-PBC score and the GLOBE score, were validated in a large cohort of studies from multiple centers.

The UK-PBC score was validated in a cohort of 3,165 patients and evaluated multiple parameters including serum bilirubin, aminotransferase, and ALP at 12-months of treatment completion time point, in addition to albumin and platelet counts at baseline, which estimated the risk of liver-related death as well as the need for LT in 5, 10, and 15 years.[32] GLOBE score was developed based on data of 2,488 PBC patients from a large retrospective study who were treated with urso-deoxycholic acid (UDCA). The same parameters are also included in the GLOBE score, in addition to age at the start of treatment, and were assessed following 1-year treatment completion. The study was eventually validated by another cohort of North American and European patients.[33] Both prognostic models are considered superior to previous models but were not validated in other ethnicities such as in Arab populations such as those from Saudi Arabia.

## Clinical Presentation and Diagnosis

Numerous studies from Sweden, North America, and the United Kingdom evaluated asymptomatic PBC patients within an average follow-up of 4.5 to 17.8 years. On average, 36% to 89% would develop clinical symptoms with a median time of 2 to 4.2 years from the time of diagnosis to the appearance of symptoms. In addition, the 10-year survival ranged between 50% and 70%. At the same time, symptomatic PBC had a median survival duration ranging between 5 and 8 years starting from PBC symptoms onset.[22,26,34-38]

The diagnosis of PBC requires a systematic approach which starts with taking a comprehensive history as well as physical examination in any patient presenting with abnormal liver function tests, suspicious for cholestatic liver diseases. The classic biochemical abnormality includes an elevation in ALP, serum bilirubin (mainly direct bilirubin), and GGT. In order to assess PBC disease progression and treatment potential, noninvasive markers including ALP and bilirubin were analyzed in different settings and subpopulations, at different times relative to the clinical endpoints, LT, or death, which used as surrogate markers to predict outcomes.[39] Furthermore, there is

an increase in levels of immunoglobulins (mainly IgM) in patients with PBC. Since cholestasis is a prominent presentation of PBC, abdominal ultrasound should be the first-line, noninvasive imaging technique for differentiating extra- and intrahepatic cholestasis. In addition, serum AMA levels should be assessed which could be diagnostic in 95% of the PBC patients.[40] Magnetic resonance cholangiopancreatography (MRCP) can be the next imaging of choice in patients with unexplained cholestasis. Following comprehensive evaluation including imaging and serological screening, liver biopsy is indicated in patients suffering from unexplained intrahepatic cholestasis. In the setting of inherited cholestatic syndromes, genetic testing should be considered on a case-by-case basis.

### Recommendations

Diagnosis of PBC should be considered in patients with chronic cholestatic serum liver tests with an unexplained elevation of serum ALP, pruritus, and fatigue, particularly in middle age females for more than wwith the exclusion of DILI and absence of dilated biliary tree on abdominal ultrasound. The following are the diagnostic criteria for PBC:

1. Elevated ALP combined with AMA titer >1:40 is diagnostic. **(Grade III/A)**
2. Diagnosis of AMA-negative PBC can be made in patients with cholestasis and specific antinuclear antibodies (ANA) immunofluorescence (nuclear dots or perinuclear rims) or ELISA results (sp100, gp210). **(Grade III/C)**
3. Liver biopsy is not required for the diagnosis of PBC unless PBC-specific antibodies are absent, coexistence of autoimmune hepatitis (AIH) or nonalcoholic steatohepatitis (NASH) is suspected, or other (usually systemic) comorbidities are present. **(Grade III/C)**
4. AMA reactivity alone is not sufficient to diagnose PBC. Follow up of patients with normal serum liver tests and positive AMA is recommended for annual biochemical reassessment for the presence of liver disease. **(Grade III/C)**
5. Referral for liver transplantation workup must be considered if no contraindications exist in patients with MELD scores >12 or total bilirubin >103 μmol/L.**(Grade II-2/A)**

## PBC Treatment

### *Ursodeoxycholic Acid*

Ursodeoxycholic acid at a dose of 13–15 mg/kg/d is the treatment of choice for patients with PBC. The proposed mechanisms of action have to do with the anti cholestatic effect through stimulation of ductular alkaline choleretic, cholangiocyte apoptosis, and bile acid–induced hepatocyte inhibition.[41] Several studies showed a major role of UDCA in improving the laboratory parameters of patients with PBC, including hepatic profile and immunoglobulin M (IgM) levels and delaying liver disease's histological progression.[24,42] As of today, there is no clear-cut evidence of UDCA's role in improving survival. However, recent reports showed favorable and promising effects.[43,44] In order to assess for UDCA's long-term effect on PBC patients after 1 year of treatment, several prognostic models have been studied and validated: Rochester, Rotterdam, Barcelona, Paris I and II, Toronto, and Ehime and two-continuous criteria, GLOBE and UK-PBC.[45] Of these, the four most commonly used and clinically applicable ones are shown in Table 2. The two most recent key trials of second-line therapy in PBC applied either the revised Toronto criteria (POISE) or the Paris-2 criteria for selecting high-risk patients.[46,47]

**Table 2: PBC prognostic scoring systems**

| Criterion | Definition of biochemical response |
|---|---|
| Barcelona[44] | ALP decrease >40% from baseline or to normal after 1 year of UDCA |
| Paris-I[215] | ALP ≤ 3 times upper limit of normal (ULN), AST < or equal 2 times ULN and normal bilirubin after 1 year of UDCA |
| Toronto[216] | ALP ≤ 1.67 times ULN *or ALP ≤1.76 after 2 years of UDCA** |
| Paris-II[217] | ALP and AST ≤ 1.5 times ULN with normal bilirubin after 1 year of UDCA |

*Defining nonresponse as a one-stage increase. **Defining nonresponse as a two-stage increase

The current evidence does not support cortico steroid use in PBC except in overlap syndrome with autoimmune hepatitis.[48,49] Several studies for the use of synthetic corticosteroids with first-pass metabolism (Budesonide) at a dose of 6–9 mg/d for 9 months were conducted, including cohort patients with suboptimal response to

**Table 3: Paris criteria for PBC/AIH overlap syndrome**

Autoimmune Hepatitis
1. Liver biopsy with moderate or severe periportal or periseptal lymphocytic piecemeal necrosis
2. Immunoglobulin G (IgG) ≥2-fold upper limit of normal (ULN) or smooth muscle antibodies' presence
3. Alanine aminotransferase (ALT) ≥5-fold ULN

Primary Biliary Cholangitis
1. Liver biopsy with florid bile duct lesions
2. AMA Presence
3. Gamma-glutamyl transferase ≥5-fold ULN or alkaline phosphatase (ALP) ≥2-fold ULN

At least 2 of 3 accepted criteria for PBC and AIH, respectively, should be present. For diagnosis, moderate to severe lymphocytic piecemeal necrosis' (interface hepatitis) histologic evidence is mandatory.

**Table 4: Revised international autoimmune hepatitis group scoring system**

| Clinical Feature | Score |
|---|---|
| Female gender | 2 |
| ALP: AST ratio | |
| <1.5 | 2 |
| 1.5-3.0 | 0 |
| >3.0 | -2 |
| Serum globulin or IgG above normal | |
| >2.0 | 3 |
| 1.5-2.0 | 2 |
| 1.0-1.5 | 1 |
| <1 | 0 |
| ANA, SMA, LKM1 | |
| >1:80 | 3 |
| 1:80 | 2 |
| 1:40 | 1 |
| <1:40 | 0 |
| Illicit drug use history | |
| Positive | -4 |
| Negative | 1 |
| Average alcohol intake daily | |
| <25 g/d | 2 |
| >60 g/d | -2 |
| Histologic findings | |
| Interface hepatitis | 3 |
| Lymphoplasmacytic infiltrate | 1 |
| Rosette formation | 1 |
| None of the above | -5 |
| Biliary changes | -3 |
| Other changes | +2 |
| Other autoimmune disease | +2 |
| AMA positivity | -4 |
| Hepatitis viral markers | |
| Positive | -3 |
| Negative | 3 |
| Aggregate score without treatment | |
| Definite AIH | >15 |
| Probable AIH | 10-15 |

UDCA in early-stage PBC. Laboratory and histological improvement results were controversial. Budesonide is not suggested in cirrhosis patients due to the potential risk of portal vein thrombosis.[50-53] Further studies are recommended to confirm its long-term benefit, especially in patients with advanced PBC disease.[54]

There is emerging evidence for UDCA use in the prevention of recurrent PBC after transplantation, with a reduced risk of disease recurrence, graft loss, and death. Combining UDCA with cyclosporine was associated with the best outcome[55]

### *Obeticholic acid*

Obeticholic acid (OCA) is a selective farnesoid X receptor (FXR) agonist which is acquired from the endogenous FXR ligand and the bile acid chenodeoxycholic acid.[56] In comparison to chenodeoxycholic acid, FXR is effectively activated by OCA.[56,57] Hepatocytes are protected by the FXR signaling against toxicity of bile acid through upregulation of bile acid transporters and synthesis impairment.[58] Additionally, FXR signaling may provide anti-inflammatory and antifibrotic effects.[59,60]

The PBC OCA International Study of Efficacy (POISE) phase III clinical trial included patients with PBC who had suboptimal responses to UDCA or intolerance for a year (serum ALP >1.67 ULN and total bilirubin <2 ULN) in comparison to placebo.[47] The OCA group reported a significant decrease in levels of ALP and total bilirubin, compared to baseline, but had more serious adverse events. Furthermore, OCA-treated patients demonstrated a reduction in total cholesterol and high-density lipoprotein (HDL), and a slight increase in low-density lipoprotein (LDL), within 2 weeks.[47] Non-invasive measures for liver fibrosis patients failed to show a significant difference in both placebo and OCA groups at 12 months. Pruritus was the main side effect found in 38% of the placebo group, 68% of the 10 mg OCA group, and 56% of patients in 5–10 mg OCA group. Up to 10% of patients discontinued OCA treatment due to pruritis.[47]

A randomized clinical trial evaluated the effect of OCA monotherapy and reported a significant change in serum ALP, with a 53.9% reduction in the 10 mg arm as well as a 39.2% reduction in the 5 mg arm; however, no changes in the placebo arm were noted.[61] In addition, serum levels of conjugated bilirubin improved in OCA-treated patients. Similar to POISE trial, the most common side effect reported was pruritus which led to discontinuation of treatment in 35% of subjects in the high-dose group. No benefit of OCA in decompensated cirrhosis has been reported; and due to the risk of worsening liver function, its application in Child-Pugh B and C cirrhosis is not recommended. As of now, the long-term effects of OCA on survival or cardiovascular adverse events is still pending.

