HHS Public Access

Author manuscript

Liver Res. Author manuscript; available in PMC 2020 February 10.

Published in final edited form as:

Liver Res. 2019 June ; 3(2): 118–127. doi:10.1016/j.livres.2019.04.001.

Preventative care in cholestatic liver disease: Pearls for the specialist and subspecialist☆

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Abstract

Cholestatic liver diseases (CLDs) encompass a variety of disorders of abnormal bile formation and/or flow. CLDs often lead to progressive hepatic insult and injury and following the development of cirrhosis and associated complications. Many such complications are clinically silent until they manifest with severe sequelae, including but not limited to life-altering symptoms, metabolic disturbances, cirrhosis, and hepatobiliary diseases as well as other malignancies. Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are the most common CLDs, and both relate to mutual as well as unique complications. This review provides an overview of PSC and PBC, with a focus on preventive measures aimed to reduce the incidence and severity of disease-related complications.

Keywords

Biliary tract diseases; Primary sclerosing cholangitis (PSC); Primary biliary cholangitis (PBC); Cirrhosis; Inflammatory bowel disease (IBD); Metabolic bone disease; Pruritus; Prophylaxis

☆Edited by Peiling Zhu and Genshu Wang.

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Authors' contributions

A. Malik and K. Zakharia drafted the manuscript; A. Malik and A. A. Kardashian designed the tables; A. A. Kardashian and J. H. Tabibian provided critical feedback; C. L. Bowlus and J. H. Tabibian provided supervision and technical support.

Conflict of interest

The authors declare that they have no conflict of interest.

1. Introduction

"Cholestasis" is a compound expression from the Greek word meaning "standing still of bile". Liver disease that occurs due to or characterized by cholestasis is often referred to as cholestatic liver disease (CLD). CLD includes a wide variety of disorders, including genetic, congenital, immunological, infectious, and idiopathic. The site of impaired bile formation or flow through the biliary tract in CLDs can be at essentially any level, be it the hepatic canaliculi, ductules, or large ducts, and as such, manifestations and management may vary accordingly. Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) embody the most impactful CLDs, both being associated with significant morbidity and mortality worldwide. During the past decade, there have been considerable developments in the understanding and clinical care of PSC and PBC as well as their associated complications, including cirrhosis, liver failure, malignancies, bone disease, and nutritional deficiencies. This review focuses on the established and emerging preventive measures aimed at mitigating morbidity due to the symptoms, complications, and diseases associated with PSC and PBC.

2. Overview of PSC and PBC

2.1. Pathogenesis

PSC is an idiopathic, chronic, progressive CLD associated with inflammation, fibrosis, and stricture formation involving intrahepatic and/or extrahepatic biliary ducts.[1] Several genotypic and human leukocyte antigen (HLA) haplotype associations have been detected with PSC.[1–6] One proposed hypothesis is that PSC may develop following exposure of a pre-disposed individual to (as yet uncertain) exogenous factors, including, but not limited to, perturbations in the enteric microbiome.[7]

In comparison, PBC, formerly known as "primary biliary cirrhosis", is considered to be an autoimmune disease caused by environmental insults in genetically predisposed individuals (Table 1).[8] Epidemiological studies have suggested various potential etiologic insults and associations, including exposure to nail polish, xenobiotics, and smoking, among others.[9–11]

2.2. Clinical epidemiology

The incidence and prevalence of PSC vary with geographic location, and in many regions of the world, remain unknown. In the United States, the estimated incidence and prevalence of PSC range from 0.5 to 1.5 and 5–16 per 100,000 individuals, respectively.[1] Approximately 5% of patients with inflammatory bowel disease (IBD) have PSC, whereas nearly 75% of patients with PSC have IBD. In Far Eastern populations, a smaller proportion of patients with PSC (closer to 20%) have IBD, the underlying reasons for which remain unclear. PSC has an approximately 2:1 male predominance pattern and is most commonly diagnosed around 30–40 years of age, though presentation may be much earlier or later in life.[1]

Compared to PSC, PBC affects women more commonly, with a 9:1 female-to-male ratio (Table 1). PBC has a higher global incidence and prevalence, with an age-adjusted incidence of 2.7 and prevalence of 40 per 100,000 person-years, respectively.[12–14] A large proportion

of patients with PBC are asymptomatic and with early stage disease when diagnosed;[15] however, African American and Latino populations have been reported to have more severe liver disease upon initial diagnosis, the reason for which are not well understood.[16]

