BMJ Best Practice

Primary biliary cholangitis

Straight to the point of care

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Summary

Primary biliary cholangitis (PBC) is characterized by progressive intrahepatic bile duct damage and loss.

PBC is significantly more common in women than in men. Peak incidence is around age 40 years, and median age at diagnosis is 65 years.

The combination of a cholestatic pattern of serum liver tests (elevated alkaline phosphatase, gamma-glutamyl transferase, or both) and a PBC-specific autoantibody (typically antimitochondrial antibody) is sufficient for diagnosis in most patients, with no need for biopsy confirmation.

PBC is progressive in most patients; although, in many people, the rate of progression can be so slow that it may not be clinically relevant. Cirrhosis and its typical complications arise in the end stage.

Symptoms (typically pruritus and fatigue) can significantly lower the quality of life, even in patients with a very slowly progressive disease. These symptoms warrant treatment in their own right using specific regimens.

Progression of the disease can be slowed by therapy with ursodiol.

In patients with an inadequate response to ursodiol, second-line options include obeticholic acid, elafibranor, or seladelpar.

Transplantation is an effective treatment for patients who develop end-stage liver disease with PBC.

Definition

Primary biliary cholangitis (PBC) is a chronic disease of the small intrahepatic bile ducts that is characterized by progressive bile duct damage (and eventual loss) occurring in the context of chronic portal tract inflammation. Fibrosis develops as a consequence of the original insult and the secondary effects of toxic bile acids retained in the liver, resulting ultimately in cirrhosis. The almost universal presence of autoantibodies (classically antimitochondrial antibodies) has led to the widely held view that PBC is an autoimmune disease.[1]

Epidemiology

The prevalence of PBC in the US is approximately 35 per 100,000 of the population overall, with an incidence of approximately 3 to 5 cases per 100,000 per year.[3] [4] It is significantly more common in women than in men (up to a tenfold difference); however, men appear to have a poorer prognosis.[4] [5] [6] Studies suggest that at least one in 1000 women over the age of 40 years has PBC.[7] Peak incidence is around age 40 years.[7] Median age at diagnosis is 65 years.[2] Patients can present from their 20s onward and younger patients may experience more aggressive, less treatment-responsive disease.[2] There are anecdotal reports only of the disease in children.

Data on ethnic variations are limited, but risk for PBC appears to be broadly similar (although not identical) in different ethnic groups within the same geographical environment (an observation in keeping with an environmental factor being involved in disease pathogenesis). The possibility of the disease should be considered in all ethnic groups.

The incidence and prevalence of PBC in European countries is slightly lower than that in the US, with a prevalence of 22 cases per 100,000, and an annual incidence of 1 to 2 new cases per 100,000 people.[8] In both Europe and the US the prevalence of PBC is increasing, which may be due to earlier diagnosis and decreased mortality due to treatment with ursodiol.[9] The disease is substantially less common (although not well studied) in African and Asian countries, compared with Europe and the US. However, the incidence of the disease has been widely reported to be increasing in China; one meta-analysis of PBC in the Asia-Pacific region showed the prevalence was 19 per 100,000 in Japan and China.[10] [11] [12]

PBC is associated with immune-system and metabolic disorders, including thyroid disease, scleroderma, Sjögren syndrome/sicca complex (dry eyes and mouth), celiac disease, and osteoporosis.[13] [14] [15] In one controlled interview-based study of 1032 patients, autoimmune diseases were found in 32% of PBC cases, compared with 13% of controls (P <0.0001).[13]

Etiology

PBC is thought to be an autoimmune disease. There is a very high incidence of autoantibodies, most characteristically directed against mitochondrial antigens (antimitochondrial antibody). These antibodies, which are present in over 95% of patients, are principally directed against pyruvate dehydrogenase complex E2 subunit (PDC-E2), although reactivity is also seen, to a lesser degree, against other PDC components and the E2 subunits of related enzyme complexes.[16] Patients with PBC also have a higher incidence of autoantibodies directed at disease-specific nuclear antigens (ANA).[17] The most common ANA antibodies seen in PBC are anti-sp100 and anti-gp210.[14]

There is a genetic predisposition to developing PBC; an affected first-degree relative increases the risk almost tenfold, and concordance between monozygotic twins is 63%.[18] Certain HLA antigens have also been associated with the development of PBC; they are thought to modulate the individual's reaction to environmental stimuli and the biological processes involved in disease pathogenesis.[18][19] Loss of tolerance to PDC-E2 and the development of PBC is thought to be triggered by an environmental exposure in genetically-susceptible individuals. Putative environmental triggers include smoking, exposure to volatile compounds, hair dye, nail polish, use of hormone replacement therapies, shingles, and urinary tract infections.[13] [20] [21][22]

Pathophysiology

The pathophysiologic process in PBC is damage to, and progressive destruction of, the biliary epithelial cells lining the small intrahepatic bile ducts. There is loss of immune tolerance to biliary epithelial cells, leading to inflammation, cholestasis, and progressive fibrosis.[18] In the end stages of the disease there can be a complete loss of small intrahepatic ducts. Loss of bile duct cross-sectional area within the liver leads to cholestasis with variable and progressive bile acid retention. The predominantly hydrophobic bile acid pool can, when retained in this way, cause secondary damage within the liver, further contributing to progressive bile duct loss. There is therefore a self-sustaining element to the damage process.

Fibrosis occurs within the liver as a consequence of progressive damage, and this can lead to cirrhosis over a variable time period. The factors that dictate the rate of fibrosis development and the risk of cirrhosis (which both appear to vary significantly between patients) are at present unclear. This means that it is difficult, in practice, to predict the risk of developing advanced liver disease in any patient in the early stages of disease.

Case history

Case history #1

A 50-year-old woman undergoing health screening is found to have a cholestatic pattern on her liver function test results. Her alkaline phosphatase and gamma-GT concentrations are elevated, although transaminases, bilirubin, and albumin concentrations are normal. On questioning she mentions that she had been getting increasingly tired over the last few years but felt that this was simply a result of her age and work pattern. She also describes occasional itch that feels as if it is deep underneath the skin and that is not associated with a rash. She herself had no other past medical history but had a family member who had autoimmune thyroid disease. Clinical exam reveals no abnormal findings other than excoriations related to itch and xanthelasmata around the eyes.

Other presentations

Although most patients with PBC present early in the disease process with abnormal liver biochemistry (with or without the symptoms of itch, fatigue, or abdominal pain), occasionally patients will present with advanced liver disease. In these patients, the clinical features of cirrhosis would be more prominent than the features of PBC. Possible features would include ascites, splenomegaly, skin thinning, weight loss, and variceal bleeding. Jaundice may be significantly more prominent than would be expected in people with cirrhosis of different etiologies. PBC can present from the 20s onward and there is increasing evidence to suggest that it is more severe in nature and less responsive to first-line therapy in younger patients.[2]

Approach

The following findings would raise the clinical suspicion of PBC:[14] [15]

- Abnormal liver biochemistry: the finding of abnormal liver enzymes, in particular elevated alkaline phosphatase (ALP) and/or gamma-glutamyl transferase (GGT) concentrations, in the context of normal or less significantly elevated transaminases in a patient with no other apparent liver etiologic process.
- Clinical features typical of PBC: these include fatigue, xanthelasma formation around the eyes, dry eyes and dry mouth (sicca complex), abdominal discomfort, and itch in the absence of an obvious skin cause, in particular where the perception is of itch deep under the skin. Excoriations that occur as a consequence of scratching activity can lead to a false clinical suspicion of primary skin disease. All these clinical features can occur in the absence of any features that would make the clinician specifically concerned about the possibility of liver disease. The majority of patients presenting with early-stage symptomatic PBC will not be jaundiced. In the majority of people in whom the diagnosis of PBC is missed it is, in a large part, because the presence of liver disease in general has not been suspected.
- Characteristic features of advanced liver disease: these may occur in a patient presenting with no other apparent etiology. The clinical features in this scenario would be typical of cirrhosis, including metabolic changes (weight loss, muscle mass loss, and skin thinning) and portal hypertensive features (splenomegaly, ascites, and variceal bleeding). Jaundice is almost always prominent in patients with histologically advanced PBC.

History

It is important to note that many patients do not exhibit any of the characteristic clinical features suggestive of either PBC specifically or liver disease in general.

On history, in addition to the supportive clinical features outlined above, patients with PBC will frequently describe a positive family history of either PBC itself or of other autoimmune disease.[23] There is an increased risk of PBC in the relatives of patients with PBC, with the risk being greatest in first-degree female relatives ages 45-60 years.[24] There may also be a personal history of associated autoimmune disease. The strongest specific associations are with Sjögren syndrome, scleroderma, and celiac disease, although thyroid disease in particular should be considered as an associated disease in patients, because of its contribution to fatigue.