### *Fibrates*

Peroxisome proliferator activator receptor (PPAR) is a lipid-lowering medication which activates a nuclear receptor and has various roles in metabolic processes including bile acid homeostasis. Based on the current literature, fenofibrate at 160 mg/d for 48 weeks demonstrated a 50% reduction in ALP in patients with no response to UDCA.[62] In addition, in non-responding patients to UDCA monotherapy, a combination of bezafibrate at 400 mg/day with UDCA, showed 67% normalization of ALP and 30% normalization of all liver parameters compared to 0% improvement in the placebo group. Furthermore, fibrates had a useful consequence on fibrosis markers and liver stiffness. Potential adverse events with fibrates use include musculoskeletal pain, elevation in

**Recommendations**

1. UDCA 13–15 mg/kg/d is the treatment of choice for patients with PBC. **(Grade I/A)**
2. Early disease and good biochemical response are associated with favorable outcomes. **(Grade II-2/B)**
3. We recommend OCA use at 5 mg/d in patients with inadequate biochemical response after 12 months of UDCA use. **(Grade I/B)**
4. OCA use is not recommended in patients with decompensated liver disease (Child-Pugh B or C). **(Grade I/B)**
5. We do not recommend the use of cortico steroids in PBC except in overlap syndrome with autoimmune hepatitis. **(Grade III/C)**

serum creatine, ALT, and AST. Similar to OCA, fibrates are not recommended for decompensated cirrhosis patients.[46]

## PRIMARY SCLEROSING CHOLANGITIS

### Background

Primary sclerosing cholangitis is a chronic, idiopathic, cholestatic, heterogeneous disease, that involves the bile ducts and liver, which often progress to end-stage liver disease. The disease is characterized by progressive extrahepatic and intrahepatic bile ducts fibrosis, and persistent biliary inflammation, that leads to multifocal bile duct strictures formation, which can affect the entire biliary tree.[63]

### Pathophysiology

As of yet, the pathogenic mechanisms behind PSC are not completely understood; however, it is believed to be multifactorial. It is considered an immune-mediated disease associated with other conditions such as inflammatory bowel disease (IBD). Environmental triggers could initiate various adaptive and innate immune system events resulting in progressive fibrosis, cholangiocyte damage, and lymphocyte migration in genetically susceptible people to PSC. These events are typically medicated by human leukocyte antigen (HLA) and non-HLA haplotypes in particular DR3, B8, A1, and DQ2. A rise in levels of serum autoantibody is also seen in those patients, with ANA seen in 53%, anticardiolipin (aCL) antibodies in 66%, and antineutrophil cytoplasmic antibodies (ANCA) in 87%.[63-65]

### Epidemiology

The incidence of PSC has been on the rise and is believed to be the same among European and North American countries. Several studies have suggested a PSC incidence rate of 0.5 to 1.3 and prevalence of 3.85 to 16.2 per 100,000 population/year.[66] As of now, epidemiological studies from developing countries are still lacking which may restrict PSC's global incidence and impact.

### Clinical Presentation

PSC is more likely to affect males, with the mean age of 40 years. Overall, 20%–40% of patients have no physical abnormalities and are asymptomatic at the time of diagnosis. In patients with ulcerative colitis (UC) and elevated ALP levels, PSC diagnosis is often incidentally combined with suggestive findings on endoscopic retrograde cholangiopancreatography (ERCP) or MRCP. The most frequent signs at diagnosis are hepatomegaly in 44% and splenomegaly in 39% of patients.[67] Furthermore, pruritus and fatigue are a common presentation in 70% of patients with PSC, similar to other cholestatic liver diseases, with a significant impact on quality of life. In general, pruritus worsens at night in humid and warmer weather with some dermatological complications including skin excoriations.[68] Fatigue is a common symptom, which is still poorly understood and tends to progress as the day goes.[69,70] Most of these symptoms are likely to remit and then recur spontaneously.

Bacterial cholangitis with recurrent febrile episodes and jaundice have been reported in 10%–15% of patients during the course of PSC. Other clinical presentations may include cirrhosis, liver failure, hepatic encephalopathy, ascites, and variceal bleeding, which are more likely to occur in progressive disease. In 3.3% of PSC patients, precirrhotic portal hypertension can be detected due to obliterative retinopathy or nodular regenerative hyperplasia.[71] The risk of malignancy is significantly higher in PSC patients in the form of cholangiocarcinoma (CCA).

Concomitant IBD has been reported in approximately 70% of PSC patients, in which UC represents 13% of cases. At the same time, 5% of patients with IBD are likely to be diagnosed with PSC as well, though, PSC is not related to the IBD course.[72] The incidence of osteoporosis with PSC has been reported at 4%–10%, and correlated with duration of IBD, low body mass index, and older age.[73] In late stage disease, fat-soluble vitamin deficiency, and steatorrhea are more likely to take place due to chronic cholestasis.[74]

There are several subtypes of PSC. Overall, the classic subtype accounts for 90% of cases affecting the whole biliary tree. In 5% of patients, the small intrahepatic bile ducts are affected and known as small duct PSC. In addition, 5% of adults and 35% of children with PSC may experience overlap syndrome with autoimmune hepatitis.[75] Immunoglobulin G4 (IgG4)-positive sclerosing cholangitis is a distinct entity reported in 10% of patients with PSC

with more severe disease and rapid progression to liver transplantation in a shorter time duration.[76]

PSC also needs to be differentiated from secondary sclerosing cholangitis (SCC), in which prolonged obstruction of extrahepatic biliary tree results in significant injury to cholangiocytes, causing fibrosing inflammatory destruction of intrahepatic and/or extrahepatic biliary system. SCC patients have a similar picture to PSC with multifocal biliary stricturing process. This phenomenon is associated with several reasons such as blunt or surgical abdominal trauma, intraductal stone disease, recurrent pancreatitis, as well as intra-arterial chemotherapy, leading to long-term biliary obstruction. Other conditions associated with SSC include autoimmune pancreatitis, recurrent pyogenic cholangitis, portal biliopathy, AIDS-related cholangiopathy, primary immune deficiency, as well as eosinophilic and/or mast cell cholangitis.[77]

## Diagnosis of PSC

Most patients with PSC are likely to be asymptomatic or present with unspecific symptoms which makes the diagnosis process more challenging. Often, the presence of fatigue, pruritus, and jaundice is suggestive of PSC. Combined with proper imaging, histological and laboratory investigations, the diagnosis of PSC can be ascertained in the presence of cholestatic liver disease. Furthermore, PSC laboratory findings include GGT as well as ALP, which cannot be explained otherwise, in addition to characteristic bile duct abnormalities with segmental dilatations and multifocal strictures, seen by percutaneous transhepatic cholangiography (PTC), ERCP, or MRCP. As part of the investigation process, the levels of IgG4 should be checked for potential elevation in all patients with PSC. Furthermore, the secondary causes of sclerosing cholangitis as well as cholestasis of other reasons if present should be ruled out. For patients with small duct PSC, the symptoms are similar to typical PSC but have normal cholangiogram, this type can be confirmed by histopathology. IBD and non-IBD patients with unexplained cholestasis would require further investigation to exclude PSC.[78,79]

### *Imaging studies*

Even with ERCP being the gold standard for PSC diagnosis, MRCP has been suggested recently as a first-line, noninvasive imaging method with equivalent accuracy and high sensitivity (86%) and specificity (94%). ERCP is considered an invasive imaging technique associated with several adverse events such as bacterial cholangitis and pancreatitis. Yet, ERCP continues to be utilized in daily clinical practice mainly for cases with early-stage PSC limited to the intrahepatic bile duct and if MRCP is contraindicated.[80] Based on the model, comparing various imaging methods in patients with suspected PSC, an initial MRCP imaging, if negative, to be followed by ERCP is currently the most cost-effective approach.[81] The PSC's characteristic cholangiographic findings include annular, short, multifocal strictures between normal or minimal dilated segments, described as a "beaded pattern".