2.3. Signs and symptoms

Approximately 50% of patients who are diagnosed with PSC are asymptomatic at the time of diagnosis. In these patients, the diagnosis is often made following the evaluation of abnormal serum liver tests in patients with IBD or incidentally noted abnormal serum liver tests in individuals undergoing routine or health insurance-related screening. Among those who do have symptoms, fatigue and pruritus tend to be the most common and complicated. Fatigue is non-specific, as it can be seen in other CLDs and advanced liver disease in general, and its etiology in CLDs is unclear. Pruritus is a presenting symptom in approximately one-third of patients with PSC.[17] It is exacerbated by heat, pregnancy, wool exposure, and can be worse at night. It has been proposed that increased levels of circulating bile salts, opioidergic molecules, and other metabolites may cause pruritus in CLD, though these have been only variably replicated.[18,19] Though PSC is a chronic, usually slowly progressive disease that can remain asymptomatic for a prolonged period of time, some patients follow an aggressive, highly symptomatic disease course and/or present with jaundice, recurrent acute cholangitis, and already advanced liver disease, all of which may portend a worse prognosis.

Patients with PBC tend to invariably develop symptoms within a median of 2–4.2 years of diagnosis.[20,21] Having early symptomatic disease appears to be associated with a shorter median survival;[20,21] indeed, one study for example showed a median survival of 7.5 years for symptomatic patients as compared to 16 years for asymptomatic patients.[22] PBC shares generally similar symptoms with PSC, including pruritus and fatigue. Fatigue is the most common symptom, affecting approximately 78% of patients with PBC and is associated with autonomic neuropathy, hypothyroidism, and overall decreased survival.[23–26] Pruritus is a more specific symptom in PBC (and CLDs in general), affecting approximately 30–70% of patients. Several etiologies have been proposed to account for this symptom, including increased opioidergic neurotransmission and circulating bile salts, similar to PSC.[27–29] Proposed therapies for pruritus in PBC as well as PSC are discussed in a subsequent section.

In addition to the signs and symptoms associated with bile acid stasis, CLDs accompany with immunological disorders (and their respective signs and symptoms), including thyroid disease, cutaneous calcinosis, Raynaud’s phenomenon, and sicca syndrome.

2.4. Diagnostic approach

The diagnosis of PSC is based on a chronically cholestatic biochemical profile, typically elevated serum alkaline phosphatase (ALP), along with cholangiographic evidence of multifocal biliary tree strictures.[30] Liver biopsy may be useful to rule out disease mimics or overlap syndrome with autoimmune hepatitis, rule in small duct PSC (a variant phenotype), or when the diagnosis of PSC is in question based on atypical serologic, cholangiographic, or other clinical findings.[31] Periductal “onion skin” fibrosis is considered a pathognomic microscopic characteristic of PSC but is seldom found in biopsy specimens; the more typical

histopathological findings include paucicellular, nonsuppurative cholangitis and ductular reaction with varying degrees of biliary fibrosis (on which Ludwig staging is based).[32] Elevated serum IgG4 levels are present in 10% of patients with PSC and are associated with rapidly progressive disease; some of these patients may in fact have IgG4-associated sclerosing cholangitis, which is frequently responsive to corticosteroid therapy.[33–36] Hence, it is recommended that all patients with PSC be tested at least once for IgG4 levels. With regard to cholangiography, magnetic resonance cholangiography (MRCP) has largely supplanted endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes, with the latter being reserved for cases requiring therapeutic intervention or acquisition of specimens.[37]

The diagnosis of PBC is made on the presence of ALP levels 1.5 times higher than the upper limit of normal for at least six months, positive antimitochondrial antibody (AMA), and absence of extrahepatic biliary obstruction on imaging studies.[38–40] AMA is 90–95% sensitive and specific for PBC.[41,42] As with PSC, liver biopsy is not required for diagnosis but may be advisable in cases with diagnostic uncertainty (*e.g.* negative AMA) and to exclude other and/or concomitant diseases. Typical histologic findings include chronic, non-suppurative, lymphocytic cholangitis involving septal and interlobular ducts with varying degrees of biliary fibrosis.