Symptoms of autonomic dysfunction, such as postural dizziness and loss of concentration, are occasionally seen.

Physical exam

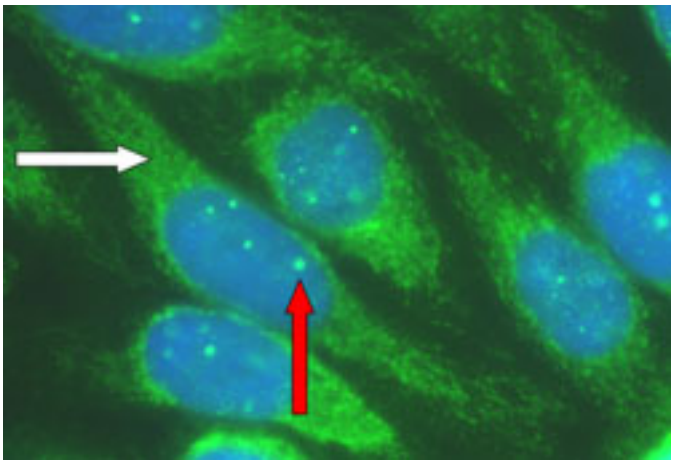
Physical exam of patients without cirrhosis is usually unremarkable. Xanthelasmata or hepatomegaly are occasionally present, although nonspecific for PBC.

Patients with advanced cirrhotic disease will have the generic features of cirrhosis on physical exam.

Investigation

The diagnosis of PBC is based on three factors:[14] [15]

- The presence of cholestatic liver biochemistry with prominent elevation of ALP and/or GGT. Patients with early-stage disease will typically not be jaundiced, although in the late stages of disease bilirubin concentrations can be substantially elevated.
- Autoantibody profile compatible with PBC: antimitochondrial antibody (AMA) or PBC-characteristic antinuclear antibody (ANA), such as anti-sp100 and anti-gp210.[16] [25]

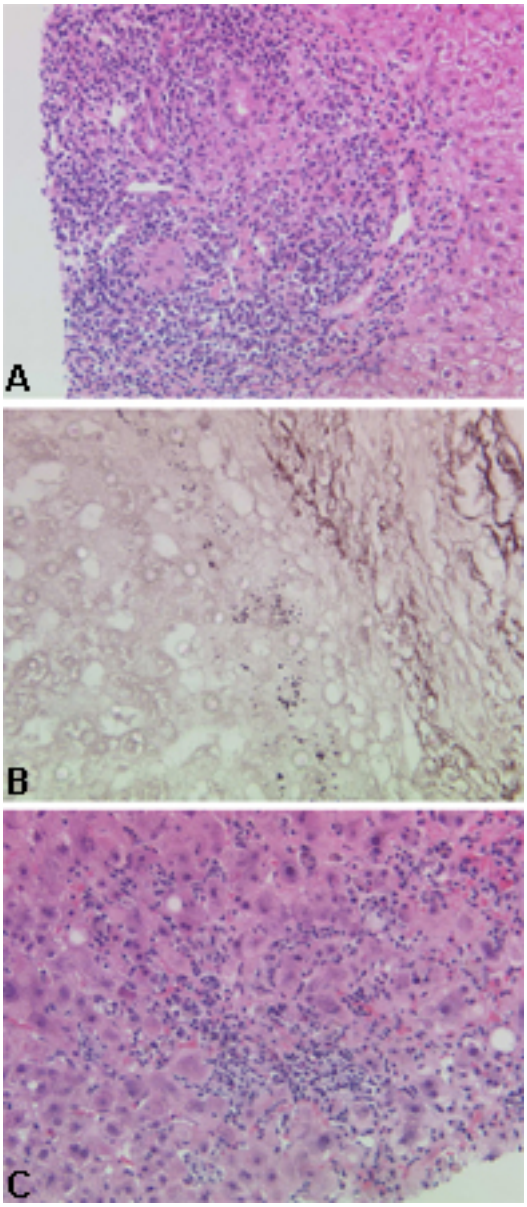


Characteristic autoantibody patterns in primary biliary cholangitis. White arrow: antimitochondrial staining; red arrow: multiple nuclear dot ANA staining

From the collection of DEJ Jones; used with permission.

Autoantibody profile can be obtained with either immunofluorescence or enzyme-linked immunosorbent assay (ELISA). AMA is present in 90% to 95% of diagnosed patients and is considered a hallmark of PBC.[14]

- Compatible or diagnostic liver histology on liver biopsy with, in particular, the presence of classic bile duct lesions accompanied by portal tract inflammation and granuloma formation.



Characteristic histologic appearances of primary biliary cholangitis: (a) early-stage disease; (b) advanced-stage disease; (c) disease with a significant inflammatory component

From the collection of Professor Alastair Burt, Newcastle University; used with permission.

US and European clinical practice guidelines recommend that the diagnosis can be made when two of the three features are present.[14] [15]

Biopsy is not usually necessary to confirm the diagnosis of PBC.[14] [15] This is a reflection of the high value of serologic markers of the disease, the complications of biopsy, and the issues that can arise from sampling error in what is frequently a patchy disease.[26]

A test for fibrosis should be performed in all patients on diagnosis to stage the disease.

Imaging with abdominal ultrasound or magnetic resonance cholangiopancreatography (MRCP) may be considered to rule out other causes of cholestasis and bile duct obstruction.

A subgroup of patients (<10% of the whole PBC population) have a more inflammatory process, interpreted by some in the field as a variant of PBC and by others as an overlap with autoimmune hepatitis.[14] [15]

The presence of this inflammatory variant is confirmed by liver biopsy. The identification of this important subgroup of patients is one of the remaining indications for liver biopsy in PBC. Suspicion of this variant and indication for the need to perform a biopsy in this context is based on the following factors:

- Presence of disproportionate elevation of alanine aminotransferase (ALT)
- Presence of an elevated serum IgG concentration (>2 g/dL)
- Presence of rapidly worsening fatigue
- Less frequently, presence of hepatitis-relevant serologic markers, diffuse pattern ANA, or smooth muscle antibody, the absence of which does not preclude the possibility of the presence of an overlap process potentially responsive to immunomodulatory therapy.

Elevated polyclonal serum IgM concentrations are also seen in patients with PBC and, although not part of the classic diagnostic criteria, can be useful in cases where doubt has arisen.[27] The clinical significance of AMA- or PBC-specific ANA in the context of normal liver biochemistry is unclear. No treatment is warranted in this group, unless a significant degree of fibrosis is present, but observation for the future development of PBC is appropriate.

Assessment of severity and prognosis

Assessment of severity and prognosis can be difficult in practice, particularly in patients with early-stage disease. Blood-based or imaging-based noninvasive tests are preferred for assessing fibrosis; liver biopsy is no longer indicated for this purpose, unless in specific situations (e.g., absence of PBC-specific antibodies, suspicion of coexistence of autoimmune hepatitis or metabolic dysfunction-associated steatohepatitis [previously known as nonalcoholic steatohepatitis] or other comorbidities), or when there is inadequate response to ursodiol therapy in order to characterize histologic lesions that underlie the resistance to treatment.[15] Moreover, the course of the disease may be progressive, despite treatment, thus noninvasive assessment of fibrosis is crucial at diagnosis and follow-up of these patients.

The American Association for the Study of Liver Diseases (AASLD) suggests a combination of imaging-based and blood-based techniques to detect significant fibrosis and advanced fibrosis, particularly in those undergoing initial fibrosis staging.[28] Imaging-based tests may be preferentially incorporated into the initial fibrosis staging process owing to their higher accuracy over blood-based techniques and can help identify advanced fibrosis and cirrhosis in adults with chronic PBC.[28] Either transient elastography (TE) or magnetic resonance elastography is recommended by the AASLD to stage fibrosis in adults with chronic liver disease.[28] The AASLD advises against using imaging-based tests as a standalone test to assess regression or progression of liver fibrosis.[28]

Fibrosis stage is an independent predictor of outcome in PBC, even in patients with biochemical treatment response.[29] Liver stiffness measurement (LSM) by TE is the best surrogate marker for severe fibrosis.[30] Progression of liver stiffness is predictive of poor outcome.[14] European guidelines suggest repeating LSM every 2 years in patients with early-stage disease, and every year in patients with advanced stage disease.[30] Serum markers of fibrosis, including serum levels of hyaluronic acid, procollagen III aminoterminal propeptide, collagen IV, enhanced liver fibrosis test, and FibroTest®, are not recommended for fibrosis staging and should only be used where radiologic testing is unavailable. Similarly, noninvasive scores (e.g., APRI, FIB-4, AAR, red blood cell distribution width to platelet ratio,

red blood cell distribution width to lymphocyte ratio, and neutrophil to lymphocyte ratio) lack diagnostic accuracy and are not recommended.[30]