### *Liver biopsy*

In the presence of accurate imaging techniques, liver biopsies are less likely to add useful diagnostic information and changing the PSC patient management approach. However, it is considered an important workup tool for suspected small duct PSC and potential overlap syndrome. Once obtained, the most characteristic histological feature is periductal concentric "onion-skin" fibrosis which can only be identified in less than 25% of liver biopsies. Furthermore, PSC could have nonspecific histological changes with some degree of similarity to primary biliary cholangitis patients. The degree and severity of hepatic lobules and/or portal triads are commonly utilized for PSC staging similar to PBC.[82,83]

**Recommendations**

1. MRCP is the preferred investigation technique for the diagnosis of PSC in patients with cholestatic biochemical profile over endoscopic ERCP. **(Grade I/A)**
2. In patients with typical cholangiographic findings for PSC, liver biopsy is not indicated. **(Grade I/B)**
3. Liver biopsy is recommended to diagnose cases of small duct PSC or to exclude other conditions such as suspected autoimmune hepatitis overlap. **(Grade I/B)**
4. Screening for varices in patients with signs of advanced disease and platelet counts of $<150 \times 10^3$/dL is recommended. **(Grade II-1/B)**

## PSC Treatment

Currently, no effective pharmacological therapy for PSC is available. Immunosuppressants, including corticosteroids, are often considered as treatment options for PSC in the presence of IgG4-associated disease or overlap syndrome. At the same time, moderate histological, biochemical, and clinical improvement have been demonstrated with UDCA only. However, the need for a LT, or risk of CCA and mortality is not significantly associated with UDCA treatment. In addition, it is not recommended for early PSC disease.[84]

For PBC, UDCA has been reported as an effective treatment, whereas its role in managing PSC-related liver diseases is not well recognized. In PSC patients, oral UDCA (13–15 mg/kg/d) has been recommended by EASL as first-line pharmacotherapy life-long, which is not in line with AASLD recommendations advising against UDCA use.[77,83] As of today, the recommended dosing schedule for UDCA is still not clear, which includes both, a high dose of 30 mg/kg/d and a lower dose of 15–20 mg/kg/d. Based on the current literature, liver chemistry improvements have been observed with higher UDCA dosage (20–30 mg/kg/d) and standard-dosage (8–15 mg/kg/d). Other studies have reported further liver recovery on a histological level. Furthermore, several clinical trials failed to report any significant improvements in clinical endpoints using UDCA in patients with PSC, such as delay in the development of CCA, progression to LT, portal hypertension, cirrhosis, or death.[85] However, a placebo-controlled, double-blind controlled trial involving 150 patients over 5 years was stopped because patients randomly assigned to UDCA at doses of 28-30 mg/kg/d were significantly more likely to reach the primary endpoint of development of cirrhosis, varices, cholangiocarcinoma, need for LT, or death. The reasons for the unexpected outcome in the UDCA group than the placebo group were unclear, but based upon these data, high-dose UDCA should be avoided in PSC patients.[86,87]In addition, high-dose UDCA was also associated with an increased risk of colorectal neoplasia among patients with ulcerative colitis and PSC.[88]In patients with PSC, common complications such as fatigue, pruritus, and osteoporosis require supportive care. In general, management of cholestasis' underlying cause helps in relieving associated pruritus. In addition, PSC patients with a dominant stricture in bile ducts would benefit from therapeutic interventions. Further details are provided in the section on the management of extrahepatic complications of cholestasis.

**Recommendations**

1. Corticosteroids and other immunosuppressants are not indicated for the treatment of PSC in adults; however, they can be considered with evidence of an overlap syndrome or IgG4-associated disease. **(Grade I/C)**
2. High-dose UDCA should not be used for the management of patients with PSC. **(Grade 1/A)**
3. Antimicrobial therapy with correction of bile duct obstruction in dominant strictures is considered the optimal treatment option for cholangitis. **(Grade I/A)**
4. The use of long-term, prophylactic antibiotics in patients with recurrent bacterial cholangitis is recommended. **(Grade I/B)**
5. Patients with refractory bacterial cholangitis need to be evaluated for liver transplantation. **(Grade I/B)**

Patients with PSC, who developed bacterial cholangitis related to dominant stricture, respond mostly to therapeutic drainage of the obstruction, along with antibiotics. Long-term prophylactic antibiotics are often considered in recurrent bacterial cholangitis, which can be severe, and considered as a primary indication for LT.[89] Due to the lack of effective nonsurgical treatment for PSC and associated complications, more invasive therapy such as endoscopy and liver transplants are commonly considered on a case-by-case basis.

## Role of ERCP in Treatment of PSC

In general, ERCP is indicated in PSC patients with significant radiological, laboratory, and/or clinical findings during the course of the disease, with the aim to identify biliary strictures amenable to intervention and to exclude superimposed malignancy. For this purpose, a dominant stricture related to PSC is defined as stenosis ≤1.5 mm in diameter of the common bile duct (CBD) and/or ≤1.0 mm of right (RHD) or left hepatic duct (LHD).[90] During the follow-up period, 45% to 58% of PSC patients may present with dominant stricture and findings suspicious for CCA. Before attempting endoscopic therapy, fluorescence in-situ hybridization (FISH), endoscopic biopsy, and/or brush cytology must be performed to exclude the possibility of malignancy.[89]

Major bile ducts subtotal or total stenosis is linked to decreased survival. Repeated endoscopic balloon dilations of dominant stenosis allow the long-term preservation of a functioning common bile duct. The usage of ERCP in managing dominant strictures was investigated in a prospective study that included 171 PSC patients.[91] Study subjects were followed

**Recommendations**

1. ERCP with balloon dilatation is recommended for PSC patients associated with dominant stricture and significant cholestasis. **(Grade I/B)**
2. Biliary stent insertion should be reserved for cases where stricture dilatation and biliary drainage are unsatisfactory. **(Grade I/B)**
3. For PSC with a dominant stricture identified on imaging, the patient should receive ERCP with cytology, biopsies, and FISH, before any attempt at endoscopic therapy to exclude the diagnosis of CCA. **(Grade I/B)**
4. Antibiotic prophylaxis for PSC patients booked for ERCP is recommended to prevent post ERCP cholangitis. **(Grade I/B)**

up for 20 years and showed transplant-free survival of 52% at 10 years and 81% at 5 years. In addition, patients with dominant strictures had a 6% CCA rate. Currently, the best therapeutic endoscopic method for PSC is still controversial and includes stent placement, balloon or catheter dilatation, and sphincterotomy. PSC patients with dominant strictures may not benefit from stenting after balloon dilation. Compared to endoscopic dilatation only, an increase in complications associated with biliary stenting has been reported. Hence, this treatment approach should be reserved for strictures refractory to dilatation. Perioperative antibiotics should be considered to avoid any risk of cholangitis precipitated by injecting contrast agents into an obstructed duct.[92] Biliary sphincterotomy is not suggested as a routine procedure before biliary stenting to avoid ascending cholangitis risks. However, it is advised in challenging, and frequent cannulation-requiring procedures.[93]

## Liver Transplantation in PSC

Liver transplantation is one treatment approach to manage PSC. Its indication includes poor quality of life, progressive muscle wasting, hepatic encephalopathy, hepatocellular carcinoma (HCC), intractable ascites, portal hypertensive gastropathy or variceal bleeding, intractable pruritus, CCA, and recurrent cholangitis. The available literature advocates for Roux-en-Y choledocho-jejunostomy following extrahepatic biliary tree's resection to reconstruct the biliary system.[94] Survival rates have been shown to be 93.7%, 92.2%, 86.4%, and 69.8% at 1-, 2-, 5-, and 10-years, respectively. Overall, 20%–25% of patients may develop recurrent PSC within 5–10 years after LT.[95] Complications following LT include de-novo IBD occurrence, IBD increased activity, and PSC recurrence.[96]

### Recommendations

1. Referral for liver transplantation should be considered for PSC patients with decompensated cirrhosis and advanced liver disease. **(Grade I/A)**
2. PSC patients with severe recurrent bacterial cholangitis or cholangiocyte dysplasia are eligible for liver transplant evaluation. **(Grade III/C)**

## Inflammatory Bowel Disease and PSC

The clinical presentation and course of PSC combined with IBD varies. In general, colitis tends to be more quiescent or mild with a high rate of pancolitis. IBD can be diagnosed during the course of PSC, and in the majority of patients, it precedes PSC by a median time interval of 10 years. De-novo IBD may take place in post-LT PSC patients. Furthermore, PSC can be detected during the course of IBD and sometimes several years following proctocolectomy. For other patients, IBD and PSC are diagnosed concomitantly. Patients with active colitis may have a normal colonoscopy with common features of rectal sparing on a biopsy. In cases of UC without PSC, backwash ileitis is infrequent compared to 16.7% in UC patients with PSC. Compared to Crohn's disease (CD) alone, ileocolitis and colitis are more frequent in PSC patients with CD. However, isolated ileal disease is rarely reported (2%–5%) compared to 30% in typical CD.[97,98] Furthermore, PSC-IBD is identified as a distinctive entity with a high risk of dysplasia and colorectal cancer.

The risk of secondary malignancy has been reported earlier, as 76% of PSC patients with colorectal neoplasia have right-sided distribution. Thus, full colonoscopy is indicated as a standard of care for proper surveillance. Furthermore, IBD patients who received LT should still go through an annual colonoscopy with surveillance biopsies, due to the increased risk of colon cancer. Therefore, surveillance colonoscopy every 1–2 years intervals is recommended in PSC patients with IBD from the time of diagnosis. Patients with no evidence of colitis on their initial screening colonoscopy should undergo a repeat colonoscopy every 3–5 years. If symptoms of colitis emerge earlier, a colonoscopy should be considered.[89,97]

### Recommendations

1. Full colonoscopy with biopsies is recommended in patients with a new diagnosis of PSC and no previous history or symptoms of IBD. **(Grade I/A)**
2. In patients with IBD and PSC, surveillance colonoscopy with biopsies at 1 to 2-year intervals from the time of diagnosis of PSC is recommended to exclude colorectal neoplasia. **(Grade I/B)**
3. The use of UDCA as a chemoprevention agent for colorectal cancer in patients with UC and PSC is not recommended. **(Grade I/B)**
4. PSC patients with IBD should be treated according to guidelines of IBD. **(Grade I/B)**

For patients with both IBD and PSC, the relevant guidelines must be followed for IBD treatment. In UC and PSC patients, UDCA use has been suggested to decrease the risk of colorectal dysplasia; yet, available evidence on its use as a chemo-preventative agent is limited and not suggested on regular basis. PSC patients who received LT would benefit from azathioprine and cyclosporine over tacrolimus, due to a lower rate of *de novo* disease development and IBD exacerbation. In PSC-IBD patients, proctocolectomy outcome and safety are associated with liver disease

severity. In addition, the reconstruction of ileal pouch-anal anastomosis after colectomy is related to an increased risk of pouchitis. The decision to pursue ileal pouch-anal anastomosis instead of ileostomy in PSC-IBD is likely to decrease the risk of local perianastomotic varices.[98]

