Primary Biliary Cirrhosis

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This guideline has been approved by the AASLD and represents the position of the association.

Preamble

These recommendations provide a data-supported approach to the management of primary biliary cirrhosis (PBC). They are based on the following: (1) formal review and analysis of the recently published world literature on the topic (Medline search); (2) American College of Physicians *Manual for Assessing Health Practices and Designing Practice Guidelines* [1]; (3) guideline policies, including the AASLD Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association Policy Statement on Guidelines[2]; and (4) the experience of the authors in the specified topic. Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting recommendations, the Practice Guideline Committee of the AASLD requires a Class (reflecting benefit versus risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation (Table 1, adapted from the American College of Cardiology and the American Heart Association Practice Guidelines[3]).

Etiology of Primary Biliary Cirrhosis

PBC is often considered a model autoimmune disease because of its hallmark serologic signature, the antimitochondrial antibody (AMA) and specific bile duct pathology.[4,5] The etiology of PBC is thought to be due to a combination of genetic predisposition and environmental triggers.[6]

Although the genetic predisposition is clear, major histocompatibility complex associations are varied.[7] Several large epidemiologic studies have been performed and have suggested an association with urinary tract infections, reproductive hormone replacement, nail polish, past cigarette smoking, and toxic waste sites, as well as xenobiotics in an animal model of PBC.[8-10]

One critical and unique feature of PBC is the high degree of specificity for involvement of the small intrahepatic bile ducts. Staining of small bile ducts with monoclonal antibodies against mitochondrial autoantigens demonstrates an intense staining at the apical surface of biliary epithelial cells.[11,12]

The characteristic serologic hallmark of PBC is the AMA, a highly disease-specific autoantibody found in 90%-95% of patients and less than 1% of normal controls.[13] The targets of the disease-specific antimitochondrial response are all members of a family of enzymes, the 2-oxo-acid dehydrogenase complexes and include pyruvate dehydrogenase complex (PDC-E2), branched chain 2-oxo-acid dehydrogenase complex, and 2-oxo-glutaric acid dehydrogenase complex. These enzymes catalyze the oxidative decarboxylation of keto acid substrates and are located in the inner mitochondrial membrane.[14,15] Fewer than 5% of patients with PBC are AMA-negative in one study.[16] Both immunofluorescence, and now more commonly enzyme-linked immunosorbent assays, are used to test for AMA.

There is a 100-fold to 150-fold increase of autoreactive CD4 PDC-E2–specific T cells in liver and regional lymph node compared to blood in patients with PBC, and a 10-fold to 15-fold increase in autoreactive CD8 PDC-E2–specific T cell infiltrates in liver compared to blood. These data strongly suggest that the antimitochondrial response is either directly related to pathology or intimately associated with the etiological insult.[17,18]

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IAIH-G, International Autoimmune Hepatitis Group score; Ig, immunoglobulin; PBC, primary biliary cirrhosis; PDC-E2, pyruvate dehydrogenase complex; UDCA, ursodeoxycholic acid.

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Table 1. Grading System for Recommendations

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful

Level of Evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinion of experts, case studies, or standard-of-care

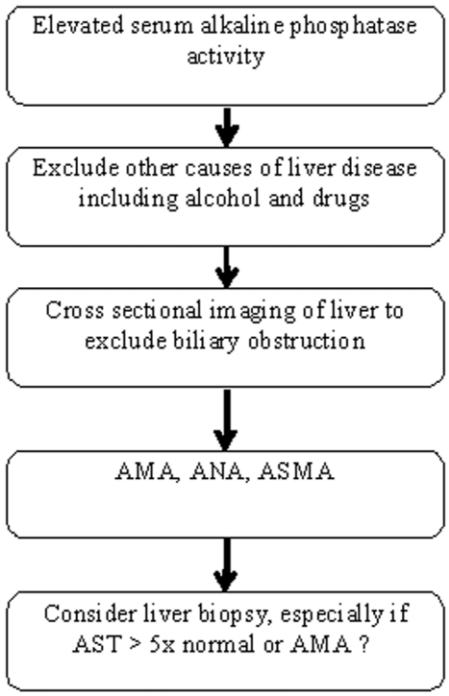

Fig. 1. Suggested diagnostic algorithm for patients with suspected PBC. AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody.

Natural History

PBC is a chronic cholestatic disease with a progressive course which may extend over many decades. The rate of progression varies greatly among individual patients. Over the past decades, there have been many changes in the diagnosis and management of PBC. More patients are being recognized with earlier stage disease and many of these patients respond well to medical therapy. In both Europe and North America the number of liver transplants for PBC is falling.[19,20]

Patterns of Clinical Disease and Natural History in the Pre-Ursodeoxycholic Acid Era

AMA may be detectable in serum when patients are symptom-free and liver tests are normal. Based on one small study, it is believed that many of these patients may eventually develop abnormal liver tests and symptoms. The median follow-up time from the first positive AMA test to persistently abnormal liver tests in this series was 6 years with a range between 1 and 19 years. However, none of the patients developed cirrhosis during the follow-up.[21] It is estimated that 0.5% of the general population is AMA-positive, which means that fewer than 10% of patients with AMA will develop PBC.[22]

The proportion of asymptomatic patients (which has been variably defined) who will subsequently develop PBC-related symptoms has been investigated in several series from the United Kingdom, North America, and Sweden.[23-28] All of these studies provide evidence of progressive disease in a substantial proportion of patients, with between 36% and 89% becoming symptomatic during average follow-up periods ranging from 4.5-17.8 years. In the two most recent studies,[27,28] the median time from diagnosis to the appearance of symptoms was found to be 2 and 4.2 years.