Patients with PBC treated with ursodiol demonstrate a different disease course depending on baseline (pre-treatment) features and biochemical response after 12 months of treatment. Risk stratification is required:[30]

- At baseline - the distinction of early- from advanced-stage disease is based on LSM by TE, serum levels of bilirubin and albumin and, when available, histology.
- On treatment - the evaluation of prognosis is based on the assessment of biochemical response to ursodiol after 12 months using qualitative criteria (e.g., Paris-I, Paris-II, Rotterdam, Toronto, Rochester, Ehime criteria), or recently proposed quantitative criteria (e.g., UK-PBC score and GLOBE score).[15] [31] [32] Multiple studies show a high risk of adverse events for patients with inadequate response to ursodiol one year after initiation; however, no single approach for classifying treatment response has been adopted uniformly.[27] Both the UK-PBC and GLOBE scores have been developed using data derived and validated from large cohorts, and have been shown to be superior to qualitative criteria, and to the Model for End-Stage Liver Disease and Child-Pugh scores.[15]

Individual concentration values for ALP and transaminases have no prognostic value. In population terms, the presence of PBC-specific ANA may be associated with a worse prognosis.[33] [34] It is unclear, however, how the presence of such ANA should be interpreted in an individual patient and used to inform decisions regarding treatment.[35] [36] Young age at diagnosis (<45 years) and male sex have also been associated with poor prognosis, as have the finding of interface hepatitis on histology and persistent elevation of serum aminotransferases.[27]

DIAGNOSIS

History and exam

Key diagnostic factors

age 40-65 years (common)

- Peak incidence is around age 40 years.[7] Median age at diagnosis is 65 years.[2] Patients can present from their 20s onward and younger patients may experience more aggressive, less treatment-responsive disease.[2] There are anecdotal reports only of the disease in children.

female sex (common)

- PBC is significantly more common in women than in men (up to a tenfold difference).[4] [5] [6] Studies suggest that at least one in 1000 women over the age of 40 years have PBC.[7]

family history of PBC (uncommon)

- An affected first-degree relative increases the risk of PBC almost tenfold.[18]

Other diagnostic factors

personal history of autoimmune disease (common)

- Both nonorgan-specific and organ-specific autoimmune disease.[22] [23] [24]

family history of autoimmune disease (common)

- Both nonorgan-specific and organ-specific autoimmune disease.[22] [23] [24]

history of hypercholesterolemia (common)

- Feature of cholestasis. Typically elevated HDL and lipoprotein X.[37]

itch (common)

- Present in approximately 30% of patients. Frequently misinterpreted as representing the presence of skin disease, particularly when excoriations as a result of scratching activity are present.[36]

fatigue (common)

- Probably common but actual frequency depends on definition. Frequently not mentioned by patients, who feel it is unrelated to disease.[36] [40]

dry eyes and dry mouth (common)

- Mild features of associated Sjögren syndrome. Eye problems can be particularly prominent in contact lens wearers. Poor saliva production frequently reported by patients as dysphagia.[23]

abdominal discomfort (common)

- Feature of cholestasis. Beyond the classic symptoms of PBC, patient-reported concerns may include abdominal pain.[15]

sleep disturbance (common)

- Daytime somnolence in particular, prominently associated with fatigue.[41]

hepatomegaly (common)

- The liver can frequently be slightly enlarged (smooth-edged and nontender).

xanthelasmata (uncommon)

- Present around the eye. Typically not associated with other cutaneous features of hypercholesterolemia.[38] [39]

postural dizziness/blackouts (uncommon)

- Feature of autonomic dysfunction. Can be exacerbated by vasoactive drugs.[42]

memory and concentration problems (uncommon)

- Can be associated with autonomic dysfunction.[43]

jaundice (uncommon)

- Absent in most patients in most populations at presentation.[38] [39]

ascites (uncommon)

- Feature only of very advanced disease.[38] [39] Very unlikely unless the patient is also jaundiced.

splenomegaly (uncommon)

- Feature of advanced disease and suggestive of the presence of portal hypertension.

skin pigmentation (uncommon)

- Typically accompanies jaundice where present, causing skin color change out of proportion to the degree of biochemical jaundice.[38] [39]

Risk factors

Strong

female sex

- PBC is significantly more common in women than in men (up to a tenfold difference).[4] [5] [6] Studies suggest that at least one in 1000 women over the age of 40 years have PBC.[7]

age between 40 and 65 years

- Peak incidence is around 40 years.[7] Median age at diagnosis is 65 years.[2]

family history of PBC

- An affected first-degree relative increases the risk of PBC almost tenfold.[18]

Weak

family history of autoimmune disease

- Patients with PBC will frequently describe a positive family history of other autoimmune disease.[22] [23] [24]

smoking

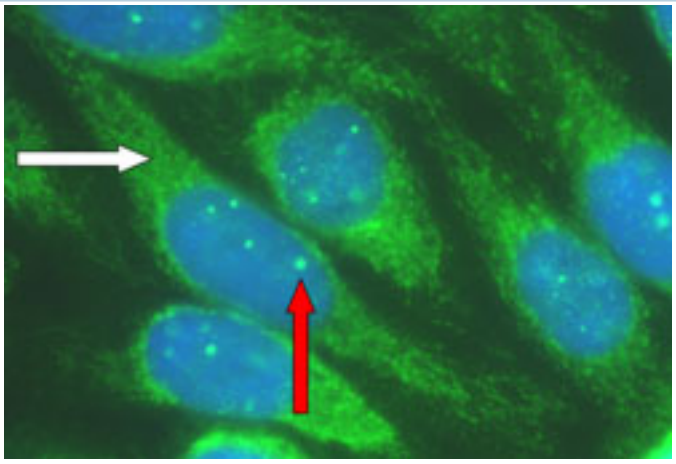
- Smoking is associated with PBC in the white population. This association remains to be validated in other populations.[22]

urinary tract infection

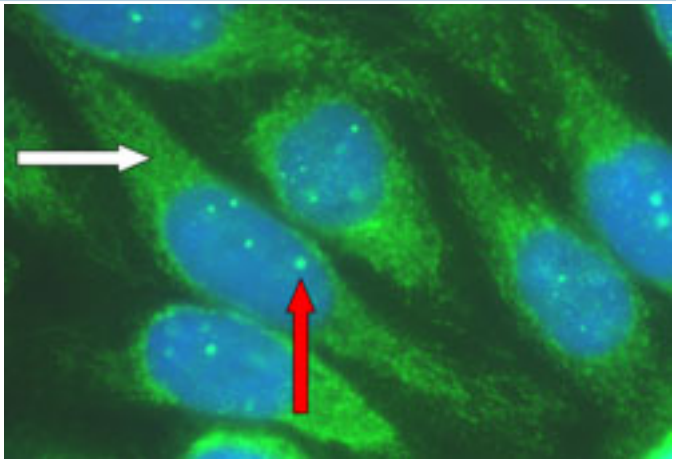
- Urinary tract infection is associated with PBC in the white population. This association remains to be validated in other populations.[22]

Tests

1st test to order

Test	Result
alkaline phosphatase (ALP) • Suggestive of the presence of cholestasis (of which PBC is one cause) if alkaline phosphatase is of liver origin (isoenzymes or co-elevation of gamma-GT can be helpful in determining this if there is clinical doubt).	**elevated**
gamma-glutamyl transferase (GTT) • Suggestive of presence of cholestasis (of which PBC is one cause).	**elevated**
bilirubin • Suggestive (although not confirmatory) of disease progression with the presence of advanced fibrosis.	**Normal or elevated in advanced disease**
alanine aminotransferase (ALT) • Less than 10% of patients with PBC have a more inflammatory process than usual, and the presence of this inflammatory variant is confirmed by liver biopsy. Suspicion of this variant may be raised by a disproportionately elevated ALT.	**Normal or mildly elevated**
serum albumin • Suggestive (although not confirmatory) of impaired liver synthetic function compatible with the presence of advanced liver disease.	**Normal or decreased in advanced disease**
antimitochondrial antibody (AMA) immunofluorescence • Seen as diffuse staining throughout the cytoplasm.  *Characteristic autoantibody patterns in primary biliary cholangitis. White arrow: antimitochondrial staining; red arrow: multiple nuclear dot ANA staining* *From the collection of DEJ Jones; used with permission.* • Use of immunofluorescence and ELISA will vary according to local practice.[25] Use of both methodologies is only needed in situations of clinical doubt.	**present**
antinuclear antibody (ANA) immunofluorescence • This pattern of staining of multiple dots within the nucleus, along with a nuclear rim staining pattern not seen in this example, is characteristic of PBC and must be distinguished from the diffuse	**staining pattern either antinuclear rim (indicates reaction with nuclear pore complex) or multiple**