## Cholangiocarcinoma and other Hepatobiliary Malignancies

Cholangiocarcinoma (CCA) is defined as an extra- or intrahepatic bile duct cancer with high mortality and 5-years survival of <10% with late diagnosis. Following HCC, CCA is the 2nd most common liver tumor accounting for 10%–15% of all hepatobiliary malignancies. The CCA cumulative incidence ranges between 7% and 14%, with a lifetime incidence of 6%–36%. Its risk factors include biliary cirrhosis, cholestasis, as well as bile duct strictures in PSC. In PSC patients, the risk of CCA is not dependent on disease duration as half of CCA cases are detected within the first year of PSC diagnosis, with an annual incidence of 0.5%–1.5% following the first year. In terms of age, younger PSC subjects are diagnosed with CCA compared to CCA in non-PSC subjects. The role of IBD in PSC prognosis is still unclear. In a retrospective study from Mayo Clinic (Minnesota), a total of 399 PSC patients with IBD were evaluated. It was concluded that prolonged duration of IBD was linked with CCA's increased risks; however, colectomy failed to modify this risk.[99-101]

Early diagnosis of CCA in PSC patients is challenging, particularly in dominant strictures cases where benign and neoplastic lesions are morphologically similar on radiographic images. In general, CCA associated with PSC confined to the biliary tree's extrahepatic portion is not common (<10%). The diagnosis of CCA in these cases requires imaging studies specifically in the setting of clinical deterioration of weight loss, abdominal pain, and sudden, worsening jaundice, which indicates advanced disease.

In order to facilitate CCA early diagnosis as well as PSC surveillance, long-term assessment of serological biomarkers is recommended. Carbohydrate antigen 19-9 (CA19-9) is the main serum biomarker studied and used to diagnose CCA, although increased levels of CA 19-9 are also associated with other hepatic complications. Compared to PSC patients without CCA, patients with CCA tend to present with higher CA19–9 serum levels. Furthermore, a lower CA19–9 level is observed in PSC-related CCA compared to CCA patients without PSC. In order to diagnose CCA in symptomatic patients, a cut-off value of 129 U/mL (normal <55 U/mL) for CA19–9 is used with 98% and 79%, specificity and sensitivity, respectively. However, 37% of PSC patients would still have CA19–9 levels >129 U/mL without CCA.[102,103] Moreover, a transient and significant rise in CA19–9 serum level may indicate bacterial cholangitis as a secondary complication in PSC patients.

Several imaging modalities are available for CCA. Combined MRI with MRCP or a multiphasic contrast-enhanced multidetector-row computed tomography (MDCT) scan is considered standard of care for CCA diagnosis. In PSC patients, bile duct brushing obtained with ERCP is simple and highly specific (97%) for CCA. However, the low sensitivity (43%) may prevent its utilization as a diagnostic tool for early detection of CCA in PSC patients.[104]

Surgical intervention for CCA provides the only cure in early-stage disease; yet, few patients are eligible for resection procedure. However, it provides 5-year survival rates of <30% in cases with a negative resection margin. Therefore, neoadjuvant chemoradiotherapy combined with LT is considered in PSC-CCA when confined to the liver hilum or to hepatic parenchyma. Compared to conventional resection, this treatment approach has been associated with less recurrence risk and 5-year survival of up to 80%.[105,106] As such, it should be considered as an alternative option to resection for node-negative hilar with localized CCA.

Hepatocellular carcinoma (HCC) complicating PSC were mentioned in some series but seems to occur quite infrequently.

Gallbladder involvement is a common finding in 40% of PSC cases, which requires close follow-up based on gallbladder carcinoma risks. However, the majority of gallbladder lesions are more likely to be benign, including stones. In general, the prevalence of gallbladder mass lesions hovers around

### Recommendations

1. Evaluation for CCA in PSC patients with sudden clinical or liver biochemical-related parameters deterioration should always be considered. **(Grade I/B)**
2. Screening for CCA via regular cross-sectional imaging with ultrasound or MRI and serial CA19-9 every 6–12 months is recommended. **(Grade I/C)**
3. Surgical resection is suggested for CCA patients with the absence of cirrhosis. **(Grade II-2/B)**
4. Liver transplantation following neoadjuvant therapy in experienced transplant centers is recommended for patients with early-stage CCA not amenable to surgical resection.**(Grade I/B)**
5. Cholecystectomy should be offered to eligible patients with PSC and gallbladder mass lesions to prevent secondary gallbladder adenocarcinoma. **(Grade I/C)**

6%, in which more than 50% are malignant. Gallbladder annual surveillance via ultrasound evaluation is the key. Once diagnosed, cholecystectomy should be considered for eligible PSC patients with gallbladder mass lesions as a prophylactic approach for gallbladder adenocarcinoma.[105]

## OVERLAP SYNDROMES OF AUTOIMMUNE HEPATITIS

### Background

"Overlap syndrome" is a term used to describe an overlap between AIH and either PBC or PSC, with features of both diseases occurring simultaneously or consecutively. The consecutive onset of both conditions supports the association between these particular autoimmune disorders. Overlap syndromes can be classified based on various pathophysiologic mechanisms and clinical presentations as either: (i) a pure coincidence of two independent autoimmune diseases; (ii) a different genetic background that determines the clinical, biochemical, and histologic appearance of one autoimmune disease entity; and (iii) a representation of the middle of a continuous spectrum of two autoimmune diseases.[78,107] Due to the absence of well-validated diagnostic criteria and heterogeneous clinical presentations, the diagnosis of overlap syndrome will require prompt pattern recognition, by complete histological evaluation by an experienced pathologist, exclusion of other causes, and interpretation of radiological and serological findings.

**Recommendation**

1. Overlap syndromes should be considered as a differential diagnosis in patients with either PSC, PBC or AIH, that deviates from the classical presentation of the disease in laboratory, histological, or clinical investigations. **(Grade II-3/C)**

### Classification of Overlap Syndromes and Diagnosis

Overlap syndrome of autoimmune hepatitis is classified into three classical phenotypes of AIH, PBC, and PSC, based on clinical characteristics and serological markers for AIH and either PBC or PSC. Additionally, the overlap feature between AIH and other indeterminate autoimmune cholestatic syndrome variants such as AMA-negative PBC, small-duct PSC, and autoimmune cholangitis, have been defined as "AIH-cholestatic overlap syndrome".[108] In general, overlapping features are observed in liver histology, serologic findings, biochemical tests, clinical findings, and symptoms. An overlap syndrome between PSC and PBC is rare, as both possess high disease-specific features which were reported in a few patients only. In a cohort of 261 patients with autoimmune liver disease, the estimated PBC-PSC overlap frequency was 0.7% over a period of 20 years of prospective follow-up.[109] A differential diagnosis of overlap syndrome should be considered in patients with autoimmune liver disease, which deviates away from its classical serological, and biochemical findings, from a normal clinical course, including the expected therapy responses.[110]

## AUTOIMMUNE HEPATITIS-PRIMARY BILIARY CHOLANGITIS OVERLAP SYNDROME

### Definition and Diagnostic Criteria

Autoimmune hepatitis-primary biliary cholangitis is a diagnostic term used for patients with clinical features of AMA-positive PBC and AIH.[111] Due to the wide spectrum of clinical characteristics and presentations, specific criteria were designated for diagnosing AIH and PBC overlap syndrome. These include the simplified International Autoimmune Hepatitis Group (IAIHG) scoring system, the revised IAIHG scoring system, the IAIHG scoring system, and the Paris criteria with a wide variability of specificity and sensitivity reported for each.[112-115] The Paris criteria in particular were promulgated in 1998 with higher specificity (97%) and sensitivity (92%), for overlap syndrome diagnosis.[112] Furthermore, these are the most commonly utilized criteria which are recognized by AASLD and EASL to establish the overlap syndrome diagnosis in the presence of AIH's histologic findings (moderate to severe lymphocytic piecemeal necrosis) [Tables 3 and 4].[111-117]

The effectiveness of the original and revised IAIHG scoring systems which were used frequently for assessment of possible overlap syndrome in PBC patients was questioned recently. This is mainly due to the complex parameters needed in the systems, in addition to the fact that it was created for distinguishing AIH from PBC and not for diagnosing AIH in PBC patients. As a result, the position paper by IAIHG suggests that using these scoring systems to establish patients' subgroups is not recommended.[113,114]

For overlap syndrome with AIH diagnosis in PBC patients, the application of simplified criteria for AIH diagnosis is recommended. Compared to the revised and original IAIHG scoring system, it is an easier diagnostic tool in overlap syndromes, with minimal limitations [Table 5].[115]

### Epidemiology

In comparison to PSC and AIH overlap, PBC and AIH overlap is the most frequently occurring autoimmune liver disease.[116] In the absence of diagnostic criteria consensus, there is a wide range prevalence of AIH-PBC overlap. In PBC patients, AIH-PBC overlap prevalence is estimated to range between 4.3% and 9.2% compared to 2%–19% in AIH

when revised IAIHG criteria are used.[117,118] A significant observation is the high prevalence of AIH-PBC overlap syndrome among Hispanic patients with PBC disease, using simplified IAIHG criteria or Paris criteria, followed by non-Hispanic patients (31% and 13%, respectively). More frequent complications such as encephalopathy, variceal bleeding, esophageal varices, and ascites were reported, however, statistical significance was not reported.[119]

### Clinical Presentation

Patients may have a sequential development of overlap syndrome starting with PBC followed by the development of AIH.[120] Yet, patients may have a simultaneous presentation of both diseases. In general, overlap syndrome should always be suspected in patients with either PBC or AIH, in which the clinical course deviates from the classical presentation of each disease alone in the absence of a known trigger such as drug-induced liver injury or viral infections. Acute deterioration of liver function or suboptimal response to treatment of a previously well-controlled autoimmune liver disease, should also raise the suspicion of an overlap syndrome. Clinically, patients with overlap syndrome have a predilection to other autoimmune diseases, oftentimes more than one. A retrospective study of 71 patients with overlap syndrome reported 43.6% of patients to have other associated autoimmune diseases, including thyroid disease (18.3%), Sjogren syndrome (8.4%), celiac disease (4.2%), psoriasis (4.2%), rheumatoid arthritis (4.2%), vitiligo (2.8%), and systemic lupus erythematosus (2.8%).[121]