Patients with early disease in the absence of ursodeoxycholic acid (UDCA) therapy have a shortened survival comparable to a healthy population regardless of symptoms.[27,28] The 10-year survival of asymptomatic patients in three contemporary series ranged from 50%-70%; whereas the median duration of survival for symptomatic patients ranged from 5-8 years from the onset of symptoms.[27,28]

In an older study of 279 patients from the United States,[24] the median survival of symptomatic patients was 7.5 years, much shorter than the median survival of 16

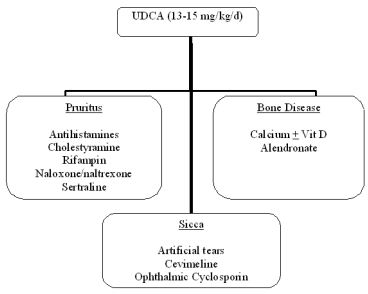

Fig. 2. Treatment of PBC.

years for asymptomatic patients. This marked difference in survival has not been found in the study from Northeast England, a finding possibly explained by an excess of deaths unrelated to liver disease in asymptomatic patients who were on average a decade older.[29]

Histologic stages have been found to predict survival.[30,31] The rate of histologic progression has been assessed in three large groups of patients in the absence of a therapeutically effective agent.[30,32,33] The median time to develop extensive fibrosis was 2 years. After 4 years, the probability of remaining in the early stage was 29% (confidence interval: 15%-52%), while cirrhosis was diagnosed in 50% of patients who initially had only interface hepatitis without fibrosis. Only a minority (20%) of patients who were precirrhotic showed histologic stability. Overall, the histologic stage progressed by one stage every 1.5 years.

The development of liver failure (ascites, bleeding, hepatic encephalopathy, or hyperbilirubinemia [>6 mg/dL]) during a follow-up of 5 years has been estimated to be 15% in the large community-based study of 770 patients in Northeast England[27] and 25% of the 236 patients enrolled in the European azathioprine trial.[30]

The rate of development of esophageal varices and its impact on survival were evaluated in a prospective study of 256 patients (28% of whom had cirrhosis) who were observed for a median time of 5.6 years.[34] A total of 31% of patients developed esophageal varices. After the development of varices, the 3-year survival was 59%, whereas after a first bleeding episode, it was 46%.

Natural History in the UDCA Era (Circa 1990)

UDCA is currently the only drug approved for the treatment of patients with PBC. Several randomized trials, combined analyses, and long-term observational studies have shown that this agent not only improves biochemical indices but also delays histologic progression and improves survival without transplantation.[32,35-46] Accordingly, most patients are now treated with UDCA.

In an early study, the rate of histologic progression to cirrhosis was significantly less in the UDCA group than in the control group (13% versus 49%).[35] In a trial involving 192 patients, UDCA therapy significantly delayed histologic stage progression after a median follow-up of 3.4 years.[39] In the French trial of UDCA, the risk of progression from stages I-II to stages III-IV was 7% ± 2% with UDCA and 34% ± 9% with placebo.[32] Predictive factors for cirrhosis developing included serum bilirubin higher than 1 mg/dL, and moderate to severe lymphocytic piecemeal necrosis on the liver biopsy.[47]

The effect of UDCA therapy on the development of esophageal varices was addressed in a prospective study of 180 patients who received UDCA versus placebo and were observed for up to 4 years.[48] A total of 139 patients had no varices and 41 had varices at baseline. After 4 years, the risk of developing varices was 16% for the UDCA-treated patients and 58% for those receiving the placebo. However, UDCA did not reduce the low rate of bleeding.

Survival

To overcome the lack of power of clinical trials in assessing the long-term effectiveness of therapy, a Markov model has been used to study the effect of UDCA on the natural history of PBC.[46] The study included 262 patients who had received 13-15 mg/kg UDCA daily for a mean of 8 years (range 1-22 years), and their survival was substantially better than that predicted by the model. The overall survival rates without liver transplantation were 84% and 66% at 10 years and 20 years, respectively. The survival rate was better than the spontaneous survival rate as predicted by the updated Mayo model (relative risk: 0.5, $P < 0.01$). In early-stage patients, 6% were predicted to progress to liver transplantation or death after 10 years and 22% by 20 years. The survival rate of these patients was similar to that in the control population. In contrast, the probability of death or liver transplantation was significantly increased in patients treated in late stages of the disease (relative risk: 2.2, $P < 0.05$).

Several clinical, biochemical, and histologic features have prognostic significance in PBC although bilirubin level is the best predictor of survival and is the most important component in all mathematical models of prognosis in PBC.[49,50] Some of these models have been useful in predicting survival in UDCA-treated patients as well (http://www.mayoclinic.org/gi-rst/mayomodel1.html).

Diagnosis of Primary Biliary Cirrhosis

The diagnosis of PBC should be suspected in the setting of chronic cholestasis after exclusion of other causes of liver disease. The diagnosis is suspected based on cholestatic serum liver tests and largely confirmed with tests for AMA. A liver biopsy can be used to further substantiate the diagnosis if needed.

Liver Biochemical Tests

Most patients with PBC have abnormal liver tests including elevations of alkaline phosphatase, mild elevations of aminotransferases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) activity, and increased levels of immunoglobulins (mainly immunoglobulin M [IgM]). Some patients with PBC may have high ALT or AST activities associated with hyperglobulinemia (increase in IgG). The changes in biochemical

tests are related in part to the stage of the disease and to severity of histologic lesions.[30,51,52] In patients without cirrhosis, the degree of elevation in alkaline phosphatase is strongly related to the severity of ductopenia and inflammation; the increase in aminotransferase activity and IgG levels reflects mainly the degree of periportal and lobular necrosis and inflammation; hyperbilirubinemia reflects the severity of ductopenia and biliary piecemeal necrosis. A rise in serum bilirubin, gamma globulins, and hyaluronic acid together with a fall in serum albumin and platelet count are the early indicators of the development of cirrhosis and portal hypertension.[51,52] As in other cholestatic diseases, serum cholesterol levels are often elevated.[53] Individual serum bile acid levels can be elevated but are not routinely determined.

Autoantibodies

AMA is found in nearly 95% of patients with PBC.[5] Antinuclear antibody and anti–smooth muscle antibody are found in nearly half of patients with PBC.[5] In approximately 5%-10% of the patients, AMA antibodies are absent or present only in low titer ($\leq$ 1/80), when immunofluorescent techniques are used. The presence or absence of antibody, rather than the magnitude of antibody level, is most important. In some patients, antinuclear antibodies, particularly anti-GP210 and/or anti-SP100 are present and may correlate with prognosis[54]; in some other AMA-negative patients, antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex) are present using enzyme-linked immunosorbent assay or western blotting techniques.