2.5. Disease treatment

To date, there is no approved pharmacologic therapy for PSC. Ursodeoxycholic acid (UDCA) has been the most studied drug for treatment of PSC but its therapeutic impact remains controversial. A large Scandinavian trial reported that a dose of 17–23 mg/kg/day brought clinical and biochemical improvement in patients but the results did not attain statistical significance and hence did not improve the survival.[43–45] High dose (28–30 mg/kg/day) UDCA have also been associated with higher rates of death, need for liver transplantation (LT), and colorectal carcinoma.[46] Thus the general use of UDCA for patients with PSC is not recommended by American Association for the Study of Liver Diseases (AASLD). Obeticholic acid (OCA) is under trial to investigate the role in reversing fibrosis and preventing cirrhosis in PSC.[47] Several other treatments have been tested, including azathioprine, budesonide, methotrexate, mycophenolate mofetil, pentoxifylline, tacrolimus, nicotine, and pirfenidone, without proven benefit.[48–61] Numerous agents, including but not limited to oral vancomycin and curcumin,[62,63] are currently under various phases of investigation for treatment of PSC, targeting a variety of different signaling pathways.[64] With regard to non-pharmacologic treatment, the current therapeutic mainstays are endoscopic (discussed in detail in a recent review and summarized in a subsequent section herein) and surgical.[65] Surgical therapies include resection and LT. Resection is primarily performed in patients with pre-cirrhotic, focal disease (*e.g.* early-stage distal biliary cholangiocarcinoma (CCA)), while LT is recommended in those who have advanced cirrhosis or conditions meeting criteria for exception status, *e.g.* recurrent acute cholangitis with ≥2 episodes of bacteremia or a one-time episode of sepsis, hilar CCA meeting specific criteria, and/or intractable pruritus.[66] LT in PSC has been shown to significantly improve survival, with a 5-years survival rate of approximately 80%; however, the risk of recurrence of PSC post-LT has been reported to be 34–67%.[67]

Unlike in PSC, UDCA is the primary Food and Drug Administration (FDA) approved therapy for PBC (Table 1). UDCA at a dose of 13–15 mg/kg/day has been shown to reduce the risk of developing varices or requiring LT, improve serum liver biochemistries, and prolong survival in patients with PBC, particularly when started early in the disease course.[68–70] Improvements in liver biochemistries can occur within weeks of starting UDCA, with 90% of the improvement seen within 6–9 months. UCDA has not been shown to significantly many of the symptoms associated with PBC, including fatigue and pruritus, or complications such as bone or thyroid disease. The use of UCDA has minimal side effects including non-progressive weight gain in the first year of therapy, dyspepsia, and hair loss.[71] Recently, OCA, a farnesoid X receptor agonist, was approved by the FDA for treatment of PBC.[72–79] OCA can be used in combination with UDCA or as monotherapy in patients who are unable to tolerate UDCA and appears to be effective in reducing ALP levels. However, it has not yet been shown to improve survival or disease-related symptoms and can cause pruritus and headache as a side effect.[80–82] Similar to PSC, LT in PBC has shown excellent 1-year and 5-years survival rates of 90% and 85%, respectively.[83] A few studies have reported post-LT PBC recurrence rates of 8–18% and 22–30% at 5 and 10 years, respectively.[84]

2.6. Symptom management

2.6.1. Fatigue—To date, no known effective therapy exists for fatigue related to CLDs. The general therapeutic approach involves ruling out secondary causes (*e.g.* depression, hypothyroidism) and providing supportive care. Trials of vancomycin, metronidazole, and rifaximin have shown promising effects on fatigue in patients with PSC, but further investigation is needed before these agents can be routinely recommended for this indication.[85,86] Modafinil at doses of 100–200 mg/day may have some improvement in fatigue domain scores as an effective therapy in treating daytime somnolence associated with shift work but is not routinely recommended.[87] New-onset pruritus should be further evaluated to rule out the formation of a dominant bile duct stricture (DS). Once a DS has been ruled out, symptomatic control with use of cholestyramine, sertraline, rifampicin, and/or naltrexone in a stepwise manner is recommended.[88] Hydroxyzine, gabapentin, ondansetron, antibiotics, extracorporeal albumin dialysis and plasmapheresis, may also be considered.[89–92]

2.6.2. Pruritus—Unfortunately, UDCA does not relieve pruritus in a large proportion of patients; therefore, other interventions to manage pruritus are often needed. Bile acid sequestrants, such as cholestyramine, have been associated with improvement in pruritus symptoms in patients with PBC.[93,94] The recommended dose of cholestyramine is 4 g per dose, with a maximum of 16 g per day, administered 2–4 h before or after UDCA. In patients who are refractory to bile acid sequestrants, other recommended therapies include rifampicin 150–300 mg twice daily, oral opiate antagonists such as naltrexone 50 mg daily, and sertraline 75–100 mg daily.[95]