### Disease Natural History

The AIH-PBC overlap syndrome patients' natural history can be inconsistent. Overlap syndrome patients are associated with higher rates of portal hypertension, gastrointestinal bleeding, ascites, esophageal varices, as well as death or the need for LT in comparison to those diagnosed with PBC or AIH alone.[122]

### Management and Treatment

Based on the current literature, no standardized protocol exists for the management of overlap syndrome. One reason is the lack of large RCTs due to the disease's low prevalence rate. A recent meta-analysis included eight RCTs with a total of 214 AIH-PBC overlap patients for analysis. They compared the use of UDCA alone to the use of a combination of corticosteroids and UDCA for the management of AIH-PBC overlap syndrome. Endpoints were clinical symptoms of pruritus and jaundice, changes in ALP and ALT, histologic regression, death, or need for LT, and adverse events. They concluded that although combination therapy of UDCA with corticosteroids had significantly improved ALP, ALT, and histologic regression, but without significant difference in adverse events compared to UDCA alone. In addition, the combination therapy also failed to improve symptoms of pruritus and jaundice or reduction of death or need for LT.[49] Nonetheless, the EASL guidelines recommend the addition of corticosteroid therapy to UDCA for those with severe interface hepatitis in its most recent guidelines.[49] The AASLD guidelines recommend UDCA with or without other immunosuppressive agents for the treatment of overlap syndrome, while highlighting the lack of evidence for optimal therapy and timing of the treatment.[111] Patients with no response to combination therapy of UDCA with corticosteroids may require alternative immunosuppressive agents such as azathioprine or mycophenolate mofetil.[123]

**Recommendation**

1. A diagnosis of PBC/AIH overlap syndrome should be considered in the presence of simultaneous mixed hepatocellular and cholestatic hepatitis picture, with positive autoimmune markers including AMA, and supported by liver biopsy findings of moderate to severe interface hepatitis, or sudden deterioration of stable disease (i.e. PBC or AIH evident clinically or based on laboratory diagnostics) in consecutive presentation. **(Grade II-3/C)**
2. A close observation of patients with overlap syndromes is recommended as they tend to exhibit significantly higher rates of liver-related complication and need for LT compared with those with AIH or PBC alone. **(Grade II-3/C)**

**Recommendation**

1. Patients with PBC/AIH overlap syndromes based on clinical, laboratory, and histological investigations may benefit from a combination therapy of UDCA and immunosuppressive agents to be started as initial therapy. **(Grade III/C)**
2. Overlap syndrome patients with a consecutive pattern would require treatment for the initial presenting disease followed by other modalities to be added if no response to the initial agent. **(Grade III/C)**

## AUTOIMMUNE HEPATITIS–PRIMARY SCLEROSING CHOLANGITIS OVERLAP SYNDROME

### Epidemiology and Diagnostic Features

AIH-PSC overlap is one of the various rare syndromes seen in young adults, adolescents, and children.[124] Compared to AIH/PBC overlap syndrome, more uniform diagnostic

criteria were endorsed for the diagnosis of AIH/PSC overlap syndrome. It is characterized by histologic or overt cholangiographic findings of PSC, in combination with robust histologic features of AIH, historically or concurrently.[125] In particular, PSC characteristic cholangiographic changes include annular, short, multifocal strictures, with dilated or normal ducts intervening segments, that involve the extrahepatic or intrahepatic biliary tree or both, which results in typical "beads-on-a-string" or "beaded like" appearances.

The AIH-PSC overlap syndrome has a sequential development in adults as it initially presents with AIH features followed by PSC diagnosis after many years.[126,127] However, patients with an initial presentation of PSC alone, are rarely diagnosed with AIH later on as a sequential disease. When the revised IAIHG criteria were applied to large series of PSC patients, the prevalence of AIH-PSC overlapping features ranged from 7% - 14%.[128]

### Clinical Presentation

In contrast to AIH, there is a strong association between PSC and IBD. Compared to patients with AIH only, a high prevalence of IBD is reported in AIH-PSC overlap patients, similar to PSC patients.[129,130] Almost 16% of AIH adults may experience IBD which could be suggestive of concurrent PSC. For these cases, cholangiographic assessment is crucial. In addition, the diagnosis of AIH-PSC overlap should be considered in younger AIH patients with poor response to classical immunosuppressive therapy, and in those with histologic bile duct changes, cholestatic liver tests (increased bilirubin or ALP levels), and pruritus.[129]

**Recommendation**

1. AIH/PSC overlap syndrome often occurs in a sequential manner, with AIH being a common initial disease. In any AIH patient presenting with cholestatic pattern and cholangiographic change or in patients who develop IBD, a diagnosis of AIH/PSC overlap syndrome should be considered. **(Grade II-3/C)**
2. AIH/PSC overlap syndrome has demonstrated better survival rates compared to classical PSC, but worse outcome compared to classical AIH and AIH-PBC overlap. Close, long-term follow up is recommended for these cases. **(Grade IIIC)**

### Disease Course

Due to the progressive nature of the disease and lack of effective therapy for PSC, end-stage liver disease could develop up to 17 years following initial diagnosis with a 10-year survival of 65%.[84] However, the introduction of combination therapy (UDCA with immunosuppressive) in AIH-PSC overlap has improved survival rates compared to classical PSC. Yet, it has a worse outcome compared to classical AIH and AIH-PBC overlap disease.[127]

**Recommendations**

1. Management of AIH/PSC overlap syndrome with UDCA and immunosuppressive therapy may be considered based on anecdotal reports. **(Grade III/C)**
2. Biochemical improvement in PSC or AIH/PSC overlap syndrome may not necessarily translate into better long-term clinical outcome; hence, a referral for LT in end-stage disease should be considered. **(Grade III/C)**

### Management and Outcomes

Unlike classical PSC, both EASL and AASLD guidelines have recommended a combination of immunosuppressive and UDCA therapy for AIH-PSC overlap syndrome patients. However, EASL emphasizes that it was based on anecdotal reports and not evidence-based.[78,84] Unlike in PBC and AIH, biochemical improvement in PSC or AIH-PSC overlap may not necessarily translate into better long-term clinical outcomes, nor does it predict survival free of liver-related complications or death.[131]

Potential risks and complications of PSC should be considered in the management plan for AIH-PSC overlap syndrome including pruritus, clinically significant dominant strictures, in addition to surveillance for colorectal cancer, gallbladder cancer, and cholangiocarcinoma in IBD patients (please refer to PSC section for details), although the data on actual risk is still lacking.[132] For end-stage diseases, a referral for liver transplantation assessment is recommended.

## AUTOIMMUNE HEPATITIS–CHOLESTATIC OVERLAP SYNDROME

### Epidemiology and Diagnostic Features

The combined presentation of indeterminate cholestasis, as well as AIH overlap, is known as AIH-cholestatic overlap syndrome, which was labeled previously as autoimmune cholangitis. It is a heterogeneous disease category involving small-duct PSC with AMA-negative PBC patients. In general, the disease is more prevalent in the age group of 40 to 50 years.[133] AIH patients are commonly observed with features of indeterminate cholestasis, with an estimated 5% - 11% overall frequency similar to the frequency of PSC overlap and PBC overlap disease, in AIH patients.[134] The diagnosis of this syndrome is suggested in patients with a clinical diagnosis of AIH, who have cholestatic features

(either histologic, biochemical, or clinical) and absence of AMA, with normal bile duct histology and cholangiography.

Patients with AIH-cholestatic overlap are distinguished from AIH by lower levels of AST, gamma-globulin, and IgG in addition to higher levels of ALP and lower frequency of autoantibodies. They are also distinguished from PBC by higher levels of AST and bilirubin, lower serum IgM, and greater occurrence of autoantibodies. Their female predominance, lower levels of ALP, higher frequency of autoantibodies, and absence of IBD are more characteristic compared to PSC.[133]

**Recommendation**

1. AIH patients presenting with indeterminate cholestasis (i.e., negative AMA with normal bile duct pathology and cholangiography) should be differentiated from classical overlap syndrome via laboratory tests, liver biopsy, and imaging. **(Grade III/C)**

### Management and Outcomes

The overall response rate to treatment is significantly poorer than that of classical AIH, slightly lower than that of AIH large-duct PSC overlap, but similar to AIH small-duct PSC overlap.[107] The use of immunosuppressive agents or UDCA has been reported to be generally ineffective. Yet, no other treatment recommendations for AIH-cholestatic overlap have been suggested from the EASL or AASLD guidelines. Empiric therapy with corticosteroids alone, UDCA alone, or corticosteroids in combination with UDCA depending on the patient risk, predominant manifestation, and intensity of the cholestasis can be offered with unclear effect.[107]

**Recommendation**

1. Considering this disease entity is not well understood with limited evidence, empiric therapy of corticosteroids alone, UDCA alone, or in combination, can be used based on the patient risk, predominant manifestation, and intensity of the cholestasis. **(Grade III/C)**

## IGG4-RELATED SCLEROSING CHOLANGITIS

Immunoglobulin 4-related sclerosing cholangitis (IgG4-SC) is a condition in which biliary manifestations are associated with IgG4-disease.[135,136] It is characterized by elevated IgG4 in the serum, chronic IgG4 plasma cells, and lymphocytic inflammation of the intrahepatic and the extrahepatic biliary system ultimately causing sclerosis and stricture.[135,137-139] IgG4-SC is frequently associated with other forms of IgG4-associated diseases, in particular autoimmune pancreatitis (AIP).[137,140] IgG4-SC was initially considered a biliary manifestation of AIP; however, it was later assigned as a stand-alone entity.[138,141-143]