Histology

PBC is characterized by chronic, nonsuppurative cholangitis that mainly affects interlobular and septal bile ducts. When focal lesions show intense inflammatory changes and necrosis around bile ducts, the term "florid duct lesion" is often used. The inflammatory infiltrate consists essentially of lymphocytes and mononuclear cells in close contact with the basal membrane of cholangiocytes undergoing necrosis. The infiltrate consists of plasma cells, macrophages, polymorphonuclear cells (especially eosinophils), and in some cases epithelioid granulomas which are present more often in the early stage of disease.[5] There are few (if any) arterial lesions. In contrast, portal venules are often compressed and occluded by the inflammatory reaction. Terminal hepatic venules are often retained in their central location with progression of fibrosis and sometimes even in cirrhosis. Bile duct paucity or ductopenia is usually defined in less than 50% of portal tracts containing ducts.

The size of the liver biopsy specimen is important. The probability of observing cholangitis and bile duct destruction increases with the number of portal tracts because of the typical patchy distribution of the lesions. At least 10-15 portal tracts should be present, and multiple sections should be reviewed to adequately appreciate or rule out cholangitis and ductopenia. These would include periportal/periseptal copper deposition, periportal/periseptal feathery degeneration with or without Mallory-Denk bodies, and cholestatic rosettes. Actual bile stasis is not appreciated until decompensated liver disease has occurred.

Histologic lesions are classically divided into four stages. Stage I is characterized by portal inflammation with or without florid bile duct lesions. In this stage, inflammation remains confined to the portal triads. Disease progression is characterized by the gradual increase of periportal lesions extending into the hepatic parenchyma referred to as interface hepatitis (stage II). Periportal regions become focally irregular, and the lesion is characterized by cellular necrosis or apoptosis, separation of hepatocytes by inflammatory cells, and macrophages. There are two main types of interface hepatitis. The first is lymphocytic piecemeal necrosis, the association of hepatocellular necrosis or apoptosis with lymphohistiocytic cells. This is similar to the lesion found in autoimmune hepatitis (AIH). Second is biliary piecemeal necrosis, which is marked by a striking ductular reaction, sometimes referred to as ductular proliferation, and accompanied by edema, neutrophil infiltration, periductular fibrosis, and necrotic hepatocytes, the latter associated with cholestasis. The French have shown that severity of interface hepatitis is highly predictive of development of extensive fibrosis.[47,55] Stage III is characterized by a distortion of the hepatic architecture with numerous fibrous septa. Cirrhosis with the existence of regenerative nodules defines stage IV. Nodular regenerative hyperplasia is a known complication of PBC and should be differentiated from cirrhosis.

With the high disease specificity of a positive AMA test, the role of liver biopsy to diagnose PBC is questionable with alkaline phosphatase activity $\geq$ 1.5 times normal and AST values $<$ 5 times normal.[56] Liver biopsy may be recommended in AMA-negative patients and to exclude other concomitant diseases such as AIH and nonalcoholic steatohepatitis.[46,47,55]

Role of Imaging

Expert noninvasive imaging of the liver and biliary tree is mandatory in all patients with biochemical evidence of cholestasis. If the diagnosis is uncertain, then cholangiography may be necessary preferentially with noninvasive

magnetic resonance imaging or endoscopically to exclude primary sclerosing cholangitis or other biliary tract diseases. Transient elastography (Fibroscan; Echosens, Paris, France) is a new noninvasive tool to evaluate the degree of liver fibrosis, which has been studied in patients with PBC,[57] but it is not yet approved by the U.S. Food and Drug Administration.

Diagnostic Approach

The diagnosis of PBC is generally based on the following criteria: (1) biochemical evidence of cholestasis with elevation of alkaline phosphatase activity; (2) presence of AMA; and (3) histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts if a biopsy is performed. The differential diagnosis includes a cholestatic drug reaction, biliary obstruction, sarcoidosis, AIH and primary sclerosing cholangitis.

Recommendations: Diagnosis

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

- ***Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation.***
- ***Presence of AMA.***
- ***Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts (Class I, Level B).***

Clinical Manifestations of PBC

Symptoms

Fatigue. Fatigue is the most common symptom in PBC and has been found in up to 78% of patients.[56-62] Fatigue is nonspecific and occurs in many conditions other than PBC. Fatigue does not correlate with the severity, histologic stage, or duration of PBC. Severe fatigue may impair the quality of life in patients with PBC[61,62] and may be associated with decreased overall survival.[63] Its etiology is unknown. Recently, an autonomic neuropathy has been described in association with fatigue in patients with PBC.[64] Fatigue does not improve with treatment of depression, is often constant over time,[65] is frequently associated with excessive daytime somnolence, and may be a manifestation of untreated hypothyroidism which occurs in about 20% of patients with PBC.[65,66]

Pruritus. Pruritus is a more specific symptom of PBC than fatigue and formerly occurred in 20%-70% of patients with PBC. It is now less common because patients with PBC are often asymptomatic at diagnosis.[59,67,68] It can be local or diffuse, usually worse at night while lying in bed, and is often exacerbated by contact with wool, other fabrics, heat, or pregnancy. Once pruritus occurs in PBC, its severity may diminish over time.[67] However, it is unlikely to disappear completely without treatment until a patient develops cirrhosis and liver failure. The cause of pruritus in PBC is unknown.[69,70] It is proposed that the pruritus of cholestasis, including that secondary to PBC, is mediated at least in part by increased opioidergic neurotransmission[70] while other studies support a role for components of bile.[71]

Other Symptoms. Sicca Syndrome (dry eyes and/or mouth) is common. Cutaneous calcinosis, Raynaud's phenomenon, and dysphagia are uncommon associated symptoms.

Physical examination

The physical examination is usually normal. Occasionally, xanthelasma and xanthoma are recognized. Spider angiomata and splenomegaly are found in the setting of portal hypertension. Jaundice is a late finding in patients with advanced liver disease.

Portal Hypertension

Similar to other liver diseases, portal hypertension most often develops late in the course of PBC, when patients have well-established cirrhosis. However, in contrast to other liver diseases, portal hypertension may also develop in patients with early, precirrhotic PBC. These patients may hemorrhage from esophageal varices, gastric varices, or portal gastropathy despite having normal or near normal liver synthetic function. Nodular regenerative hyperplasia is associated with obliteration of the portal venules and may lead to portal hypertension in some of these patients.[72,73] Patients can survive for many years after variceal hemorrhage without liver transplantation.[72,74] Ascites and hepatic encephalopathy may develop in patients with histologic advanced PBC and cirrhosis.