DIAGNOSIS

Test	Result
nuclear staining pattern that is characteristic of autoimmune hepatitis and systemic lupus erythematosus.  *Characteristic autoantibody patterns in primary biliary cholangitis. White arrow: antimitochondrial staining; red arrow: multiple nuclear dot ANA staining* *From the collection of DEJ Jones; used with permission.* • Use of immunofluorescence and ELISA will vary according to local practice.[25] Use of both methodologies is only needed in situations of clinical doubt.	**nuclear dots (indicates reaction with Sp100 protein), or both**
antipyruvate dehydrogenase complex-E2 ELISA • Indicates presence of antimitochondrial antibody. • Titers of >1:40 are regarded as significant. • Use of immunofluorescence and ELISA will vary according to local practice.[25]	**present**
anti-M2 ELISA • Indicates presence of antimitochondrial antibody. • Titers of >1:40 are regarded as significant. • Use of immunofluorescence and ELISA will vary according to local practice.[25]	**present**
antiglycoprotein-210 ELISA • Indicates presence of antinuclear rim antinuclear antibody. • Titers of >1:40 are regarded as significant. • Use of immunofluorescence and ELISA will vary according to local practice.[25]	**present**
anti-Sp100 ELISA • Indicates presence of multiple nuclear dots antinuclear antibody. • Titers of >1:40 are regarded as significant. • Use of immunofluorescence and ELISA will vary according to local practice.[25]	**present**
abdominal ultrasound scan • Obstructive duct lesions must always be excluded radiologically before the diagnosis of PBC is made.[27]	**excludes obstructive lesion within visible bile ducts**
magnetic resonance cholangiopancreatography (MRCP) • Can be used as an alternative to ultrasound to detect bile duct stones and lesions causing extrahepatic obstruction, particularly of the distal	**excludes obstructive lesion within visible bile ducts and hepatocellular carcinoma**

Test	Result
bile duct.[15] Endoscopic ultrasound (EUS) can be an alternative to MRCP for evaluation of distal biliary disease.[14] [15]	
transient elastography • Noninvasive test for identification of fibrosis.[14][44]	**measures degree of fibrosis on scale of 0-4**

Other tests to consider

Test	Result
serum immunoglobulin • Elevation of IgM is supportive of the diagnosis of PBC.[45] • Elevation of IgG supportive of significant inflammatory/autoimmune hepatitis overlap features should be confirmed by liver biopsy.[46]	**polyclonal elevation of IgM and IgG**
liver biopsy • Not usually needed to confirm the diagnosis.[14] [15] [30] • Liver biopsy should only be carried out if there is diagnostic uncertainty or concern about the presence of potentially corticosteroid-responsive inflammatory disease.	**bile duct lesions (biliary ductular cell disruption within inflamed portal tracts) and granulomata formation; later disease stages: bile duct loss (ductopenia) with progressive biliary fibrosis; a more inflammatory pattern with interface hepatitis can be seen in a minority of patients (<10%)**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Obstructive bile duct lesion	• Previous history of bile duct surgery/obstruction. • Pain is much more prominent than with PBC. • Bacterial cholangitis as a complication is much more likely than in PBC.	• Antimitochondrial antibody or disease-specific antinuclear antibody not associated. • Abdominal ultrasound finding of duct dilatation (confirmed by magnetic resonance cholangiopancreatography [MRCP] or endoscopic retrograde cholangiopancreatography [ERCP] according to local practice) confirmatory.
Small-duct primary sclerosing cholangitis	• Different demographics than PBC (primary sclerosing cholangitis [PSC] is more common in younger males). • Association with inflammatory bowel disease.	• Antimitochondrial antibody or disease-specific antinuclear antibody not associated. • Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) suggestive of PSC may be present. This marker is absent in the majority of patients with PBC. • Abdominal ultrasound finding of duct irregularity (confirmed by magnetic resonance cholangiopancreatography [MRCP] or endoscopic retrograde cholangiopancreatography [ERCP] according to local practice) is confirmatory. • Liver biopsy characteristic of PSC.
Drug-induced cholestasis	• History of relevant drug exposure. Can also occur as a consequence of exposure to herbal/nonpharmaceutical preparations.	• Antimitochondrial antibody or disease-specific antinuclear antibody not associated. • Liver biopsy characteristic of cholestasis.
Cholestasis of pregnancy	• Associated with pregnancy.	• Antimitochondrial antibody or disease-specific antinuclear antibody not associated. • Bile acids elevated, transaminases more prominent than alkaline phosphatases.
Infiltrative malignancy within liver	• Associated with other systemic features suggestive of malignant disease.	• Cross-sectional imaging. • Liver biopsy if doubt persists.

Criteria

American Association for the Study of Liver Diseases[14]

The diagnosis of PBC can be established when two of the following three criteria are met:

- Biochemical evidence of cholestasis based on alkaline phosphatase elevation.
- Presence of antimitochondrial antibody (AMA), or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative.
- Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts.

Approach

Two goals of treatment of PBC should be considered in all patients.[15]

1. To slow or stop progression of the disease to prevent the development of cirrhosis and its complications (or managing those complications and the resulting risk to life if cirrhosis is already present).
2. To manage the symptoms of the disease to improve patient quality of life. To a significant degree the treatments that modify progression of the disease do not modify the symptoms of the disease (and vice versa), and it is therefore important that appropriate symptomatic management be undertaken in addition to disease-modifying treatment.

The diagnosis of PBC can give rise to significant concern in patients because of the negative connotations associated with a diagnosis of liver disease (perception of others that lifestyle-related issues are contributory; something that is not the case in PBC), and concern regarding risk to life and potential need for transplantation.

In the majority of patients the disease is likely to be only slowly progressive. Discussion with patients regarding the need for long-term disease-modifying treatment needs to be counterbalanced by information regarding the relatively slowly progressive nature of the disease. It is not at present possible to identify, at disease outset, the relatively small group of patients who do have a more rapidly progressive disease. Time spent at the point of diagnosis discussing the nature and implications of PBC with patients is well spent.

Modification of disease progression

Ursodiol is the recommended first-line treatment for the modification of disease progression. Second-line options include obeticholic acid, elafibranor, or seladelpar; these may be used in combination with ursodiol for patients with an inadequate response to ursodiol, or as monotherapy in patients who cannot tolerate ursodiol.

Ursodiol

First-line treatment suitable for use in all patients is ursodiol (a bile acid analog).[14] [15] Expert consensus is that ursodiol shows therapeutic benefit and has a very benign safety profile, and the drug is recommended for all patients to modify disease progression. However, up to 40% of patients fail to respond adequately to ursodiol in terms of biochemical improvement and are at significantly increased risk of dying of PBC or needing liver transplantation.[48] [49] Nonresponse is more common in patients presenting below the age of 50 years.[48]

Obeticholic acid

Obeticholic acid is a bile acid analog that has additional actions over and above those of ursodiol through its farnesoid X receptor (FXR) agonist properties. It is approved by the Food and Drug Administration (FDA) for the treatment of PBC in combination with ursodiol in adults who have an inadequate response to ursodiol (for at least 1 year), or as monotherapy in adults unable to tolerate ursodiol. It is only approved for the treatment of patients without cirrhosis or patients with compensated cirrhosis and no evidence of portal hypertension.[14] [15] The pivotal trial of obeticholic acid used an alkaline phosphatase of >1.67 times the upper limit of normal and/or a bilirubin level at or above the upper limit of normal as entry criteria, and this is, therefore, an appropriate definition of inadequate response to ursodiol for clinical practice.[50] An improvement in disease-related symptoms or survival has not been established in clinical trials as yet.

Obeticholic acid is contraindicated in patients with decompensated cirrhosis (or a prior decompensated event), compensated cirrhosis with evidence of portal hypertension, and complete biliary obstruction.[47] The FDA restricted the use of obeticholic acid in patients with PBC with advanced cirrhosis because it can cause serious liver injury leading to liver decompensation or liver failure in this patient population.[51] However, the FDA has also identified cases of serious liver injury in postmarketing clinical trial data among patients who did not have cirrhosis.[52]

Liver function tests should be performed and frequently monitored in all patients taking obeticholic acid, in order to detect worsening liver function as early as possible. However, it is not clear whether this monitoring is sufficient to address the risk of serious liver injury.[52] Closely monitor patients with compensated cirrhosis, concomitant hepatic disease, and/or severe intercurrent illness for new evidence of portal hypertension or increases in total and direct bilirubin and prothrombin time (above the upper limits of normal). Obeticholic acid should be permanently discontinued in patients with any evidence of liver disease progression, including those who develop clinical or laboratory evidence of hepatic decompensation, those who have compensated cirrhosis and develop portal hypertension, or those who experience clinically significant hepatic adverse effects. Obeticholic acid should also be discontinued in patients with no evidence of efficacy. Patients should be advised about the signs and symptoms of worsening liver injury to contact their healthcare professional immediately if any of these signs or symptoms develop.[52]

Severe pruritus has been reported with obeticholic acid, which may require a dose reduction, temporary interruption of treatment, and/or additional pharmacologic treatments (e.g., bile acid resins, antihistamines). Monitor lipids during treatment as dose-dependent reductions in HDL-C have been reported.