### Epidemiology

The incidence and prevalence of AIP among the general population of Japan were reported at 1.4/100,000 and 4.6/100,000, respectively. A total of 39% of the included cohort had IgG4-SC, reflecting an estimated incidence and prevalence of 0.5/10,000 and 1.8/100,000, respectively.[144] Considering 10% of IgG4-SC patients are less likely to have associated AIP, the IgG4-SC prevalence may be set at 2/100,000.[145]

### Pathogenesis of IgG4-SC

Similar to other IgG4-related diseases, IgG4-SC is associated with the presence of a high number of IgG4 plasma cells in the involved organ. However, this feature is not specific to IgG4-related diseases.[136] Characteristic histopathological features of IgG4-SC include obliterative phlebitis, storiform fibrosis, and dense lymphoplasmacytic infiltration.[136,146]

### Clinical features of IgG4-SC

In general, males are more commonly affected, with a range of 79% - 83% of affected patients.[137,135] In addition, it is likely to affect Japanese adults with a mean age of 66 years (range of 23–88.5 years).[137,145,147] Similar data were reported from the United Kingdom and the United States.[148,149]

In total, 28% of IgG4-SC patients are asymptomatic.[137,149] Obstructive jaundice is the most common clinical feature in IgG4-SC affecting 35%–77% of patients.[137,148-150] Other features include pruritus (13%), abdominal pain (11%), and cholangitis (10%). Acute pancreatitis, poor appetite, and weight loss are less likely to be noted. IgG4-SC may present with concomitant IgG4-associated diseases such

**Table 5: Simplified international autoimmune hepatitis group scoring system**

| Clinical Feature | Score |
|---|---|
| ANA or SMA | 1 |
| Titer ≥1:40 | |
| Serum IgG | 1 |
| >Upper limit of normal | 1 |
| >1.1 times upper limit of normal | 2 |
| Histologic findings | |
| Compatible with AIH | 1 |
| Typical of AIH | 2 |
| Hepatitis viral markers | |
| Negative | 2 |
| Aggregate score without treatment | |
| Definite AIH | ≥7 |
| Probable AIH | ≥6 |

**Table 6: Clinical diagnostic criteria of IgG4-related sclerosing cholangitis**

| |
|---|
| **Diagnostic Items** |
| 1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of the bile duct wall |
| 2. Hematological examination shows elevated serum IgG4 concentrations (≥ 135 mg/dL) |
| 3. Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis |
| 4. Histopathological examination shows: |
| a. Marked lymphocytic and plasmocyte infiltration and fibrosis |
| b. infiltration of IgG4-positive plasma cells>10 IgG4-positive plasma cells/HPF |
| c. Storiform fibrosis |
| d. Obliterative phlebitis |
| Option: effectiveness of steroid therapy |
| A specialized facility, in which detailed examination such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out |
| **Diagnosis** |
| Definite diagnosis |
| 1.+3. |
| 1.+2.+4. a.b. |
| 4. a., b., c. |
| 4. a., b., d. |
| Probable diagnosis |
| 1.+2.+ option |
| Possible diagnosis |
| 1.+2. |
| It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility |

as AIP, which could vary among different populations (i.e., 87% in Japanese population; 95% among the USA and the UK populations)[136,137,148,149] Body systems of IgG4-related diseases less likely to be associated with IgG4-SC include kidneys (1.15%–26.4%), salivary gland (5.6%–15%), retroperitoneum (7%–9.4%), lungs (0.7%–3.8%), lymph nodes (3.8%), and aorta (1.15%).[137,148]

## Diagnosis of IgG4-SC

Diagnosis of IgG4-SC requires confirmatory radiological, laboratory, and histological assessments. However, no single specific diagnostic test is available as of today for clinical use. A clinical diagnostic criterion for IgG4-SC was proposed by Ohara *et al*., which was then adopted by EASL in 2014 [Table 6].[138,151] Furthermore, a second diagnostic criterion based on cholangiographic findings was established in 2012 by Nakazawa *et al*.[139] In 2019, a group from Japan proposed the third clinical practice guideline for IgG4-SC.[145] Both 2012 and 2019 criteria were based on the utilization of cholangiography analysis, serum IgG4 levels, association with AIP, or other organs IgG4 disease, and histopathological findings.[138,139]

In general, elevation in serum IgG4 has been reported in 84%–90% of IgG4-SC patients. Moreover, a cut-off value of 135 mg/dL for IgG4-SC diagnosis is widely accepted in the clinical practice although, Ohara *et al*. reported 10.5% of IgG4-SC patients have serum values below this level.[137-139,145,152] Yet, elevated serum IgG4 was reported to be of no specific value based on cohorts of cholangiocarcinoma (CC) in PSC patients.[153] Ohara *et al*. have shown 7.7% of the pancreatic cancer, CC, and PSC patients in control group had elevated serum IgG4 levels (>135mg/dl).[139] Elevated IgG4 at cut-off levels of 119 mg/dL for IgG4-SC compared to pancreatic cancer, 117 mg/dL for IgG4-SC compared to PSC, and 138 mg/dL for IgG4-SC compared to CC, Ohara *et al*.[152] showed an 87.6%–93.9% specificity and 89.8%–91.2% sensitivity for the diagnosis of IgG4-SC. On further subgroup analysis of the four radiological types of IgG4-SC, types 3 and 4 IgG4-SC had IgG4 levels of 138 mg/dL with lower sensitivity and specificity. Hence, a higher cut-off value of serum IgG4 was set at 207 mg/dL for better differentiation of IgG4-SC from CC.[152]

## IgG4-SC Imaging Diagnosis

ERCP is considered the standard-of-care for IgG4-SC radiological evaluation and diagnosis. Nakazawa *et al*. in 2006 had established a cholangiographic classification for IgG4-SC, adopted by both by Ohara *et al*. in 2012 and the new Japanese guidelines in 2019.[138,145,153] Based on this classification, IgG4-SC is sub-divided into four types: a) type 1 involves diffuse stenosis of intra- and the extrahepatic bile ducts; b) type 2 is divided into 2a and 2b which includes intrahepatic bile ducts narrowing with restenotic dilatation (segmental) or without restenotic dilation (diffuse), respectively; c) type 3 involves stenosis which is present in both the hilar hepatic lesion as well as common bile duct lower part; and d) type 4 involves only hilar hepatic lesion.[138,153] Based on the current literature, type 1 IgG4-SC is the most common (64%) followed by type 4 and type 3 (10% for both).[137] Other reports indicated intrahepatic biliary stricture as the most common finding (70%) in IgG4-SC patients.[148] In addition to ERCP, CT scan and MCRP can also be used for radiological IgG4-SC diagnosis. Endoscopic ultrasound is an additional radiological modality that can be applied in IgG4-SC diagnosis.[154]

One advantage for ERCP is cytology sampling which could be utilized to exclude CC. In addition, bile duct biopsy is recommended for IgG4-SC diagnosis, although more difficult to obtain[138,145] It could demonstrate all previously mentioned features of obliterative phlebitis, storiform fibrosis, and lymphoplasmacytic infiltration in order to reach a diagnosis.[136,138,145] IgG4-SC cholangiographic features could mimic those for CC, PSC, and pancreatic cancer.[139,155] Furthermore, IgG4-SC histopathological features as well

as other IgG4-related diseases can sometimes mimic sarcoidosis and multifocal fibrosclerosis.[136,148]

### Treatment of IgG4-SC

Corticosteroid therapy is recommended for all IgG4-SC patients, and prednisolone is one with an effective outcome.[137,138,145,151] The recommended dose is 0.5–1 mg/kg/d or a starting dose of 30–40 mg daily as an initial dose for 2–4 weeks.[135] Afterwards, the dose can be reduced gradually, tapered down to a 5 mg maintenance dose on a weekly basis achieved in 2–3 months, with laboratory and radiological monitoring.[138,145,147,151] Most patients (90%–100%) respond very well to prednisolone therapy with good disease control.[137,147-149] Once on a maintenance dose, it is recommended to continue for 3 years.

The risk of relapse on maintenance therapy is estimated to range between 19% and 54%[137,148] For these cases, it is recommended to reintroduce prednisolone. Additional treatment options for relapse include azathioprine, mycophenolate mof`etil, and methotrexate, with no clear evidence of benefit.[137,145,149] Endoscopic management and biliary drainage are recommended in patients with evidence of obstructive jaundice. In addition, 40.6%–50% of IgG4-SC patients benefited from endoscopic stent placement.[137,145,150] Surgical intervention is not usually recommended in IgG4-SC; however, patients suspected of CC and pancreatic cancer are eligible candidates.[137,148]

### Prognosis and Outcomes of IgG4-SC

Based on the literature, the follow-up duration varied significantly and ranged between 29.5 and 49.2 months.[137,148,149] During this period, the disease outcome was favorable with a restenosis rate of 1.6%–16.5% in 1–5 years. Decompensated cirrhosis is a rare feature for IgG4-SC in the Japanese population.[137] However, it was reported in 5.2% and 7.5% of the US and United Kingdom patients, respectively.[148,149] At the same time, secondary CC is uncommon and liver- and biliary-related mortality are estimated to range between 0.8% and 2.6%.[137,145,148,149] None of the reported patient cohorts from Japan and the United States required liver transplantation; however, one patient from the UK study required transplantation.[137,148] The cumulative 5-year and 10-year survival rates from mortality related to liver disease and biliary disease were reported at 98.9% and 97.7%, respectively.[137]