Bone Disease

Osteoporosis is the bone disorder seen most often in PBC[75] and occurs in up to one-third of patients.[76,77] The relative risk for osteoporosis in PBC compared to an age-matched and sex-matched healthy population is 4.4.[76] It is usually asymptomatic, not associated with any specific laboratory abnormalities, and detected by bone densitometry. The debilitating bone disease that was seen decades ago and often complicated by multiple fractures is now uncommon.[78-80] The cause of osteoporosis in PBC is uncertain. Patients with PBC appear to have "low-turnover" osteoporosis in which bone formation is inhibited and bone resorption is low or normal.[78,81-82] Vitamin D metabolism is normal in patients with PBC except for those with jaundice and clinically advanced disease.[83-85]

Hyperlipidemia

Serum lipids may be strikingly elevated in PBC.[86,87] The mechanism of hyperlipidemia in PBC is different from that in other conditions. Levels of high-density lipoprotein cholesterol are typically elevated and unusual lipoprotein particles, such as lipoprotein X, may accumulate.[88] Mean cholesterol levels were 370 and 265 mg/dL in two studies of patients with PBC and levels ranged from 120-1775 in individual patients.[88,89] High-density lipoprotein cholesterol is disproportionately elevated compared to low-density lipoprotein cholesterol, and patients with PBC are not at increased risk of death from atherosclerosis.[87,89,90]

Vitamin Deficiency

Although patients with PBC may have decreased bile acid secretion resulting in increased risk of lipid malabsorption, clinically important deficiencies of the fat-soluble vitamins A, D, E, and K are uncommon.[83,91-93] Vitamin D metabolism is maintained and serum levels of 25-hydroxy vitamin D and 1-25 dihydroxyvitamin D are usually normal in most patients, including those with osteoporosis.[94] The exception occurs in severely jaundiced patients who are awaiting liver transplantation who may also have osteomalacia. Vitamin A, D, E, and K levels may be decreased, resulting in night blindness, osteopenia, neurologic impairment, and decreased prothrombin activity, respectively.[95,96]

Special Cases

AMA-Negative PBC

Patients with AMA-negative PBC refers to those who lack AMA but whose clinical presentation, liver histology, and natural history are nearly identical to patients with typical AMA-positive PBC. Nearly all of these patients have antinuclear and/or anti–smooth muscle antibodies.[97-102]

Minimal differences in histopathology, immunology, and human leukocyte antigen status exist between the AMA-positive and AMA-negative groups. Mitochondrial antigen is expressed on the apical membranes of biliary epithelial cells from individuals with AMA-negative as well as AMA-positive PBC, suggesting that their pathogenesis is similar.[103]

The diagnosis of AMA-negative PBC requires a liver biopsy that demonstrates the typical features of bile duct destruction seen in PBC. The diagnosis is more certain if granulomas are present. A recent large Japanese retrospective study has shown AMA-negative cases of PBC have less pruritus and more nonhepatic autoimmune diseases (e.g., rheumatoid arthritis and scleroderma).[104] IgM levels are lower in AMA-negative than AMA-positive patients with PBC.[99]

A recent meta-analysis has examined published reports[105] of patients treated for AMA-negative PBC, which only totaled 52 patients. The authors concluded no difference in biochemical response to UDCA was observed when patients with AMA-positive and AMA-negative PBC were compared.

Overlap of AIH with PBC

There is no formal definition of the overlap syndrome between PBC and AIH. Overlap features of PBC usually refers to simultaneous AIH in patients who have a diagnosis of AMA-positive PBC and not to patients with AIH who have coincidental AMA. Studies reported to date are of insufficient size to indicate with any degree of certainty just how a diagnosis of PBC overlapping with AIH is different from uncomplicated PBC. Limited observational data suggests that response to therapy with UDCA for PBC/AIH overlap is no different from that observed in patients with PBC alone. A PBC/AIH overlap syndrome may also refer to patients with sequential PBC followed by AIH as described recently in a case series[106]; less commonly, AIH followed by PBC has been described.

Diagnosis of PBC/AIH Overlap

There are two scoring systems that have been used to evaluate patients with PBC for simultaneous evidence of overlapping AIH. Both of these scoring systems are arbitrary; they are decided upon by expert opinions without the availability of long-term follow-up data. The first is the International Autoimmune Hepatitis Group (IAIH-G) score, the original draft of which was validated in two independent patient populations diagnosed with AIH. This score was subsequently revised,[107] and it is this score that has been used in several recent studies to identify possible PBC/AIH overlap. But this IAIH-G score was designed for AIH and positive points for AIH are given when there is an absence of factors unrelated to a diagnosis of PBC, e.g., viral hepatitis and alcohol abuse. In addition, negative scores for AMA and/or biochemical/histologic features of biliary disease would be assigned by IAIH-G. A second score has been used to support the presence of a PBC/AIH overlap by looking for the presence of two of the three following features: (1) ALT activity $>$ 5 times upper limits of normal; (2) IgG $\geq$ 2 times upper limits of normal and/or positive anti–smooth muscle antibody; and (3) liver biopsy with moderate or severe periportal or periseptal inflammation.[108]

There have been several individuals with PBC who have been given a diagnosis of PBC and have then been evaluated for "features of AIH" using one of these two

methods.[109-111] However, it is unclear if the biochemical, serological, and immunological data were collected at the same time as the liver histology. Additionally, external factors such as drug reactions or concomitant diseases may affect any and possibly all of these measurements.

Clinical Course of "Overlap" Syndrome

Small studies have reported outcomes in patients with simultaneous PBC/AIH overlap. Twenty-six patients with PBC/AIH overlap who were followed for a mean of 5-6 years were compared with 135 patients with classical PBC.[112] This study indicated a worse outcome in terms of complications of portal hypertension, death, or need for liver transplant in patients with PBC and a "probable" or "definite" IAIH-G score. However, an estimated 50% of patients in either group had received treatment with UDCA and some in both groups had received a variety of other therapies. UDCA with or without immunosuppressive therapy has been used, but no clear consensus in optimal therapy for these patients exist.[110-113] There are no randomized, controlled data which indicate how best to treat patients thought to have simultaneous PBC/AIH overlap.