2.6.3. Sicca symptoms—General measures are used to improve eye care and oral health in patients with sicca symptoms. Treatment of dry eyes, includes humidification of the household environment, artificial tears such as hydroxypropyl methylcellulose and

carboxymethylcellulose, or cyclosporine ophthalmic emulsion as a second line therapy if not responsive to artificial tears.[95] Oral health includes regular visits to the dentist, mouth rinsing with water, use of fluoride-containing toothpaste, daily flossing, and sugar avoidance. Saliva substitutions or cholinergic agents such as pilocarpine and cevimeline can also be considered and may be very effective in some patients.[95] Dry skin could be treated with moisturizing creams and/or ointments.

3. General preventive measures

Patients are often asymptomatic at the time of diagnosis, which may give a false impression of lack of significant disease. This, coupled with the fact that approved medical therapy is lacking PSC and that therapy for PBC is ineffective in some patients, renders preventative strategies particularly important for patients with these disorders. Preventive measures to prevent complications from and slow down the progression of the underlying disease process are discussed hereinafter.

3.1. Alcohol consumption

More than four drinks (48 g of ethanol) per day is associated with an increased risk of cirrhosis, hepatocellular carcinoma (HCC), and premature death.[96] Acites, hepatic encephalopathy and variceal bleeding risk were reported to be approximately 50% after 5 years.[97] Alcohol is a direct toxin to hepatocytes and thus causes hepatitis and fatty infiltration.[98] Ethanol can also induce hepatic cholestasis, the mechanism of which is not well understood but may be related to compression of intrahepatic biliary radicals or derangement of basolateral uptake and bile acid transport. Hence, it may mimic a CLD.[99] There is no known safe alcohol consumption level in patients with underlying liver disease. One study reported that alcohol plays both a synergistic and additive roles in cirrhosis development in patients with other hepatic diseases (*e.g.* hepatitis C).[98] Alcohol has also been reported to be a risk factor for CCA in patients with PSC.[100] One study on untreated patients with PBC demonstrated that moderate amount of alcohol consumption is an independent predictor of late stage PBC disease.[101] Hence, it is recommended to abstain completely from alcohol consumption.

3.2. Immunizations

Acute hepatitis due to superinfections with hepatitis A and B viruses can be more severe in the presence of chronic liver disease.[102–105] It is imperative that all patients with chronic liver disease due to any cause to be tested for hepatitis A and B infections. If no immunity is found, vaccinations should be administered (Table 2).[106–108] Several studies in patients with chronic liver disease have shown that the seroconversion after hepatitis A and B vaccinations was achieved in 94% and 100% of patients respectively.[109] One time pneumococcal vaccination is also recommended in patients with cirrhosis to prevent spontaneous bacterial peritonitis (SBP) due to streptococcal pneumonia infection before the age of 65, which should then be administered at 5–10 years intervals at or after the age of 65.[110] Yearly influenza vaccination should also be administered given the association of influenza with increased mortality in individuals with cirrhosis.[111]

3.3. Toxins (medications and vitamins)

Numerous common medications, vitamins, and over the counter supplements are known to cause liver injury, and may be particularly unsafe in patients with underlying chronic liver disease. Careful review of medications should be done during each patient encounter, and patients should be informed about possible adverse hepatic side effects. If a hepatotoxic medication is identified, efforts should be made to find alternative treatment options; if no other options are available, a plan for regular monitoring for liver signs and symptoms of toxicity should be devised. If evidence of toxicity is detected, the offending agent should be promptly discontinued.[112] Medications including non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and benzodiazepines should be avoided in patients with cirrhosis. NSAIDs are commonly associated with idiosyncratic liver toxicity, greater bleeding risk, and renal injury in patients with cirrhosis.[113] Acetaminophen at a daily dosage that does not exceed 2 g is safer than NSAIDs in individuals with chronic liver disease, as it has dose-dependent predictable toxicity to the liver and is not nephrotoxic and does not increase the risk of gastrointestinal (GI) bleeding. Similarly, vitamin A is hepatotoxic in large doses, *i.e.* 100,000 IU per day, but is safe in regular doses.[114] Iron overload can be hepatotoxic to patients with the chronic liver disease since it can lead to free radical injury to hepatocytes.[115] Iron supplements should typically not be used, as patients with liver disease already often have excessive iron stores in the liver.[116] Estrogen therapy should be avoided in patients with CLD as it can promote cholestasis and exacerbate pruritus.