In June 2024, the European Medicines Agency (EMA) recommended revoking the conditional marketing authorization for obeticholic acid as they considered that the benefit-risk balance was no longer favorable based on results from a phase 3 confirmatory study, which did not confirm the clinical benefit of obeticholic acid in patients with PBC.[53] However, the decision to revoke the marketing authorization was temporarily suspended in September 2024, and the marketing authorization remains valid for the time being. The FDA's advisory panel has also voted against full approval of the drug, but it currently remains available under accelerated approval while the advisory panel decision is being reviewed.

Elafibranor

Elafibranor is a peroxisome proliferator-activated receptor (PPAR)-alpha and -delta agonist. Elafibranor is approved by the FDA and EMA for use in combination with ursodiol in patients with an inadequate response to ursodiol, or as monotherapy in patients who cannot tolerate ursodiol.

In one phase 3 trial, elafibranor significantly improved biochemical response (alkaline phosphatase level <1.67 times the upper limit of normal, with a reduction of ≥15% from baseline, and total bilirubin at or below the upper limit of normal) and reduced serum alkaline phosphatase compared with placebo at 52 weeks.[54] The most common adverse effects associated with elafibranor included abdominal pain, diarrhea, nausea, and vomiting.[54] Elevated creatine phosphokinase levels and muscle injury were also more common in patients who received elafibranor, including one patient who developed serious rhabdomyolysis.[54] Elafibranor is not recommended for patients who have or develop decompensated cirrhosis.

Seladelpar

Seladelpar is a PPAR-delta agonist. Seladelpar is approved by the FDA and EMA for use in combination with ursodiol in patients with an inadequate response to ursodiol, or as monotherapy in patients who cannot tolerate ursodiol.

In one phase 3 trial, seladelpar significantly improved biochemical response, alkaline phosphatase normalization, and reduced moderate-to-severe pruritus at 12 months compared with placebo.[55] Adverse effects more common with seladelpar included headache, abdominal pain, nausea, and abdominal distention.[55] Seladelpar is not recommended for patients who have or develop decompensated cirrhosis.

Nonresponse with features of autoimmune hepatitis

In some cases, nonresponse reflects the presence of a more inflammatory process with some features typical of autoimmune hepatitis. Treatment for patients with suspected PBC/autoimmune hepatitis overlap is directed at the predominant histologic pattern of injury.[15] See Autoimmune hepatitis (Management approach) .

Management of end-stage disease

Established end-stage disease is managed symptomatically and prognostically as for any other form of cirrhosis. See Cirrhosis (Management approach) .

Liver transplantation is an effective treatment for patients with end-stage disease in whom the risk of the procedure does not outweigh the expected benefit.[15] [56] It is now recognized that PBC can recur in the transplanted organ in up to one third of patients.[57] Studies have shown the administration of ursodiol and cyclosporine (a calcineurin inhibitor) may have a role in reducing disease recurrence.[57] [58]

Management of symptoms

Symptoms of PBC can significantly affect quality of life independently of the effect of disease on survival. Management of these symptoms is an important treatment goal in its own right. The principal symptoms requiring treatment are pruritus and fatigue.

Pruritus:

- Pruritus is a specific feature of some (but not all) patients with PBC. The severity of pruritus in PBC is not related to the severity of the underlying disease and is, accordingly, not well treated by disease-modifying drugs. Itch can be a significant problem causing marked impairment of quality of life. It is, however, usually controllable by medical therapy.[59] Prior to commencing specific treatment for cholestatic itch, it is important to exclude other potential causes for itch. The physician should rule out dermatologic and systemic disease (including chronic renal impairment and hematologic malignancy) and obstructive lesions within the biliary tree, because PBC is associated with an increased risk of gallstones and associated complications. It is key in all patients with presumed cholestatic itch that the extrahepatic bile duct be assessed by ultrasound to exclude an additional obstructive element.
- Following exclusion of such an obstructive lesion, the first-line treatment is cholestyramine.[14] [15] [60] This can be difficult for patients because of the flavor, but the addition of fruit juice may help with this. It is important that it be spaced away from ursodiol and all other oral drugs by at least 4 hours, because of the potential for cholestyramine to bind to ursodiol and to alter absorption of other drugs and fat-soluble vitamins.

- Second-line treatment is instituted if patients are either unresponsive to, or intolerant of, cholestyramine. Either rifampin or naltrexone is recommended.[14] [15][61] [62] Rifampin can cause hepatocellular dysfunction, and it should be introduced cautiously and with liver serum biochemistry monitoring. Deterioration in liver function and elevation of serum liver enzymes with rifampin are indications for its discontinuation.[61] [62] [63] Some patients may experience an opiate withdrawal-like reaction after starting naltrexone. The dose should be increased gradually.[15]
- Selective serotonin-reuptake inhibitors (e.g., sertraline) may be used in the management of cholestatic itch, when patients are unresponsive to the above treatments.[15]
- Although there is good evidence for efficacy, drugs other than cholestyramine remain unlicensed for the treatment of cholestatic itch.
- There are limited series data to support physical approaches to pruritus treatment, which include molecular adsorbent recirculating system (MARS), plasmapheresis, or nasobiliary drainage, in patients resistant to medical treatment. MARS is a proprietary system that can be utilized in conjunction with renal replacement systems to provide an additional albumin dialysis element. The theory behind its use in pruritus (it has also been proposed for use in liver failure) is that the presumed pruritogen in the circulation is albumin bound and can only be removed by using MARS to establish an albumin gradient.
- Antihistamines (e.g., hydroxyzine, diphenhydramine) sometimes have a nonspecific antipruritic effect, which may be due to their sedative properties, but are not recommended as specific therapy; they are, however, useful adjuncts for some.[15]
- Transplantation is an occasionally indicated treatment for severe and resistant cholestatic itch, if all other treatments have been exhausted.[15] [64]

Fatigue:

- At present there are no licensed interventions for the management of fatigue in PBC.[14] [15][65] There are reports associating fatigue with sleep disturbance and with autonomic dysfunction, suggesting that review and modification of lifestyle issues and drugs that may worsen either sleep abnormality or autonomic dysfunction is appropriate.[41] [42] All other treatments for fatigue are experimental. Patients with significant fatigue can become socially isolated causing worsening of their perceived quality of life. Minimizing this is an important element of patient coping strategy.
- It is important to identify other disease processes and therapies linked to PBC either directly or indirectly, which may be contributing to the fatigue. These include other autoimmune conditions such as hypothyroidism or autoimmune anemias, and comorbidities such as type 2 diabetes.[15]

Management of associated problems

Osteoporosis, Sjögren syndrome, and other autoimmune diseases that are associated with PBC are managed as they would be in the absence of PBC. Osteoporosis is a common complication in patients with PBC, although the degree of increased risk is unclear.[14] [15] The potential for fat-soluble vitamin malabsorption in cholestasis means that, among other approaches, calcium and vitamin D supplementation should be considered for the prevention of osteoporosis in all patients with PBC, although the evidence basis to support this is limited. See Osteoporosis and Sjögren syndrome .

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
early-stage disease		
	1st	**ursodiol**
	adjunct	**obeticholic acid or elafibranor or seladelpar**
	2nd	**obeticholic acid or elafibranor or seladelpar**
with cholestatic pruritus	**plus**	**antipruritic treatment**
with fatigue	**plus**	**lifestyle modification**
developing end-stage liver disease or refractory pruritus		
	1st	**liver transplantation**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

early-stage disease

1st **ursodiol**

Primary options

» ursodiol: 13-15 mg/kg/day orally given in 2-4 divided doses

» All patients should be treated with pharmacotherapy to modify disease progression. First-line treatment suitable for use in all patients is ursodiol.[14] [15]

» Up to 40% of patients fail to respond adequately to ursodiol in terms of biochemical improvement and are at significantly increased risk of dying of PBC or needing liver transplantation.[48] [49] Nonresponse is more common in patients presenting below the age of 50.[48]

» Ursodiol can cause nausea or weight gain but has no significant side effects.[66] Changing the pattern of dosing (building up the dose slowly or changing to multiple daytime dose from single night-time dose and vice versa) can improve tolerance. Treatment must be spaced away from cholestyramine (by at least 4 hours) to avoid binding and reduction in the efficacy of both drugs.

adjunct **obeticholic acid or elafibranor or seladelpar**

Treatment recommended for SOME patients in selected patient group

Primary options

» obeticholic acid: 5 mg orally once daily for 3 months, may increase to 10 mg once daily if inadequate response

OR

» elafibranor: 80 mg orally once daily

OR

» seladelpar: 10 mg orally once daily

Acute

» Obeticholic acid, elafibranor, or seladelpar may be used in combination with ursodiol for patients with an inadequate response to ursodiol.