Consecutive PBC/AIH

There are case reports[114,115] of patients with AMA-positive PBC who respond biochemically to UDCA therapy yet subsequently present with clinical features of AIH. These patients may no longer have AMA seropositivity, and liver histology becomes more typical of AIH which responds to immunosuppressive therapy. Patients with PBC may have florid duct lesions and almost all have evidence of bile duct damage, usually with cholestatic features. A review of 289 cases of PBC followed for the long term suggests that 4.3% have simultaneous features of PBC and AIH and 2.4% develop an acute AIH superimposed on their PBC.[116] These authors make reference to five cases of AIH who then developed PBC. More recently, eight patients drawn from more than 1400 patients with PBC were described who developed AIH after years of stable PBC.[116]

AMA-Positive AIH

There are few data on the prevalence of detectable serum AMA in patients who otherwise have typical features of AIH. These data may be extracted from histologic review of patients with AIH, in whom small bile duct pathology was superimposed on a background of AIH.[117] In this case series, none of the five patients who tested positive for AMA (among 166 patients) had bile duct changes on examination of liver histology. There are case reports of patients with overt AIH who nevertheless tested AMA-positive,[118,119] but on long-term follow-up, these patients do not develop PBC.[120]

Clearly, there is a need for better long-term analysis regarding the natural history of both PBC and AIH. The effect of therapy on the IAIH-G score and its components will need to be controlled for, and only then will the clinical significance of these overlapping features become realized.

Therapy for Primary Biliary Cirrhosis

UDCA in a dose of 13-15 mg/kg/day is the only therapy for PBC approved by the U.S. Food and Drug Administration. The drug is initiated gradually and generally given in two divided doses. A number of studies have shown the benefit of UDCA in this context.[37-42] Individual studies have demonstrated consistent evidence of improved liver biochemistries. Some studies with extended follow-up have also shown improved survival.[38,41,42] Other information comes from combining data sets to increase sample sizes which has allowed assessment of the effects of therapy.[42] Some meta-analyses have questioned these results.[121] Often, these meta-analyses include studies of short duration and those that have used what is now known to be an inadequate dose of UDCA.[122]

UDCA is widely used and has demonstrated the ability to produce a reduction in need for liver transplantation for this condition.[123] The drug is used for patients with any stage of PBC as long as their liver biochemistries are abnormal. A liver biopsy in not required for the diagnosis for PBC in many settings, and the stage of biopsy does not determine whether UDCA should be used but may have an impact on developing treatment strategies.[111] Patients with earlier histologic stage in general respond more favorably to UDCA, but even patients with advanced stage disease may derive improvement in survival or avoidance of need for liver transplantation with this therapy.[42]

The dose of UDCA is important. A study comparing three different doses of UDCA showed that a dose of 13-15 mg/kg/day appeared superior to either a lower dose of 5-7 mg/kg/day or a higher dose of 23-25 mg/kg/day in biochemical responses and cost.[124] The studies which show an improvement in survival have all used this dose of 13-15 mg/kg/day. A direct comparison of different drug formulations has not been studied in patients with PBC. A short-term pharmokinetic study in normal volunteers suggested substantial differences in bioavailability on the basis of preparation.[125] Cholestyramine or other bile acid binding sequestrants may interfere with UDCA absorption. Some antacids may bind bile acids, and so these should be administered at separate times. Dosage does not need to be adjusted for liver or renal disease. Monitoring is done using liver biochemical values, and liver biopsy has

not been used for monitoring. Improvement in liver tests will be seen within a matter of a few weeks and 90% of the improvement usually occurs within 6-9 months. About 20% of patients will have normalization of liver biochemistries after 2 years[126] and a further 15% or 35% of the total will have normalization by 5 years. The effect of treatment can be based on response of serum alkaline phosphatase activity or Mayo risk score, which is dependent on age, albumin, bilirubin, prothrombin time, and presence or absence of fluid retention.[49,127] The use of UDCA has been associated with a reduction of serum low-density lipoprotein cholesterol levels, a reduced risk of developing varices, and slower histologic progression. However, UDCA therapy does not improve fatigue, pruritus, associated bone disease, or autoimmune features found in association with PBC.[48,55,128,129]

Issues of patient compliance, development of superimposed liver disease, or coadministration with bile sequestrants such as cholestyramine or Colestid should be considered for patients with suboptimal response. UDCA has minimal side effects. A five-pound weight gain over the first year of therapy has been reported and is not progressive.[130] Loose stools and/or thinning of the hair have been reported infrequently.

Other drugs have been tested, but none have been found as single agents to be of benefit. These include chlorambucil, penicillamine, cyclosporine, corticosteroids, azathioprine, mycophenolate mofetil, thalidomide, methotrexate, malotilate, and colchicine.[131-141] Many of these have been used in combination with UDCA to see if further improvement in liver disease could be effected. Doubling the dose of UDCA and the addition of colchicine, methotrexate, or silymarin have not been found to be of benefit over and beyond that achieved with UDCA alone.[144-146] Budesonide may be helpful, although this is controversial.[147] Fibrates are also being evaluated.[148]

Food and Herbals Used Therapeutically

Patients frequently ask about specific foods to use or avoid. There are no specific recommendations based on clinical evidence that any particular foods should be avoided or would be of benefit. In patients who are obese and who may have superimposed steatohepatitis, a normal (ideal) body weight would be desirable. No information exists on risks of concurrent alcohol use or medications.

Complementary or alternative medicines have seldom been tested and seldom are. Silymarin was tested in combination with UDCA but offered little additional benefit.[146] No other clinical evidence exists regarding clinical safety or efficacy of other herbal products.

Recommendations:

2. ***UDCA in a dose of 13-15 mg/kg/day orally is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage (Class I, Level A).***
3. ***For patients requiring bile acid sequestrants, UDCA should be given 2-4 hours before or after ingestion (Class I, Level C).***

Management of Symptoms

Management of Fatigue

Fatigue may be multifactorial; causes other than PBC should be considered. These include anemia, hypothyroidism, depression, and a sleep disorder. Treatment with UDCA has not been reported to have an impact on the degree of fatigue in patients with PBC.

Altered serotonin neurotransmission may mediate fatigue in chronic liver disease,[149] however, ondansetron, an antagonist to serotonin receptor 3, did not relieve fatigue.[150] Fluoxetine, a selective serotonin reuptake inhibitor, also did not improve fatigue.[151]

An association between fatigue and altered sleep, and in particular excessive daytime sleepiness, has been reported in patients with PBC.[152] Modafinil is a medication used for the treatment of daytime somnolence associated with shift work.[153] The initial observation that modafinil might lessen fatigue in PBC was supported by an open-label study.[154] Modafinil at doses of 100-200 mg/day was associated with a significant improvement in the fatigue domain score as compared to baseline, as assessed by the PBC-40 questionnaire. In addition, modafinil was associated with a significant decrease in daytime somnolence.[155] At this time, there is no recommended therapy for the fatigue resulting from PBC.