3.4. Dietary fat

Fatty infiltration in the liver, which often occurs in the presence of predisposing metabolic conditions including diabetes, obesity, and elevated triglyceride levels, can further promote progression to chronic liver disease and cirrhosis through hepatic inflammation, and subsequent fibrosis and necrosis.[117] Hence a low-fat diet and a physician-supervised exercise plan are recommended for gradual weight reduction in chronic liver disease patients. Patients with PBC also often are diagnosed with hyperlipidemia, including elevated high-density lipoproteins cholesterol and lipoprotein X accumulation. However, these elevations do not confer any increased mortality risk due to atherosclerosis.[118–121] Therefore, no specific therapy is required to reduce cholesterol levels, though UDCA is often used to lower low-density lipoproteins (LDL) cholesterol levels.

3.5. Raw oysters/shellfish

Patients with CLD should avoid consuming raw oysters. Filter feeders like oysters harbor a fatal bacterium named *Vibrio vulnificus*, which causes septicemia in patients with liver disease. It has the highest seafood consumption-associated mortality rates in the United States. It is extremely important to keep a high index of suspicion in a patient with chronic liver disease and recognize that doxycycline is the life-saving medication in such circumstances. Modes of transmission include the oral route and through skin via open wounds. Patients may present with acute gastroenteritis, septic shock, and blistering on the skin regardless of the mode of transmission.[122] Hence, it is essential to educate patients to avoid consumption of raw seafood and exposure of open wounds to marine water.

3.6. Coffee consumption

Coffee is an important source of antioxidants due to its widespread use and has been associated with a protective effect in heart disease, stroke, diabetes mellitus type 2 and Parkinson disease.[123–126] Caffeine has also been proposed to have both antifibrotic (inhibits hepatic stellate cells) and anti-inflammatory effects in the liver.[127] Two cups of coffee daily in patients with chronic liver disease is associated with decreased fibrosis/cirrhosis, lower risk of hepatocellular carcinoma, and decreased mortality.[127] In patients with PSC, one study also showed delayed progression to end stage liver disease and increased survival post-LT in patients who consumed coffee.[128] Therefore, daily moderate coffee consumption can be considered in patients with PSC due to its potential beneficial effects.

3.7. Screening family members

There is an increased risk of PBC reported among first-degree relatives with positive family history.[129] Screening can be initiated by testing ALP levels, which if found elevated, can further be investigated with AMA testing.

4. Cirrhosis, portal hypertension, and their sequelae

Cirrhosis is a later-stage complication in CLD. A majority of patients with PSC will go on to develop progressive fibrosis, portal hypertension, and end-stage liver disease (ESLD), which occurs approximately 20 years from the time of initial PSC diagnosis.[130] General preventative measures for cirrhosis should also be implemented, as briefly reviewed below.

It is recommended that a screening upper endoscopy be performed in all newly diagnosed cirrhosis cases to rule out gastroesophageal varices.[131] Patients with large esophageal varices should receive treatment, be it banding or non-selective beta-blocker therapy. In patients with small varices with a high risk of bleeding (*e.g.* high-risk endoscopic stigmata), prophylactic non-selective beta-blockers are recommended.

Patients should be administered antibiotics for SBP prophylaxis if they have cirrhosis and GI bleeding, a prior history of SBP,[132] or an ascitic fluid total protein concentration less than 1.5 g/dL with either renal dysfunction or liver failure and variceal hemorrhage.[133] Norfloxacin 400 mg daily is effective in SBP prophylaxis in patients with a history of SBP or low protein ascites while norfloxacin 400 mg twice daily for seven days is effective in variceal bleeding patients.[134–136]

Hepatic encephalopathy (HE) is present in up to 80% of patients with decompensated cirrhosis and can present with a wide spectrum of severity, from mild cognitive impairment (*e.g.* difficulty remembering and mental haziness) to a comatose state.[137] Rifaximin, a non-selective, locally-acting antibiotic, used along with lactulose or as monotherapy is effective in the treatment of HE.[138,139]

Finally, screening for HCC should be implemented with either an abdominal ultrasound or cross-sectional imaging with or without alpha-fetoprotein levels at 6–12 months intervals.[140]