» Obeticholic acid is a bile acid analog that has additional actions over and above those of ursodiol through its farnesoid X receptor (FXR) agonist properties.[14] [15] It is approved by the Food and Drug Administration (FDA) for the treatment of PBC in combination with ursodiol in adults who have an inadequate response to ursodiol (for at least 1 year). It is only approved for the treatment of patients without cirrhosis or patients with compensated cirrhosis and no evidence of portal hypertension. The pivotal trial of obeticholic acid used an alkaline phosphatase of >1.67 times the upper limit of normal and/or a bilirubin level at or above the upper limit of normal as entry criteria, and this is, therefore, an appropriate definition of inadequate response to ursodiol for clinical practice.[50] Obeticholic acid is contraindicated in patients with decompensated cirrhosis (or a prior decompensated event), compensated cirrhosis with evidence of portal hypertension, and complete biliary obstruction.[47] The FDA restricted the use of obeticholic acid in patients with PBC with advanced cirrhosis because it can cause serious liver injury leading to liver decompensation or liver failure in this patient population.[51] However, the FDA has also identified cases of serious liver injury in postmarketing clinical trial data among patients who did not have cirrhosis.[52] Liver function tests should be performed and frequently monitored in all patients taking obeticholic acid, in order to detect worsening liver function as early as possible. However, it is not clear whether this monitoring is sufficient to address the risk of serious liver injury.[52] Closely monitor patients with compensated cirrhosis, concomitant hepatic disease, and/or severe intercurrent illness for new evidence of portal hypertension or increases in total and direct bilirubin and prothrombin time (above the upper limits of normal). Obeticholic acid should be permanently discontinued in patients with any evidence of liver disease progression, including those who develop clinical or laboratory evidence of hepatic decompensation, those who have compensated cirrhosis and develop portal hypertension, or those who experience clinically significant hepatic adverse effects. Obeticholic acid should also be discontinued in patients with no evidence of efficacy. Patients should be advised about the signs and symptoms of worsening liver injury to contact their healthcare

Acute

professional immediately if any of these signs or symptoms develop.[52] Severe pruritus has been reported with obeticholic acid, which may require a dose reduction, temporary interruption of treatment, and/or additional pharmacologic treatments (e.g., bile acid resins, antihistamines). Monitor lipids during treatment as dose-dependent reductions in HDL-C have been reported.

» Elafibranor is a peroxisome proliferator-activated receptor (PPAR)-alpha and -delta agonist. Elafibranor is approved by the FDA and EMA for use in combination with ursodiol in patients with inadequate response to ursodiol. In one phase 3 placebo-controlled trial of patients with PBC with an inadequate response to ursodiol, elafibranor significantly improved biochemical response (alkaline phosphatase level <1.67 times the upper limit of normal, with a reduction of ≥15% from baseline, and total bilirubin at or below the upper limit of normal) and reduced serum alkaline phosphatase compared with placebo at 52 weeks.[54] The most common adverse effects associated with elafibranor included abdominal pain, diarrhea, nausea, and vomiting.[54] Elevated creatine phosphokinase levels and muscle injury were also more common in patients who received elafibranor, including one patient who developed serious rhabdomyolysis.[54]

» Seladelpar is a PPAR-delta agonist. Seladelpar is approved by the FDA and EMA for use in combination with ursodiol in patients with an inadequate response to ursodiol. In one phase 3 trial, seladelpar significantly improved biochemical response, alkaline phosphatase normalization, and reduced moderate-to-severe pruritus at 12 months compared with placebo.[55] Adverse effects more common with seladelpar treatment included headache, abdominal pain, nausea, and abdominal distention.[55]

» Elafibranor and seladelpar are not recommended for patients who have or develop decompensated cirrhosis.

» In some cases, nonresponse reflects the presence of a more inflammatory process with some features typical of autoimmune hepatitis. Treatment for patients with suspected PBC/autoimmune hepatitis overlap is directed at the predominant histologic pattern of injury.[15] See Autoimmune hepatitis .

Acute

2nd **obeticholic acid or elafibranor or seladelpar**

Primary options

» obeticholic acid: 5 mg orally once daily initially for 3 months, may increase to 10 mg once daily if inadequate response

OR

» elafibranor: 80 mg orally once daily

OR

» seladelpar: 10 mg orally once daily

» All patients should be treated with pharmacotherapy to modify disease progression. Obeticholic acid, elafibranor, or seladelpar may be used as monotherapy in patients who cannot tolerate ursodiol.

» Obeticholic acid is a bile acid analog that has additional actions over and above those of ursodiol through its farnesoid X receptor (FXR) agonist properties.[14] [15] It is approved by the Food and Drug Administration (FDA) for the treatment of PBC as monotherapy in adults unable to tolerate ursodiol. The pivotal trial of obeticholic acid used an alkaline phosphatase of >1.67 times the upper limit of normal and/or a bilirubin level at or above the upper limit of normal as entry criteria, and this is, therefore, an appropriate definition of inadequate response to ursodiol for clinical practice.[50] Obeticholic acid is contraindicated in patients with decompensated cirrhosis (or a prior decompensated event), compensated cirrhosis with evidence of portal hypertension, and complete biliary obstruction.[47] The FDA restricted the use of obeticholic acid in patients with PBC with advanced cirrhosis because it can cause serious liver injury leading to liver decompensation or liver failure in this patient population.[51] However, the FDA has also identified cases of serious liver injury in postmarketing clinical trial data among patients who did not have cirrhosis.[52] Liver function tests should be performed and frequently monitored in all patients taking obeticholic acid, in order to detect worsening liver function as early as possible. However, it is not clear whether this monitoring is sufficient to address the risk of serious liver injury.[52] Closely monitor patients with compensated cirrhosis, concomitant hepatic disease, and/or severe

Acute

intercurrent illness for new evidence of portal hypertension or increases in total and direct bilirubin and prothrombin time (above the upper limits of normal). Obeticholic acid should be permanently discontinued in patients with any evidence of liver disease progression, including those who develop clinical or laboratory evidence of hepatic decompensation, those who have compensated cirrhosis and develop portal hypertension, or those who experience clinically significant hepatic adverse effects. Obeticholic acid should also be discontinued in patients with no evidence of efficacy. Patients should be advised about the signs and symptoms of worsening liver injury to contact their healthcare professional immediately if any of these signs or symptoms develop.[52] Severe pruritus has been reported with obeticholic acid, which may require a dose reduction, temporary interruption of treatment, and/or additional pharmacologic treatments (e.g., bile acid resins, antihistamines). Monitor lipids during treatment as dose-dependent reductions in HDL-C have been reported.

» Elafibranor is a peroxisome proliferator-activated receptor (PPAR)-alpha and -delta agonist. Elafibranor is approved by the FDA and EMA for use as monotherapy in patients who cannot tolerate ursodiol. In one phase 3 trial, elafibranor significantly improved biochemical response (alkaline phosphatase level <1.67 times the upper limit of normal, with a reduction of ≥15% from baseline, and total bilirubin at or below the upper limit of normal) and reduced serum alkaline phosphatase compared with placebo at 52 weeks.[54] The most common adverse effects associated with elafibranor included abdominal pain, diarrhea, nausea, and vomiting.[54] Elevated creatine phosphokinase levels and muscle injury were also more common in patients who received elafibranor, including one patient who developed serious rhabdomyolysis.[54]

» Seladelpar is a PPAR-delta agonist. Seladelpar is approved by the FDA and EMA for use as monotherapy in patients who cannot tolerate ursodiol. In one phase 3 trial, seladelpar significantly improved biochemical response, alkaline phosphatase normalization, and reduced moderate-to-severe pruritus at 12 months compared with placebo.[55] Adverse effects more common with seladelpar included headache, abdominal pain, nausea, and abdominal distention.[55]

Acute

» Elafibranor and seladelpar are not recommended for patients who have or develop decompensated cirrhosis.