Management of Pruritus

UDCA does not usually relieve pruritus; therefore, specific antipruritic interventions need to be prescribed. The treatment of pruritus secondary to cholestasis can be classified according to the presumed aim of the intervention.

Therapies for the Removal of the Pruritogenic Substances(s) from the Body

It is believed that the pruritogenic substances are made in the liver, excreted in bile, and as a result of cholestasis accumulate in tissues. Cholestyramine is a nonabsorbable resin used to treat hypercholesterolemia; other resins include colestipol and colesevalam. There is a consensus that cholestyramine is associated with amelioration of pruritus in many patients with PBC.[156,157] The recommended dose of cholestyramine is 4 g per dose to a maximum of 16 g/day given 2-4 hours before or after UDCA.

Morning dosing is preferred. In general, cholestyramine is well tolerated, although some patients report bloating, constipation, and diarrhea. Colestipol and colesevalam have not been evaluated in controlled studies to treat pruritus in cholestasis.[158]

Patients with severe pruritus not responsive to oral therapy have undergone procedures to separate the pruritogens from the plasma, including the extracorporeal liver support systems.[159-161]

Rifampicin

Rifampicin, an enzyme inducer, has been used to treat pruritus in patients with PBC in several clinical studies.[162-165] A dose of 150 mg daily if bilirubin was less than 3 mg/dL and 150 mg twice daily if bilirubin was 3 mg/dL or higher was used in one study.

Two published meta-analyses have reported that rifampicin administration is associated with relief of pruritus in cholestasis.[158,166] One meta-analysis included four clinical trials with a participation of a total of 57 patients in studies of variable quality.[158,167] The other meta-analysis included a total of 61 participants from three double-blind randomized prospective studies and two randomized controlled cross-over trials.[166] Rifampicin was associated with the relief of pruritus in a higher proportion of patients than the control group, with an odds ratio of 15.2 (confidence interval: 5.2-45.6, $P = 0.001$). Side effects of rifampicin remain a serious concern because cases of hepatitis and hepatic failure, hemolysis, renal impairment, and alteration in drug metabolism have been associated with the administration of this drug[67,164,168]; therefore, if rifampicin is prescribed, close and regular follow-up of blood tests including liver panel and blood counts is necessary. Rifampicin use may obviate the antidepressive effects of serotonin reuptake inhibition, and these should not be used together.[169]

Opiate Antagonists

A pharmacological increase in opioidergic tone is associated with pruritus[170] and ameliorated by opiate antagonists, suggesting that it is an opioid-receptor-mediated phenomenon.[171] There is evidence to suggest that in cholestasis there is increased opioidergic tone[172]; thus, altered neurotransmission may mediate the pruritus, and opiate antagonist drugs such as naloxone should decrease the pruritus.[173-178] A meta-analysis included five trials, three that tested the effect of opiate antagonists administered orally (i.e., naltrexone and nalmefene) and two that tested the effect of intravenous naloxone with a reported total of 84 participants.[158] Opiate antagonists were significantly more likely to decrease pruritus than the control intervention.

The limiting factor in the use of opiate antagonists is the opioid withdrawal-like reaction that can occur with this type of medication.[173,174,176] The opiate withdrawal-like reaction can be characterized by abdominal pain, high blood pressure, tachycardia, goose bumps, nightmares, and depersonalization.[174,176,179] It is not possible to predict who will develop an opiate withdrawal-like reaction. Clinical experience has suggested that patients who have severe pruritus may have a higher opioidergic tone and may be at risk for a more severe reaction. Naltrexone at a dose of 50 mg as a starting dose may be higher than desirable, thus, the provision of a lower dose can be achieved by providing a quarter (12.5 mg) of a tablet every day to be increased by a quarter every 3-7 days, until the pruritus is ameliorated. Alternatively, patients can be admitted to the hospital for intravenous infusions of naloxone as previously reported,[20] followed by the introduction of oral naltrexone and discontinuation of the infusion. Drug administration can be held or the dose kept constant if signs of an opiate withdrawal-like syndrome develop, because the reaction tends to subside spontaneously.[180] Naltrexone hepatotoxicity is not common but it has been reported; thus, follow-up of liver biochemistries is recommended.[181,182] In patients with decompensated liver disease, naltrexone metabolites can accumulate[183]; thus, reduction of the dose is necessary. The need to use naltrexone in these cases is not common because pruritus tends to cease as liver disease progresses.[67] Long-term use of opiate antagonists has been associated with a chronic pain syndrome.[184]

Other Agents

Serotonin Antagonists. The serotonin system participates in the neurotransmission of nociceptive stimuli which is the rationale provided for the evaluation of ondansetron, a serotonin antagonist at the type 3 receptor, to treat pruritus in cholestasis.[185] Ondansetron (8 mg three times daily) was reported to decrease the pruritus associated with cholestasis in studies that used subjective methodology only; however, data from studies that applied behavioral methodology and that included patients with PBC have suggested that ondansetron has only minimal therapeutic effect on the pruritus.[186-188]

Antidepressants. Antidepressants, including selective serotonin reuptake inhibitors, have been reported to have antipruritic effects.[189] Sertraline (75-100 mg) helped relieve pruritus; the effect was independent from an improvement in depression.[190]

Phenobarbital. Phenobarbital has been used in the

past but is sedating and has been associated with troublesome gingival hyperplasia.