5. Prevention and management of associated disorders and disease

5.1. Cancer surveillance

Table 3 summarizes preventative measures and management of complications of PBC and PSC. Colorectal dysplasia and cancer in patients with PSC-IBD occurs at a rate of 4–5 times that seen in patients with IBD without PSC, which itself is several-fold higher than in the general population.[141] The mechanism underlying this observation is unknown but is proposed to be due to the carcinogenic effects of an abnormal bile acid pool.[142] Individuals with PSC are also at a significantly higher risk of developing CCA, with a 10-years risk of approximately 8%, a rate that is several hundred times higher than that in the general population.[143] Therefore, patients with PSC should be advised to avoid smoking and alcohol abuse. Very rarely the occurrence of hepatocellular and pancreatic cancers have been reported.[144–147] Given the higher rates of CCA in this population, it is recommended that screening be performed with abdominal ultrasound or magnetic resonance imaging (MRI) and carbohydrate antigen (CA)19–9 levels every 6–12 months in all adults patients with PSC.[148,149] Patients with PSC also have increased risk of developing gallbladder cancer, due to the higher risk of forming gallstones.[150] Those with gallbladder polyps ≥8 mm in size should undergo cholecystectomy given the high likelihood of malignant transformation,[151] and those with polyps <8 mm should annual surveillance with ultrasound.[152]

Patients with PBC should be similarly screened for malignancy. Once PBC progresses to advanced fibrosis or cirrhosis, patients should be screened every 6 months for HCC with cross-sectional imaging with or without alpha fetoprotein at six-months intervals.[153]

5.2. IBD in PSC

Approximately 80–90% of patients with PSC have IBD.[149] IBD in patients with PSC can often be asymptomatic,[154] however, right-sided colitis with relative rectal sparing, backwash ileitis, pouchitis after ileoanal anastomosis, portal hypertension (HTN) with stomal/peristomal varices are commonly seen in IBD with PSC.[1,30] It is therefore recommended to do chromoendoscopic annual surveillance colonoscopy in patients with PSC with colitis starting from the time of diagnosis. Also, a full colonoscopy with four-quadrant biopsies every 10 cm should be obtained at the time of PSC diagnosis regardless of symptoms or presence of normal mucosa.[30] IBD is not associated with PBC.

5.3. Autoimmune hepatitis (AIH) overlap syndrome and IgG4-associated sclerosing cholangitis

AIH can co-exist/overlap with PSC in about 10% of the population.[1,30] This overlap syndrome of AIH-PSC usually effects younger individuals less than 25 years of age, and in one study AIH was followed by PSC development in children.[155] Therefore it is reasonable to evaluate younger patients with MRCP if they develop AIH or have aminotransferase levels >2x the upper limit of normal.[1] Similarly, AIH can overlap with PBC, however there is no formal definition of the overlap syndrome. Overlap syndrome should be considered when patients have clinical features of both AMA-positive PBC and AIH. The natural history of patients with AIH-PBC overlap syndrome is variable, though these patients often exhibit significantly higher rates of portal hypertension, portal hypertension-related GI

bleeding (*e.g.* from esophageal varices), ascites, and death or need for LTcompared to those with PBC or AIH alone.[156] Management for overlap syndrome should involve the use of UDCA with or without other immunosuppressive agents, though there is minimal evidence regarding the optimal therapy and timing of treatment.[157]

IgG4-associated sclerosing cholangitis, an autoimmune disease leading to biliary strictures and pancreatic duct strictures, can often mimic PSC. It can present similarly with a cholestatic pattern of liver enzyme elevation, however it usually associated with very high serum IgG4 levels (>140 mg/dl), positive IgG4-staining plasma cells, and lymphoplasmacytic infiltrates on liver biopsy.[1,30] In contrast to patients with PSC, these patients are less likely to have concurrent IBD and generally have a better response to steroids and other immunosuppressive agents.

5.4. Dominant stricture in PSC

A dominant stricture is defined as a stenosis of <1.5 mm in the common bile duct (CBD) and <1.0 mm in the hepatic ducts (HD). Dominant strictures are the initial presentation of PSC in 45% cases, and almost 50% of the patients can develop dominant strictures as the disease progresses.[158,159] PSC causes biliary obstruction at all levels of the biliary tree, but the strictures in major ducts may be amenable to ERCP. ERCP with balloon dilation and/or stent placement provides symptomatic relief from pruritus, prevents complications including cholangitis,[160–164] allows for earlier diagnosis of CCA,[165,166] and improves overall survival.[167–169] It is recommended to give prophylactic antibiotic therapy before ERCP for dominant strictures due to biliary bacterial colonization and a higher risk of post-ERCP cholangitis.[170] ERCP with or without balloon dilatation and stent placement is the first line therapy for the strictures but if the patient has altered anatomy (due to Rouxen-Y or gastric bypass) that can prevent successful ERCP, then percutaneous cholangiography is the next treatment option.[171–173]