#### Recommendations

1. IgG4-SC is an uncommon cause for cholestatic jaundice, and should be considered in patients with AIP and other IgG4-related disorders and cholestasis. **(Grade II-2/B)**
2. The diagnosis of IgG4-SC is based on several criteria including elevated IgG4, cholangiographic findings, and AIP or other IgG4 related diseases. **(Grade II -2/B)**
3. PSC and CC should be considered and ruled out in patients with IgG4-SC. **(Grade II-3/C)**
4. Prednisolone is the treatment of choice for patients with IgG4-SC with excellent outcomes in majority of patients. **(Grade II-2/A)**
5. Consider re-induction with prednisolone therapy in IgG4-SC for disease recurrence after withdrawal of maintenance treatment. **(Grade II-3/B)**
6. Endoscopic dilatation and stenting are required for IgG4-SC patients with evidence of biliary obstruction. **(Grade II-3/B)**

## CHOLESTATIC DRUG-INDUCED LIVER INJURY

Cholestatic drug-induced liver injury (C-DILI) is a term used to describe a R ratio of <2 of serum ALT to serum ALP expressed as multiples of their upper limit of normal (ULN) at the onset of hepatic injury.[155-157] A recent modification to C-DILI calculation was adopted using a modified R ratio and the same parameters, but at the peak of the liver injury.[158] Based on the current literature, C-DILI represents 23%–32% of overall drug-induced liver injuries. It has various presentations ranging from pure cholestasis due to impaired biliary secretion, without biliary injury, to cholestasis associated with an acute or chronic biliary injury.[157-161]

### Clinical Presentations and Patterns of C-DILI

Compared to patients with hepatocellular injury, patients with C-DILI are typically older, with a mean age of 54 to 60 years. Women are less commonly affected with a latency period (calculated from exposure to the development of DILI) compared to hepatocellular DILI (median of 15–31 d vs. 20–46 days). Patients with C-DILI are more likely to have jaundice compared to hepatocellular DILI (78% vs. 65%). Other common features include pruritus, skin rash, abdominal pain, and fever.[157,159,162] A common clinical feature of C-DILI is an acute cholestatic pattern that is subdivided into two subtypes. Bland cholestasis, complicating the use of anabolic steroids and oral contraceptives, is seen similarly in sepsis and heart failure. The second is cholestasis associated with liver cell injury causing a mixed pattern of

liver injury. This form is seen with macrolide antibiotics and chlorpromazine.[157,160,161,163]

Chronic cholestasis pattern has different forms. The first involves chronic cholestasis with vanishing duct syndrome and severe or complete loss of bile ducts on liver biopsy.[162,163] In some cases, it could progress to cirrhosis with features similar to PBC, with negative AMA.[160] Several causative agents have been described including amoxicillin-clavulanate, antipsychotics, antiepileptics, central nervous system medications, and cardiovascular agents.[157,159,162,164] In addition, several herbal agents such as angelica, archangelica, and artemisinin have been associated with 11% of this form of C-DILI.[162] The second form of C-DILI chronic cholestasis is known as secondary sclerosing cholangitis (S-SC) and could affect large bile ducts similar to PSC. This form has been described as a complication linked to intra-arterial infusion of chemotherapy for hepatic metastasis, as a result of ischemic injury to large bile ducts[163,165] Other medications related to this form of C-DILI include amoxicillin-clavulanate, green tea, and sevoflurane.[165,166]

### Diagnosis of C-DILI

Similar to other forms of DILI, C-DILI is a diagnosis of exclusion. It relies primarily on establishing a relationship between drug exposure and features of hepatic injury. A detailed history of all prescribed and nonprescribed medications and herbal agents is essential to reach a diagnosis.[160,167,168] No particular laboratory tests for DILI are available; however, excluding other possible liver diseases is indicated according to the clinical features. Cholangiography using MRCP or ERCP could be requested if sclerosing cholangitis is suspected. On the other hand, liver biopsy is not commonly indicated; however, it may be needed to exclude other causes for hepatic injury.[167,168]

### Treatment and Outcome of C-DILI

Early discontinuation of the causative agent is the mainstay for treatment. In an acute injury, fast recovery is anticipated; however, patients with chronic injury may need a longer recovery of more than 6 months.[157,169] UDCA is one treatment option, which has been used for symptomatic treatment with minimal supporting evidence.[167] Compared to hepatocellular DILI, C-DILI has a higher rate of chronicity (54% of patients) compared to 22% of those who had hepatocellular DILI.[166-168] On the other hand, C-DILI is less likely to have liver-related mortality, which varies based on reporting centers.[157] Furthermore, it is associated with a lower rate of liver transplantation.[157,158]

**Recommendations**

1. C-DILI is frequently encountered with commonly used medications like antibiotics. **(Grade II-2/A)**
2. C-DILI presentation varies from mild acute form to severe cholestasis that can mimic PBC or PSC. **(Grade II-2/B)**
3. The diagnosis of C-DILI is based on the exclusion of other causes of liver injury and establishing a relationship of exposure to the causative agent. **(Grade II -2/C)**
4. Early withdrawal of possible causative agents is the mainstay for the treatment of C-DILI. **(Grade II-2/A)**

## CHOLESTATIC LIVER DISEASES IN PEDIATRICS

Cholestatic jaundice in children is an uncommon condition and yet can be a serious disease leading to hepatobiliary dysfunction. Early detection by primary care physicians with timely referrals to pediatric hepatologists is crucial for optimal treatment and favorable prognosis. Cholestatic liver diseases in the pediatric population can be classified into genetical cholestatic liver diseases and fibro-polycystic liver diseases.

## GENETIC CHOLESTATIC LIVER DISEASES

Cholestasis is considered a highly selective impairment of one of many steps involved in the synthesis, secretion, and modification of bile acids, resulting in liver damage.[170] It is estimated that 45% of children with cholestatic liver diseases are genetically driven.[171] Genetic diseases of cholestasis include progressive familial intrahepatic cholestasis (PFIC), progressive familial hypercholanemia, and bile acid synthesis defects (BASD).

### Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis can be classified into PFIC1, PFIC2, and PFIC3, with an estimated incidence of 1/50,000 – 100,000.[172] All of these types represent the defects in ABCB4 gene encoding multidrug resistance (MDR3) protein, ABCB 11 gene encoding bile salt export pump (BSEP) protein, and ATP8B1 gene encoding the familial intrahepatic cholestasis 1 (FIC1) protein. Both PFIC2 and PFIC3 could represent 97% of all PFIC cases with variable ages at presentations.[173] Adult PFIC cases are likely to be associated with the MDR3 deficiency type. Furthermore, PFIC1 and PFIC2 are associated with the infantile presentation of failure to thrive, pruritus, and jaundice but normal or low GGT activities. Cholangiocyte epithelial injury and detergent bile salts inefficient inactivation

are led by PFIC3, resulting in higher GGT cholestasis, which is a classical feature for PFIC3. For adults, common symptoms range from neonatal cholestasis to biliary cirrhosis and intrahepatic cholestasis of pregnancy. Both PFIC2 and PFIC3 could carry high risks for HCC in comparison to other cholestasis types.

### Tight Junction Protein Type 2 (Familial Hypercholanemia)

Tight junction protein type 2 (TJP2) is characterized by higher serum bile acid and normal GGT with progressive cholestasis, that can lead to end-stage liver disease. TJP2 primary function is to prevent back diffusion of bile salts from canaliculi to blood circulation, leading to an increase in serum bile acid with normal GGT. For some cases, fat malabsorption and pruritus can complicate cholestasis with high liver enzymes and bilirubin, resulting in end-stage liver disease and eventually liver transplantation.[174]

### Bile Acid Synthesis Defect

Inborn errors of bile acid synthesis are a life-threatening cholestatic liver disease in infants which can result in progressive neurological disease during childhood or adult life. Failure to synthesize bile acids may lead to defective micelle formation, fat malabsorption, and cholestasis. This is a common complication resulting from bile acid substrate toxic effect on hepatocyte BASD, characterized by conjugated hyperbilirubinemia with raised transaminases and normal GGT. The histopathological analysis is more likely to show giant cell hepatitis. Both types of BASD could often be treated effectively with bile acid replacement therapy. Hence, early diagnosis is crucial for a better prognosis.[175] The approach to cholestatic genetic liver diseases in children is shown in Figure 1.

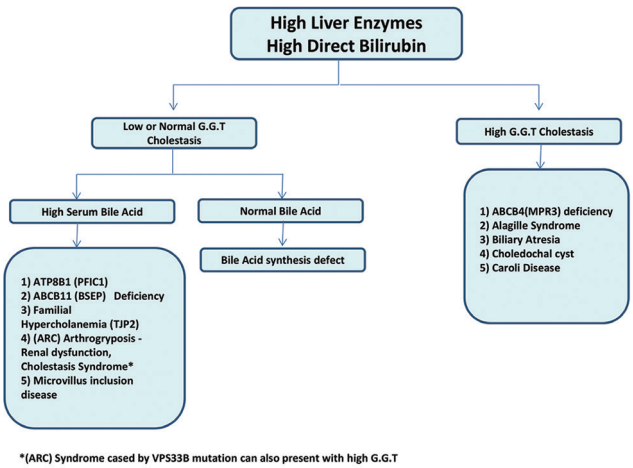


**Figure 1:** Approach to cholestasis in pediatric patients[173]

## FIBRO-POLYCYSTIC LIVER DISEASES

Fibro-polycystic liver diseases, known as ductal plate malformations, are a group of associated congenital disorders resulting from abnormal development of the biliary ductal system. They include congenital hepatic fibrosis, Caroli's disease, choledochal cysts, polycystic liver disease, and biliary hamartomas.

### Congenital Hepatic Fibrosis

Congenital hepatic fibrosis (CHF) is an autosomal recessive disease derived from biliary dysgenesis secondary to ductal palate malformation.[176] It coexists often with Caroli's disease, autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), Meckel-Gruber, Ivemark, Jeune, Joubert, and Arima syndromes.[177] Four clinical forms of CHF have been identified as the following: 1) portal hypertension, which the most common form, and severe in the presence of portal vein abnormality; 2) cholangitic cholestasis and recurrent cholangitis; 3) mixed; and 4) latent presentation for adult.[178]

Laboratory evaluation in portal hypertensive clinical form is usually unremarkable. For most patients, hepatosplenomegaly, esophageal varices, and gastrointestinal bleeding may occur in the 5$^{th}$ or 6$^{th}$ decade of life. In younger children, CHF is often accompanied by renal cysts. Ultrasound examination is the most informative diagnostic modality of CHF and often shows increased echogenicity of the liver, cysts in the hepatic parenchyma, splenomegaly, and fibrocystic changes in kidneys.[179] In addition, MRCP typically shows cystic dilatations and irregularities of the intrahepatic bile ducts and abnormally large left lobe of the liver. CHF appears pathologically by a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts, which is diagnostic, and can occur in hereditary PKD.