Antihistamines. Antihistamine drugs may have nonspecific antipruritic effect in patients with cholestasis, which may result from their sedative properties.[191,192] Antihistamine-mediated sedation may help patients sleep, which can be difficult in patients with pruritus; however, the dryness of mucous membranes associated with this type of drug may limit its use in patients with PBC and sicca symptoms.[192]

Patients with severe pruritus are at risk for depression and suicidal ideations and actions. These patients may require hospital admission for parenteral administration of medications including opiate antagonists. Intractable pruritus can be an indication for liver transplantation.[193,194]

Recommendations:

4. ***Bile acid sequestrants should be used as initial therapy for patients with PBC who have pruritus (Class I, Level B).***
5. ***The following agents can be used for pruritus refractory to bile acid sequestrants:***

a. ***Rifampicin 150-300 mg twice daily (Class I, Level A).***
b. ***Oral opiate antagonists such as naltrexone 50 mg daily (Class I, Level A).***
c. ***Sertraline (75-100 mg daily) can be tried when other measures fail (Class I, Level B).***

Management of Sicca Syndrome

General measures to improve eye care include humidification of the household environment. Artificial tears, the initial treatment of dry eyes, include hydroxypropyl methylcellulose and carboxymethylcellulose and can be used as needed over the course of the day. Anti-inflammatory and immunosuppressant agents also have been used to treat dry eyes.[195] Cyclosporine ophthalmic emulsion, the only prescription product approved for the treatment of dry eyes, was associated with a significant increase in the production of tears as compared to placebo in controlled clinical trials. In cases refractory to drugs, blocking the puncta to prevent draining of tears can be performed, in combination with artificial tears.[196]

The dramatic presentation of PBC with rampant dental caries has been reported in a patient with severe symptoms of Sjögren's syndrome.[197] General measures to improve oral health in patients with sicca symptoms include regular visits to the dentist, mouth rinsing with water, the use of fluoride-containing toothpaste, daily flossing, and avoidance of sugar between meals. Chewing sugar-free gum and hard candy can stimulate saliva production, and the use of oil-based or petroleum-based lip balm or lipstick can decrease oral dryness. Saliva substitutes are recommended for patients with xerostomia. Cholinergic agents, such as pilocarpine and cevimeline, are empirically used in Sjögren's syndrome.[198] Dysphagia can be associated with xerostomia in patients with PBC; interventions to increase saliva production and improve the process of mastication can be recommended.[199] Oral candidiasis can be a complication of dry mouth and it requires specific antifungal medications. Care must be exercised with swallowing pills that are irritating to the esophagus such as potassium supplements, tetracycline, or alendronate because of the sicca syndrome and occasional esophageal dysmotility. Drinking plenty of water and maintaining an upright position are worth stressing.

Vaginal dryness can contribute to the sicca symptom complex. Vaginal moisturizers are helpful but vaginal lubricants are not recommended for routine use because they are not moisturizers. Estrogen creams have specific indications and should be used under the direction of a gynecologist.

Itching from dry skin may complicate the sicca symptom complex, which can have a further negative impact in patients already suffering from pruritus from cholestasis. Dry skin can be treated with heavy moisturizing creams and ointments.

Recommendations:

6. ***Management of dry eyes can include the following:***

a. ***Artificial tears should be used initially (Class I, Level C).***
b. ***Pilocarpine or cevimeline can be used in patients refractory to artificial tears (Class IIa, Level B).***
c. ***Cyclosporine ophthalmic emulsion can be used in those refractory to other agents, preferably under the supervision of an ophthalmologist (Class I, Level A).***

7. ***The following therapies should be used for xerostomia and dysphagia:***

a. ***Saliva substitutes can be tried (Class I, Level C).***
b. ***Pilocarpine or cevimeline can be used if patients remain symptomatic despite saliva substitutes (Class I, Level B).***

8. ***Moisturizers can be given for vaginal dryness (Class I, Level C).***

Sjögren's Syndrome ± CREST/Raynaud's

There are two major autoimmune diseases which have been shown in a cohort study to occur significantly more often in PBC than the age-matched and sex-matched population: Sjögren's syndrome (± CREST [C-calcinosis, R-Raynaud's, E-esophageal dysfunction, S-sclerodac-

tyly and T-telangectasias]) syndrome and Raynaud's disease.[200] Several reports suggest that patients with PBC have a higher chance of autoimmune thyroid disease; however, the latter is common in the general population (4% frequency). It is very questionable whether celiac disease is or is not more common in PBC probably because genetic factors linked to race influence disease presentation.

Preventive Care and Other Considerations

The majority of individuals given a diagnosis of PBC in 2008 have no symptoms referable to their liver disease. Not surprisingly, such individuals may believe that a lack of symptoms is synonymous with lack of significant disease. This lack of symptoms makes it particularly difficult for an individual to recognize the importance of preventive strategies in PBC. The strategies refer not only to the management and consequences of their liver disease but also associated diseases such as sicca syndrome, thyroid disease, and bone disease.

In terms of liver disease progression, the same advice applies to patients with PBC as for any other form of liver disease—to avoid excess alcohol consumption, obesity, and cigarette smoking. These comorbidities both promote disease progression and may put the individual at risk of not being accepted for a liver transplant should the latter become necessary.

All individuals known to have cirrhosis need to be informed about the risk of using nonsteroidal anti-inflammatory drugs, benzodiazepines, and aminoglycoside antibiotics. Additionally they need to be advised to inform all other physicians, particularly surgeons and/or anesthesiologists, that they have cirrhosis because both hypotension and then volume replacement with saline could be deleterious.

General Advice

Hormone Replacement and Pregnancy

Estrogens promote cholestasis, so oral contraceptive pills and estrogen supplements may induce or worsen pruritus. Similarly, during pregnancy itching may become severe even early on in the pregnancy and it may fail to resolve completely after delivery in patients with PBC.

As with all other women with cirrhosis who become pregnant, it is advisable to check for varices in the second trimester when the mother's blood volume increases markedly. Treatment with beta blockers is safe in pregnancy. A short second stage of labor is optimal as the Valsalva maneuver may precipitate variceal hemorrhage.

Screening Family Members

Family members of patients with PBC are at increased risk of developing the disease, particularly among first-degree female relatives including sisters and daughters.[200] Screening is usually done by measuring the serum alkaline phosphatase level and if elevated by assessing for AMA. The value of screening these individuals for PBC has not been established, however.

Long-Term Follow-Up

UDCA should be continued indefinitely. Periodic monitoring of liver tests should be performed at 3-month to 6-month intervals. This helps detect the rare patients who go on to develop AIH.[113-116] Thyroid status should be monitored annually. For patients with known cirrhosis with a Mayo risk score $>$ 4.1, upper endoscopy to assess for varices should be done every 2-3 years. Bone mineral density should be assessed every 2-4 years, depending on baseline density and severity of cholestasis. Similarly, fat-soluble vitamin levels should be monitored annually in patients with jaundice. Cross-sectional imaging usually with ultrasound and alpha-fetoprotein levels to screen for hepatocellular cancer should be done every 6-12 months in patients with cirrhosis and older men with PBC (Table 2).