5.5. Nutritional deficiencies and steatorrhea

Reduced bile flow from stricturing disease in PSC also leads to fat-soluble vitamin deficiencies and fat malabsorption. One study reported vitamins A, D and E deficiencies in 82%, 57% and 43% of patients with PSC, respectively.[174] Hence patients with PSC who have advanced liver disease should be screened for fat-soluble vitamin deficiency, and the same applies to patients with PBC.[175] Oral supplementation is sufficient in most cases. Importantly, in patients who have steatorrhea, it is essential to rule out other (potentially comorbid) disorders, including sprue and pancreatic exocrine insufficiency, which may themselves cause fat-soluble vitamin deficiency, in select instances, replacement of long-chain triglycerides with medium chain triglycerides may be needed. By contrast, water soluble vitamin deficiencies are uncommon is PSC and PBC.[176]

5.6. Osteodystrophy

Hepatic osteodystrophy develops due to increased bone resorption and decreased bone formation, and occurs in 12–50% of patients with PSC.[177–180] Smoking and alcohol cessation, gentle weight bearing exercise regimen, and oral vitamin D and calcium supplements are recommended for osteopenia and osteoporosis in PSC. Bisphosphonate

therapy should be considered for individuals with osteoporosis.[181,182] Once diagnosed with PSC, surveillance (*e.g.* with dual-energy X-ray absorptiometry (DEXA)) is recommended, with the frequency of surveillance depending on other clinical risk factors for bone loss.[183]

One-third of patients with PBC develop osteoporosis.[184,185] Unlike in PSC, in bone resorption is low in patients with PBC.[186,187] Hence the risk of bone fracture is low, and vitamin D levels are normal except in jaundiced patients with advanced liver disease.[188–190] Therefore, bone mineral density (BMD) examination is recommended every 2–4 yearly depending on baseline BMD and disease severity. If there is evidence of osteodystrophy and/or low vitamin D levels, daily calcium (1500 IU/day) and vitamin D supplementation (1000 IU/day) can also be given in the absence of any contraindication.

5.7. Hypothyroidism

PBC is associated with hypothyroidism, and almost 10–22% of patients with PBC have a low functioning thyroid.[191] Thus, thyroid function should be tested every year in patients with PBC. Thyroid dysfunction is less common in PSC but should be investigated if symptoms compatible with hypothyroidism (*e.g.* fatigue) are present.

5.8. Screening for celiac disease

Both PSC and PBC have been shown to be associated with celiac disease.[192,193] Celiac disease superimposed on CLD can worsen malabsorption, weight loss, fat soluble vitamin deficiency, and osteoporosis. It is recommended to screen for Celiac disease in patients with PBC, and vice versa, to guide management for potential comorbid conditions.[194]

6. Other CLDs

While PSC and PBC are the most common CLDs, there are several others that occur in a variety of clinical settings and merit mention. For example, intrahepatic cholestasis of pregnancy (ICP) is characterized by generalized pruritus and elevations in serum bilirubin in the late second and/or third trimester and is the most common liver disease in pregnancy.[195] Pruritus in ICP may precede laboratory abnormalities, which also can include elevations in serum aminotransferases (usually to less than two times the upper limit of normal), elevations in ALP (up to four times the upper limit of normal), and mild to modest elevations in gamma-glutamyl transferase (GGT).[196] The reported incidence of ICP varies widely, though in the United States, it ranges from 0.3 to 5.6%. Maternal bile acids can cross the placenta and accumulate in the amniotic fluid, increasing the risk of intrauterine demise, meconium-stained amniotic fluid, preterm delivery, and neonatal respiratory distress syndrome.[197] UDCA is the preferred treatment.[198] Another, more rare, cause of intrahepatic cholestasis is progressive familial intrahepatic cholestasis (PFIC). PFIC refers to a heterogeneous group of disorders characterized by a various of genetic mutations leading to defective secretion of bile acids or other components of bile. These disorders generally present during infancy or childhood and can lead to progressive liver failure, though some may have later presentation and a more indolent course. Initial therapy involves UDCA, though LT may be needed (and is curative).[199] Lastly, benign recurrent intrahepatic cholestasis (BRIC) describes an inherited form of CLD characterized by intermittent

episodes of cholestasis.[200] Patients can present from infancy to late adulthood with attacks of conjugated hyperbilirubinemia, anorexia, pruritus, and weight loss. Episodes last for weeks to months and then completely resolve. There is no curative treatment for BRIC, and LT is generally not indicated given the episodic, benign, and non-progressive nature of the disease.[200] Further information regarding these and other CLDs not specifically addressed in this article can be found in other recent works.[201–204]