» In some cases, nonresponse reflects the presence of a more inflammatory process with some features typical of autoimmune hepatitis. Treatment for patients with suspected PBC/autoimmune hepatitis overlap is directed at the predominant histologic pattern of injury.[15] See Autoimmune hepatitis .

with cholestatic pruritus **plus** **antipruritic treatment**

Treatment recommended for ALL patients in selected patient group

Primary options

» cholestyramine: 4 g orally three times daily

Secondary options

» rifampin: 150 mg orally once daily initially, increase gradually according to response, maximum 600 mg/day given in 4 divided doses

OR

» naltrexone: 25-50 mg orally daily

Tertiary options

» sertraline: 50-100 mg orally once daily

OR

» hydroxyzine: 25 mg orally every 6-8 hours when required

OR

» diphenhydramine: 25-50 mg orally every 4-6 hours when required, maximum 300 mg/day

» The severity of pruritus in PBC is not related to the severity of the underlying disease and is, accordingly, not well treated by disease-modifying drugs.

» Ursodiol and obeticholic acid are associated with paradoxical itch in some patients. If itch develops or worsens shortly after commencing these treatments, discontinuation or addition of anti-pruritic therapy should be considered.

MANAGEMENT

Acute

» First-line treatment is cholestyramine.[14] [15] [60] Cholestyramine is safe but can be poorly tolerated because of its bitter taste. Adding fruit juice can be helpful. It is important that it be spaced away from ursodiol and all other oral drugs by at least 4 hours, because of the potential for cholestyramine to bind to ursodiol and to alter absorption of other drugs and fat-soluble vitamins.

» Second-line treatment is instituted if patients are either unresponsive to, or intolerant of, cholestyramine. Either rifampin or naltrexone is recommended.[14] [15][61] [62]

» Rifampin can cause hepatocellular dysfunction, and it should be introduced cautiously and with liver serum biochemistry monitoring. Deterioration in liver function and elevation of serum liver enzymes with rifampin are indications for its discontinuation.[61] [62] [63] Patients should also be warned about reddish-orange discoloration of tears, sweat, and secretions.

» Some patients may experience an opiate withdrawal-like reaction after starting naltrexone. The dose should be increased gradually.[15]

» Selective serotonin-reuptake inhibitors (e.g., sertraline) may be used in the management of cholestatic itch, when patients are unresponsive to the above treatments.[15]

» Antihistamines (e.g., hydroxyzine and diphenhydramine) sometimes have a nonspecific antipruritic effect, which may be due to their sedative properties, but are not recommended as specific therapy; they are, however, useful adjuncts for some.[15]

» There are limited series data to support physical approaches to pruritus treatment (using, for example, molecular adsorbent recirculating system [MARS], plasmapheresis, or nasobiliary drainage) in patients resistant to medical treatment. MARS is a proprietary system that can be utilized in conjunction with renal replacement systems to provide an additional albumin dialysis element.

with fatigue **plus** **lifestyle modification**

Treatment recommended for ALL patients in selected patient group

» At present there are no licensed interventions for the management of fatigue in PBC.[14] [15] [65]

Acute

» There are reports associating fatigue with sleep disturbance and with autonomic dysfunction, suggesting that review and modification of lifestyle issues and drugs that may worsen sleep abnormality or autonomic dysfunction is appropriate.[41] [42] All other treatments for fatigue are experimental.

» It is important to identify other disease processes and therapies linked to PBC either directly or indirectly, which may be contributing to the fatigue. These include other autoimmune conditions such as hypothyroidism or autoimmune anemias, and comorbidities such as type 2 diabetes.[15]

developing end-stage liver disease or refractory pruritus

1st **liver transplantation**

» Liver transplantation is an effective treatment for end-stage PBC. Transplantation is an occasionally indicated treatment for severe and resistant cholestatic itch, if all other treatments have been exhausted.[15] [64]

» Mayo risk score and Model for End-Stage Liver Disease (MELD) are effective at predicting risk of death in advanced liver PBC and can be useful tools in the timing of transplantation.

» Donor organ shortages, and the potential for rapid deterioration to occur in patients with advanced disease, mean that the timing of referral to a transplant unit needs to be considered carefully.

» Bilirubin concentration is a useful indicator. Patients with concentrations of >3 mg/dL (51.3 micromol/L) should be considered for referral to a transplant unit, and patients with concentrations of bilirubin >6 mg/dL (102.6 micromol/L) should be actively considered for transplantation.

» It is now recognized that PBC can recur in the transplanted organ in up to one third of patients.[57]

» At present there is no consensus regarding approaches to either the prevention or treatment of post-transplant recurrence, although use of ursodiol in both contexts is widespread. Studies have shown the administration of ursodiol and cyclosporine (a calcineurin inhibitor) may have a role in reducing disease recurrence.[57] [58] Further studies in this area are needed.

Emerging

Peroxisome proliferator-activated receptor (PPAR)-alpha agonists (fibrates)

The PPAR-alpha agonists bezafibrate and fenofibrate have shown significant biochemical benefits in conjunction with ursodiol, although until recently the evidence was low quality.[67] The results of a high-quality trial suggest a clear benefit of fibrates in combination with ursodiol, with an acceptable safety profile.[68] Fibrates are recommended as a second-line treatment for patients with PBC who have an inadequate response to ursodiol, although they are discouraged in patients with decompensated liver disease.[14] [15] [47] Further clarification of their position in the treatment pathway of PBC is needed.

Budesonide

European guidelines recommend budesonide, a corticosteroid that undergoes significant first-pass metabolism, as a second-line treatment for patients with PBC who have an inadequate response to ursodiol.[15] However, the American Association for the Study of Liver Disease suggests that its use remains controversial.[14] Further clarification on the use of budesonide in the treatment pathway of PBC is needed.

Modafinil

Under evaluation for the treatment of fatigue associated with significant daytime somnolence.

Secondary prevention

No interventions have been identified that can prevent or alter the natural history of PBC.

Patients with PBC should adhere to recommended vaccination schedules for patients with chronic liver disease, including being vaccinated for hepatitis A, hepatitis B, influenza (annual), and COVID-19.[74]

Patient discussions

Patients with early-stage disease may be advised on the following:

- To be careful about their fat intake because of the potential for gut disturbance
- To take exercise in moderation because of its general health benefits (and its potential benefits for fatigue)
- To think carefully about factors that may disturb sleep because of its association with fatigue
- To avoid excess alcohol
- To quit smoking
- To maintain social networks, as loss of social structures is an important contributor to poor life quality in symptomatic patients.

Monitoring

Monitoring

Ursodiol should be continued indefinitely. Both US and European guidelines recommend assessing biochemical response to treatment at 12 months to risk stratify patients. Low risk patients (ursodiol responders) should then have individualized follow up according to symptom burden and disease stage. High risk patients (those who display an inadequate response to treatment) should be considered for second line treatments.[14] [15]

Response to treatment can be assessed using quantitative (GLOBE and UK-PBC risks scores) or qualitative (Paris-I, Paris-II, Rotterdam, Toronto, Rochester, Ehime criteria) scoring systems.[30] The chosen tool should include ALP and bilirubin measurements as these are the two strongest variables used to predict prognosis.[15]

Liver stiffness measurement (LSM) by transient elastography (TE) has recently emerged as an important technique to assess prognosis and treatment response. US guidelines mention it as an emerging technique, whereas European guidelines define a clear role for it, both in terms of risk stratification at baseline and during follow up on treatment.[14] [15] There is currently a lack of evidence regarding the optimal time frame between subsequent LSMs, but the current suggestion is to repeat LSM every 2 years in patients with early disease and annually in patients with advanced disease.[15]

Regular screening for hepatocellular carcinoma with ultrasound +/- alpha-fetoprotein is recommended at 6 monthly intervals in patients with cirrhosis and male patients.[14] [15]

US guidelines also recommend monitoring of liver tests every 3-6 months, bone mineral densitometry every 2 years, annual TSH, annual monitoring of fat soluble vitamins in patients with jaundice, and upper endoscopy every 1-3 years if cirrhotic, Mayo risk score >4.1, or transient elastography shows a score ≥17 kPa.[14]

Deterioration in liver synthetic function (elevation in bilirubin concentration and prothrombin time and fall in albumin concentration) is an indicator of progressive disease or cirrhosis and should prompt further investigation.[27]

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
hypercholesterolemia	**long term**	**high**
Elevated total cholesterol levels are common in PBC. The implications of elevated cholesterol levels are, however, less clear-cut in patients with PBC than in the broader population, because of the contribution made by lipoprotein X (which reduces the atherogenicity of low-density lipoprotein) to total cholesterol levels.[37] There is no substantial evidence to support an elevated cardiovascular risk in patients with PBC and raised cholesterol.[14] Where appropriate the use of statins appears to be safe in PBC.[14] [15]		
osteoporosis	**long term**	**medium**
Significantly greater risk of osteopenia and osteoporosis in PBC.[14] Overall, osteoporosis is common in people with PBC because of the demographic distribution of the disease (predominantly postmenopausal women) and the effect of cholestasis on vitamin D and calcium absorption. Management is the same as for osteoporosis of other etiologies.[14]		
portal hypertension secondary to cirrhosis	**long term**	**low**
Complication of cirrhosis in patients progressing to end-stage disease. Major manifestations are ascites, splenomegaly, and variceal bleeding.[70] Noncirrhotic portal hypertension can also be seen in PBC. Management is the same as for cirrhosis of other causes.		
hepatocellular carcinoma	**long term**	**low**
Complication of cirrhosis in patients progressing to end-stage disease. More common in male than in female patients.[71] Management is the same as for hepatocellular carcinoma of other etiologies.		