As of today, no therapies can repair primary ductal plate malformations, reverse the fibrosis, or resolve aberrant biliary trees. Hence, LT is commonly suggested as the only treatment option. Children with coexisting end-stage renal failure, as a result of polycystic kidney disease, may require liver and kidney transplantation.[180]

### Caroli's Disease

Caroli's disease is a rare congenital disorder of the liver characterized by saccular dilatation of the large intrahepatic biliary ducts. It is transmitted as autosomal recessive in the same family.[181] Caroli's disease is the least common form, characterized by bile ductular ectasia without other apparent hepatic abnormalities. However,

Caroli's syndrome is the more common variant, in which bile duct dilatation is associated with CHF.[181] Common clinical features include intermittent abdominal pain and hepatomegaly. In addition, recurrent bouts of cholangitis, abscess due to bile stasis, septicemia, and stone formation are common complications.

Acute obstructive episodes are potential complications characterized by fever, pruritus, jaundice, tender hepatomegaly with modest elevations of serum bilirubin, aminotransferases, and alkaline phosphatase.[182] For these cases, ultrasound evaluation is often suggested; however, MRCP may serve as the examination of choice.[182] Recommended treatment options for Caroli's disease include supportive care with antibacterial agents for cholangitis and UDCA for lithiasis. In patients with diffuse involvement, liver transplantation is the only effective modality. Long-term follow-up with ultrasound examination and tumor marker assessment is recommended, considering the high risk of cholangiocarcinoma in this particular group of patients.[183]

### Choledochal Cysts

Choledochal cysts are congenital anomalies of the bile ducts defined as abnormal, disproportionate, cystic dilatation of the biliary duct.[184] Overall, 60% of choledochal cysts are likely to present during the first year of life; however, other cases may present in adulthood with a higher incidence in females.[184] Choledochal cysts are often associated with cystolithiasis, pancreatitis, cholangitis, portal hypertension, and malignancy.[185] Choledochal cysts can be diagnosed using imaging modalities such as ultrasound, CT, MRCP, and ERCP, with reasonable specificity.[185]

Surgical management of choledochal cysts is the treatment of choice, and is based on cyst type and associated hepatobiliary pathology.[186] In general, excision of all bile duct cysts and bile flow re-establishment by mucosa-to-mucosa biliary–enteric anastomosis is recommended. The application of external drainage alone has no definitive role in the surgical management of choledochal cysts. Long-term follow-up must be maintained in adults due to the age-related risk of malignancy and the frequency of late anastomotic strictures in patients treated without cyst resection.[186]

## MANAGEMENT OF EXTRAHEPATIC MANIFESTATIONS OF CHOLESTASIS

### Pruritus

This is a common manifestation of any cholestatic liver disease with a significant impact on a patient's quality of life. As of today, pruritus' underlying pathophysiology with fluctuation of the symptoms throughout the day is not well understood.[187] A common complication for pruritus includes discoloration of body secretions, hepatic dysfunction, and hepatitis.[188] Cholestyramine is considered the gold standard for pruritus management, which has to be spaced out from UDCA and other drugs by four hours.[189] It is usually mixed with water or sometimes fruit juice in order to improve medication tolerance.[190] Rifampin is suggested as the 2nd line of treatment, which is a pregnane X receptor agonist with great efficacy in the management of pruritus after 2 years of treatment.[191-193] Opiates antagonists can be utilized as a 3rd line of treatment with potential adverse events including withdrawal reactions, confusion, and pain.[192-194] Fibrates use in moderate to severe pruritus showed superior results to placebo, which was demonstrated in a double-blind, randomized, placebo-controlled trial, Fibrates for cholestatic itch (FITCH) where bezafibrate (400 mg daily) was used for 21 days.[195] Other therapeutic

**Recommendations**

1. Consider cholestasis work up with biochemical and imaging evaluation; possibly liver biopsy in children with prolonged jaundice. **(Grade II-2/A)**
2. Neonatal or child cholestasis is defined as conjugated serum bilirubin >1 mg/dL (>17 μmol/L), if the total serum bilirubin is ≤5 mg/dL (≤ 85 μmol/L), or >20% of total serum bilirubin when it is >5 mg/dL (> 85 μmol/L). **(Grade II-2/A)**
3. Consider imaging with ultrasound, CT, or MRCP for diagnosis of CHF, choledochal cyst, and Caroli's disease polycystic liver disease. **(Grade II-1/B)**
4. Simultaneous next-generation sequencing for multiple genes and whole-exome or whole-genome sequencing enable rapid and affordable molecular diagnosis for many genetical cholestasis including PFIC, familial hypercholanemia, and BASD that are less likely to be directly diagnosed via standard blood tests or liver biopsy. **(Grade II-2/C)**
5. It is recommended to start UCDA at the dosage of 20 mg/kg/d in divided doses in cholestasis. UDCA can be discontinued when cholestasis has resolved. **(Grade II-1/B)**
6. A caloric intake of approximately 125% more than the recommended dietary intake for infants with cholestasis, with a preference for MCT as a lipid source, is recommended. Adequate supplementation with vitamins A, D, E, and K must be monitored. **(Grade II-2/C)**

agents include sertraline with minimal efficacy and unclear mechanism of action.[196] Invasive procedures such as bile duct drainage, plasmapheresis, and extracorporeal albumin dialysis have been reported with some efficacy in several case reports[197-200] Recipients of LT are likely to experience relief from pruritus related to cholestasis.[201]

## Fatigue

It is a common presentation, specifically in PBC and other cholestatic liver diseases, with unclear pathogenesis. Part of the management approach is to rule out potential underlying contributing factors such as depression, autonomic dysfunction with postural hypotension, and hypothyroidism.[202,203] Supportive measures should be considered to facilitate the adaptation of fatigue symptoms.[204] Modafinil use for the treatment of fatigue in PBC in a randomized, double-blind, placebo-controlled study failed to show benefit despite being well tolerated by patients.[205]

## Osteoporosis

Osteoporosis is a common complication of cholestatic liver disease patients, associated with known risk factors for osteoporosis, such as low body mass index, inactivity, age, female gender, smoking, and family history. For such cases, vitamin D and calcium supplementations are recommended, with no supporting evidence.[206] Hormone replacement therapy is a therapeutic agent with potential benefit in menopausal patients.[207,208] In addition, the use of testosterone is not recommended in male patients due to the risk of HCC.

The application of bisphosphonates, specifically alendronate, in patients with osteoporosis has been reported.[209,210] Evaluation of osteoporosis patients includes bone mineral density assessment dual-energy x-ray absorptiometry (DEXA) at the time of diagnosis, with follow-up in the first year and every 5 years, based on the condition severity.[211] Patients with a risk of fat-soluble vitamin deficiency (A, E, K) and clear symptoms (e.g. steatorrhea) would benefit from enteral supplementation. In addition, vitamin K is suggested for patients with cholestatic liver disease as well as those scheduled for invasive procedures.

## Hyperlipidemia

Hyperlipidemia is a common complication of cholestatic liver disease, with a possible increase in cardiovascular risk factors in PBC patients, with a pooled risk ratio of 1.57 (95% CI,1.21–2.06).[212] UDCA will have a role in the treatment of elevated low-density lipoprotein cholesterol levels. Statins and fibrates can be used in the presence of a family history of hyperlipidemia and additional cardiovascular risk factors.[213,214]

### Recommendations

1. Cholestyramine at a dose of 4g (up to four times/d) is recommended as pruritus' 1st line of treatment. It is advised to space it out from any other drugs by 4 hours. **(Grade II-3/B)**
2. Rifampin at a starting dose of 150 mg (up to 600 mg/d) is recommended as 2nd line of treatment while monitoring the hepatic profile. **(Grade I/A)**
3. Naltrexone is recommended as 3rd line of treatment at a starting dose of 25 mg/d. **(Grade III/C)**
4. Sertraline can be used as an alternative option if the above-mentioned options fail to control pruritus. **(Grade II-2/C)**
5. It is recommended to rule out secondary fatigue causes in cholestatic liver disease, such as hypothyroidism and autonomic dysfunction patients. **(Grade III/C)**
6. Supportive measures including psychological support are recommended in patients with fatigue and cholestatic liver disease. **(Grade II-2/3/C)**
7. Initial assessment for osteoporosis severity is recommended for every patient with cholestatic liver disease. **(Grade III/C)**
8. Initial DEXA bone mineral density assessment is recommended for patients with cholestatic liver disease and have to be followed up based on disease severity. **(Grade III/C)**
9. Starting calcium (1000–1200 mg/d) and vitamin D (400–800 IU/d) supplements in cholestatic liver disease have been suggested. **(Grade III/C)**
10. Bisphosphonates treatment (specifical alendronate) for patients with DEXA T score <-2.5 or after a pathological fracture is recommended. **(Grade I/B)**
11. Parenteral vitamin K supplementation in patients going for invasive procedures is recommended. **(Grade II-2/C)**
12. Enteral supplementation with vitamin A, E, K for patients with overt steatorrhea and cholestasis is recommended. **(Grade III/C)**
13. We recommend lipid-lowering agents for patients with cholestatic liver disease and hyperlipidemia in the presence of cardiovascular risk factors. **(Grade II-2/A)**

## Contribution

All Authors have contributed equally to this manuscript.

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## Conflicts of interest

There are no conflicts of interest.

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