Complications Related to Cirrhosis

Hepatocellular Carcinoma

As with almost any form of cirrhosis, there is an increased risk of hepatocellular carcinoma.[201-203] Regular screening for hepatocellular carcinoma with cross-sectional imaging with or without alpha fetoprotein at 6-month to 12-month intervals is currently advised for patients with cirrhosis.[204] In patients without liver biopsy, screening should be considered for patients with a low platelet count, a Mayo risk score $>$ 4.1 (http://www.mayoclinic.org/gi-rst/mayomodel1.html), or varices.[127,205]

Portal Hypertension and Varices

There is conflicting evidence for when it is appropriate to screen patients for esophageal varices with PBC. One study reports that a platelet count of $<$200,000/mm^3,[206]

Table 2. Follow-Up of PBC

- Liver tests every 3-6 months
- Thyroid status (TSH) annually
- Bone mineral densitometry every 2-4 years
- Vitamins A, D, K annually if bilirubin $>$ 2.0
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score $>$ 4.1
- Ultrasound and alpha fetoprotein in patients with known or suspected cirrhosis†

*Interval determined by findings on previous EGD.
†Platelets $<$ 140,000/mm^3 or Mayo risk score $\geq$ 4.1.

another 140,000/mm^3,[205] be the cutoff points for likelihood of varices being present. These differences may relate to differences in the rate of noncirrhotic portal hypertension due to nodular regenerative hyperplasia that may have been more prevalent in the first study. Another study suggests that varices are virtually never found unless the Mayo risk score is at least 4.1.[127] Prevention of variceal hemorrhage in PBC is as for any other patient with portal hypertension. The first line of treatment is with oral nonselective beta blockers, although primary prophylaxis with endoscopic banding can be considered as well.

Management of Portal Hypertension

Patients with PBC may develop portal hypertension as a result of biliary cirrhosis, or in the precirrhotic stage of the disease, in association with nodular regenerative hyperplasia.[207,208] The approach to gastroesophageal varices and variceal hemorrhage in cirrhosis in patients with PBC follows the guidelines published by the AASLD,[209] which include a screening upper endoscopy at the time the diagnosis of cirrhosis is suspected, often in the setting of a falling platelet count or rising Mayo risk score. Nonselective beta blockers are indicated in patients with large esophageal varices.[209] Eradication of esophageal varices by endoscopic variceal ligation over several sessions is recommended to prevent an initial bleed in patients with varices at high risk for bleeding (red whale marks or cherry red spots). The guidelines suggest that the decision regarding what intervention to use be considered in the context of local expertise, resources, and patient preference.[209]

Variceal bleeding that does not respond to pharmacological and endoscopic therapy in patients with PBC in the precirrhotic stage of the disease poses a specific challenge, because orthotopic liver transplantation is not desirable in patients with good synthetic liver function. In this context, a distal splenorenal shunt, which does not deprive the liver of its blood supply or a transjugular intrahepatic portocaval shunt are therapeutic alternatives. Distal splenorenal shunts are not associated with accelerated liver failure in patients with PBC who undergo surgery for treatment of variceal bleeding.[74]

Complications Related to Chronic Cholestasis

Osteopenia/Osteoporosis

Patients with fibrotic PBC have significantly greater risk of osteopenia and osteoporosis than do age-matched and sex-matched controls.[77] Baseline and regular screening every 2-3 years using bone mineral density testing is appropriate. As for all perimenopausal and postmenopausal women, daily calcium (1500 mg/daily) and vitamin D supplements (1000 IU/daily) may be advisable if there is no history of renal stones. Vitamin D levels should be measured annually in patients with advanced disease. In patients identified as having osteoporosis, alendronate has been shown in a randomized controlled trial to significantly improve bone density when compared to placebo and etidronate. Etidronate was ineffective compared to placebo, and other bisphosphonates have not been tested in patients with PBC.[210-212] Hormone replacement therapy led to some improvement in bone mineral density but these agents are seldom used because of safety concerns.[213]

Recommendations:

9. ***Patients with PBC should be provided 1000-1500 mg of calcium and 1000 IU of vitamin D daily in the diet and as supplements if needed (Class I, Level C).***
10. ***Alendronate orally, 70 mg weekly, should be considered if patients are osteopenic in the absence of acid reflux or known varices (Class I, Level A).***

Hyperlipidemia

All chronic cholestatic liver diseases may be complicated by hyperlipidemia. For the most part this is of little consequence in PBC, and retrospective studies suggest that there is no increased risk of cardiovascular disease in patients with PBC and hypercholesterolemia.[87,90,214,215] UDCA will lower low-density lipoprotein cholesterol levels and is the initial step. However, when there is also a family history of lipid abnormalities or cardiovascular disease it may still be considered appropriate, depending on the lipid pattern, to treat with cholesterol-lowering drugs. It is unusual for cholesterol-lowering agents to be needed, but statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are safe in patients who may need treatment even if serum liver tests are abnormal,[216] and fibrates have been used safely in some[217] but not others.[218]

Liver Transplantation

In the mid-1980s, PBC was the leading indication for liver transplantation in the United States. Now, a recent study shows that despite an increase in the number of transplants performed in the United States in the past 10 years, the number of patients with PBC requiring transplant has declined by about 20%. In contrast, the rate of transplantation for patients with primary sclerosing cholangitis for which effective therapy has yet to be discovered has not changed over this period.[123] The outcome of liver transplantation for patients with PBC is more favorable than for nearly all other disease categories. Osteopenia may worsen for the first 6 months after transplantation, yet bone mineral density returns to baseline after 12 months and improves thereafter.[85] Alendronate is

a more effective treatment than etidronate,[219] but there are no studies to confirm the long-term efficacy of any treatment. Currently, PBC is the sixth leading indication for liver transplantation in the United States. Some 20%-25% of patients with PBC who undergo transplantation develop recurrent disease over 10 years. Fortunately, recurrent PBC does not often affect long-term patient or graft survival.[220] Long-term immunosuppression with a cyclosporine-based regimen seems to be associated with reduced incidence of recurrent PBC.[221] Risk factors for accelerated recurrent PBC include tacrolimus therapy and advanced donor age. UDCA improves liver biochemistries and may delay histologic progression, but its influence on the natural history of recurrent disease requires further study in the context of randomized controlled trials.[222] Liver transplantation improves fatigue and pruritus, sicca syndrome is unchanged, bone disease worsens initially and then improves, and AMA may persist or reappear but does not signal the recurrence of PBC.

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