Prognosis

PBC is a slowly progressive condition in the majority of patients. Given the age of presentation with the disease, many patients die of other causes before reaching end-stage liver disease. Epidemiologic studies suggest that mortality overall is significantly increased in patients with PBC (standardized mortality ratio of 2.8 in northeast England).[69] This increase in overall mortality results from increases in both liver-related, and nonliver-related deaths.

Liver-related mortality

There is approximately a doubling of risk of liver-related death in patients with PBC compared with relevant comparator populations.[69] However, there has been a trend toward reduction in liver-related mortality as a consequence of the diagnosis of milder forms of the disease, which may have been missed previously (and which are associated with a lower risk of liver-related death), and the effects of treatment (in particular with ursodiol but, also where advanced liver disease develops, with transplantation). The long-term nature of ursodiol treatment means that changes in population mortality rate related to liver disease will take a long time to emerge. Liver-related mortality results from the development of the complications of cirrhosis

(particularly portal hypertension with variceal bleeding), the development of advanced liver disease with hepatocellular failure and its associated complications, or hepatocellular carcinoma.[70] [71]

Nonliver-related mortality

It is becoming clear from epidemiologic studies that the risk of nonliver-related mortality is approximately doubled in patients with PBC, contributing to the overall increased risk to life.[69] This risk appears to be nonspecific (the specific risk of malignant and cardiovascular disease has been addressed in detail, with no substantial PBC-associated risk being identified). One possibility is that this mortality increase is due to frailty associated with chronic inflammation. Specific preventive measures are difficult to recommend given the lack of a clear mechanism. Good clinical practice would suggest, however, that a comprehensive review of risk factors for important diseases where preventive lifestyle modification could be of benefit is appropriate in PBC.

Quality of life

The major factors contributing to impairment of quality of life in PBC are itch, fatigue, and the clinical features associated with advanced disease.[36] [39][40][72] [73] Itch is typically a symptom of the middle stages of the disease, normally being absent from patients with the earliest disease stage (although exceptions are seen), with improvement occasionally being seen in the end stages of disease. Fatigue, in contrast, shows no association with disease severity and, indeed, appears stable over time.[73] The implication of this observation is that patients who experience significant fatigue with PBC are unlikely to improve spontaneously. Patients not experiencing significant fatigue at presentation are unlikely to develop profound fatigue over relatively short follow-up periods.

Diagnostic guidelines

International

AASLD practice guideline on imaging-based non-invasive liver disease assessments of hepatic fibrosis and steatosis (https://www.aasld.org/practice-guidelines) [28]

Published by: American Association for the Study of Liver Diseases **Last published:** 2024

Primary biliary cholangitis: 2021 practice guidance update (https://www.aasld.org/publications/practice-guidelines) [47]

Published by: American Association for the Study of Liver Disease **Last published:** 2021

Primary biliary cholangitis (https://www.aasld.org/publications/practice-guidelines) [14]

Published by: American Association for the Study of Liver Disease **Last published:** 2018

EASL clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update (https://easl.eu/publications/clinical-practice-guidelines) [30]

Published by: European Association for the Study of the Liver **Last published:** 2021

The diagnosis and management of patients with primary biliary cholangitis (https://easl.eu/publications/clinical-practice-guidelines) [15]

Published by: European Association for the Study of the Liver **Last published:** 2017

The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines (https://www.bsg.org.uk/clinical-resource/bsg-and-ukpbc-pbc-guidelines) [2]

Published by: The British Society of Gastroenterology (in partnership with UK-PBC) **Last published:** 2018

Treatment guidelines

International

Primary biliary cholangitis (https://www.aasld.org/publications/practice-guidelines) [14]

Published by: American Association for the Study of Liver Disease **Last published:** 2018

The diagnosis and management of patients with primary biliary cholangitis# (https://easl.eu/publications/clinical-practice-guidelines) [15]

Published by: European Association for the Study of the Liver **Last published:** 2017

The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines (https://www.bsg.org.uk/clinical-resource/bsg-and-ukpbc-pbc-guidelines) [2]

Published by: The British Society of Gastroenterology (in partnership with UK-PBC) **Last published:** 2018

Key articles

- Lindor KD, Bowlus CL, Boyer J, et al. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2019 Jan;69(1):394-419. Full text (https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.30145) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30070375?tool=bestpractice.bmj.com)

- European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017 Jul;67(1):145-72. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28427765?tool=bestpractice.bmj.com)

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Images

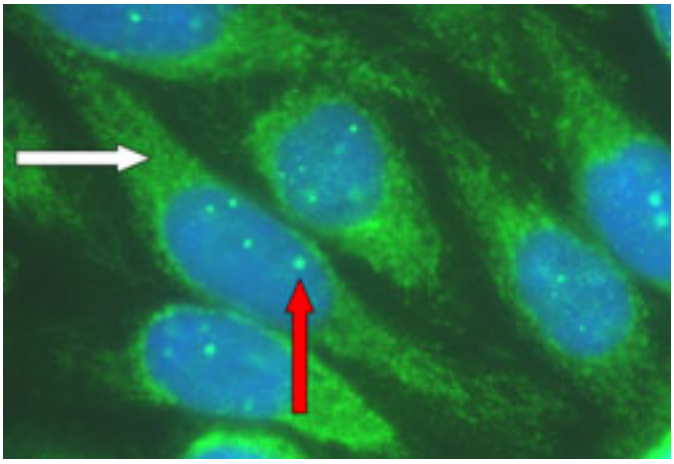

Figure 1: Characteristic autoantibody patterns in primary biliary cholangitis. White arrow: antimitochondrial staining; red arrow: multiple nuclear dot ANA staining

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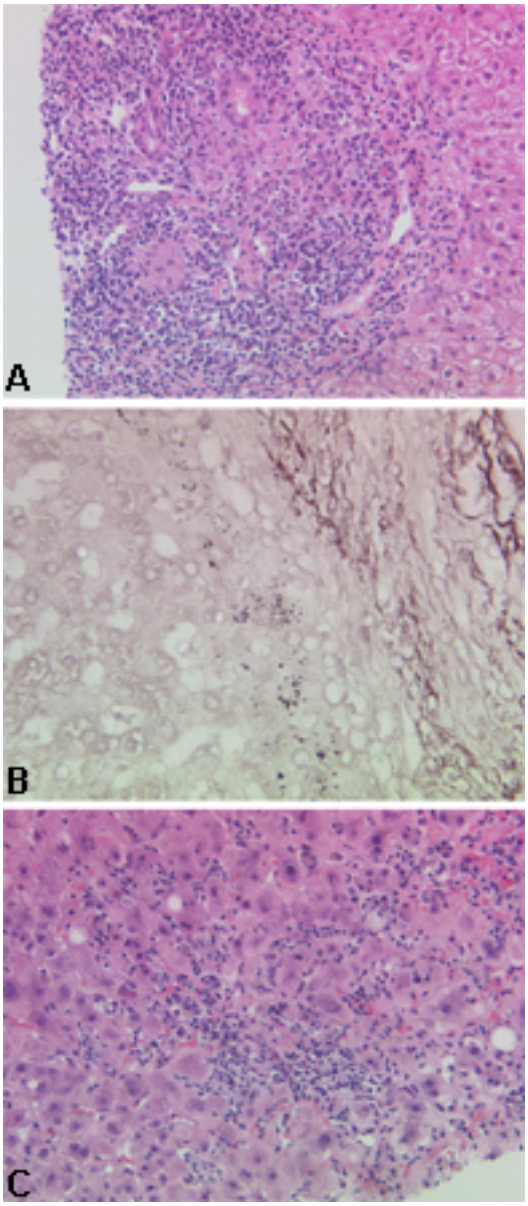

Figure 2: Characteristic histologic appearances of primary biliary cholangitis: (a) early-stage disease; (b) advanced-stage disease; (c) disease with a significant inflammatory component

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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