7. Conclusion

In conclusion, CLDs comprise a wide variety of disorders characterized by impaired bile formation or flow through the biliary tract. At present, there are limited therapeutic options to alter the course of the disease in patients with CLD, particularly PSC. Early diagnosis, treatment of symptoms, and surveillance for early detection and treatment of complications can help to reduce mortality and morbidity in both PSC and PBC, the two major CLDs. Avoidance of toxin exposure (alcohol, hepatotoxic medications) and other preventative measures including viral hepatitis vaccination and a healthy, low-fat diet may prevent additional hepatic injury and accelerated progression to advanced fibrosis or cirrhosis. General care should also involve management of fatigue and pruritus-related symptoms. Finally, management of cirrhosis-related complications, early referral for LT, and judicious hepatobiliary and colorectal cancer (CRC) surveillance can help to improve quality of life and survival.

Acknowledgements

This work was supported in part by the United States National Center for Advancing Translational Sciences grant UL1TR000135.

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Table 1

Characteristics of PSC and PBC.

Characteristics	PSC	PBC
Pathogenesis	Idiopathic	Autoimmune
Affected segments of biliary tree	Intrahepatic and/or extrahepatic bile ducts Medium to large-sized ducts	Intrahepatic ducts Small to medium-sized ducts
Incidence	0.5–1.5 per 100,000	2.7–40 per 100,000
Ratio (male:female)	3:2	1:9
Average age of onset (years)	40–50	30–40
Association with IBD	Yes, in 50–75%	No
Signs and symptoms	Fatigue, pruritus, abdominal pain, jaundice	Fatigue, pruritus, jaundice
Diagnostic tests	Elevated ALP and GGT Positive IgG4 Ab (10%) MRCP: beaded appearance of extrahepatic and intrahepatic ducts Onion skin fibrosis on liver biopsy	Elevated ALP Positive AMA MRCP: only intrahepatic ducts affected Chronic non-suppurative cholangitis on liver biopsy
Treatment	Symtpomatic treatment Liver transplantation	First line: UDCA (13–15 mg/kg/day) Second line: obeticholic acid and farnseoid agonist
Complications	Cirrhosis and portal hypertension HCC, CRC, cholangiocarcinoma Autoimmune hepatitis IgG4 sclerosing cholangitis Dominant sricture Nutritional deficiency/bone disease	Cirrhosis and portal hypertension HCC Nutritional deficiency/bone disease Hypothyroidism

Abbreviations: Ab, antibody; ALP, alkaline phosphatase; AMA, antimitochondrial antibody; CRC, colorectal cancer; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; MRCP, magnetic resonance cholangiopancreaticography; UDCA, ursodeoxycholic acid.

Table 2

General preventative measures for cholestatic liver disease.

General preventative measures for cholestatic liver disease
(i) Avoid hepatotoxins (alcohol, medications including NSAIDs, herbalsupplements)
(ii) Administer hepatitis A and B vaccinations
(iii) Administer one-time pneumovax if < 65 years old, and once >65 years old, revaccinate every 5–10 years
(iv) Yearly influenza vaccination
(v) Low-fat diet

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3

General preventative measures and surveillance recommendations for complications of PBC and PSC.

Association/complication	Preventative measure/surveillance
PBC screening	Alkaline phosphatase levels in first-degree relatives (early use of UDCA decreases mortality and morbidity)
CRC	All patients with PSC should receive a colonoscopy with biopsies
Cholangiocarcinoma	Cross-sectional imaging every 6e12 months with CT or MRI
Autoimmune hepatitis/IgG4-associated cholangitis	Check for IgG4 diagnosis More responsive to steroid therapy Less likely to have current IBD
Dominant stricture in PSC (CBD <1.5 mm)	ERCP with balloon dilation and biopsy to rule out cholangiocarcinoma
Fat soluble vitamin deficiency and osteomalacia	Check vitamin A, D, and E levels and replete as needed
Hypothyroidism associated with PBC	Check TSH annually

Abbreviations: CBD, common bile duct; CRC, colorectal cancer; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TSH, thyroid stimulating hormone; UDCA, ursodeoxycholic acid.