

# Management of Primary Biliary Cirrhosis

E. JENNY HEATHCOTE

Primary biliary cirrhosis (PBC) is a presumed autoimmune disease of the liver, which predominantly affects women once over the age of 20 years. Most cases are diagnosed when asymptomatic (60%). The antimitochondrial antibody is present in serum in most, but not in all, patients with PBC. The disease generally progresses slowly but survival is less than an age- and gender-matched general population. The symptomatic patient may have fatigue, generalized pruritus, portal hypertension, osteoporosis, skin xanthomata, fat soluble vitamin deficiencies, and/or recurrent asymptomatic urinary tract infections. Many nonhepatic autoimmune diseases are found in association with PBC and may prompt initial presentation. To date, immunosuppressive therapy has not been shown to prolong survival in PBC. The hydrophilic bile acid, ursodeoxycholic acid (UDCA), has been shown when given in a dose of 13 to 15 mg/kg daily for up to 4 years to delay the time to liver transplantation or death. This therapy also causes a significant improvement of all the biochemical markers of cholestasis but has no beneficial effects on any of the symptoms or associated disorders. Treatment with UDCA does not obviate the need for liver transplantation. Therapies to prevent complications arising from malabsorption, portal hypertension, and/or osteoporosis are required as well. Good control of pruritus can be achieved in most patients. PBC is diagnosed with increasing frequency, but the agent(s) responsible for this slowly progressive destruction of the interlobular bile ducts remains elusive and hence a specific therapy remains unavailable. (HEPATOLOGY 2000;31:1005-1013.)

## PREAMBLE

These guidelines have been written to assist physicians in the recognition, diagnosis, and management of patients with primary biliary cirrhosis (PBC). The data provided have been obtained from peer-reviewed articles published since the hallmark for this disease, namely the antimitochondrial antibody, was recognized in the early 1960s. These guidelines

are designed to aid the practicing physician in diagnosing PBC, establishing the severity of the disease, recognizing the direct complications of PBC and its associated disorders, and finally, to advise on the therapies available that will benefit patients from a symptomatic, preventative, and therapeutic standpoint. As such, what is written should be taken as guidelines and not "standards of care." The strength of each recommendation is categorized based on the quality of evidence in the literature according to the rating system indicated in Table 1.

Where appropriate throughout this report, categories A through E have been attached to the recommendations to indicate the benefit to be expected from following the suggested recommendations (Table 2).

## INTRODUCTION

PBC is a presumed autoimmune disease of the liver, which predominantly affects middle-aged women.<sup>2</sup> PBC is caused by granulomatous destruction of the interlobular bile ducts, which leads to progressive ductopenia. The consequent cholestasis is generally slowly progressive, and fibrosis, cirrhosis, and eventual liver failure occur.

Currently, the diagnosis of PBC most often is made when the patient is still asymptomatic, with abnormal liver biochemistry and/or antimitochondrial antibodies (AMA) noted in blood at the time of a routine check-up or as part of the work-up for an associated disorder.

## DIAGNOSIS OF PBC

### Biochemical Tests

Elevation in serum alkaline phosphatase (ALP) (with confirmation of hepatic origin by checking the gamma glutamyl transpeptidase [ $\gamma$ GT]) is the most common biochemical abnormality in PBC. Although at diagnosis few patients have elevation of their serum bilirubin; when present, it should be the conjugated fraction that is elevated. Elevation of serum bilirubin is a late phenomenon and an excellent predictor of survival.<sup>3</sup> As in any patient with chronic cholestasis, total serum cholesterol may be elevated.

### Radiologic Assessment of the Bile Ducts

Good ultrasound examination of the liver and biliary tree is mandatory in all patients with biochemical evidence of cholestasis. If the biliary system appears normal by ultrasound and the AMA test is positive (see below), no further radiologic delineation of the bile ducts is necessary. If the diagnosis of PBC is uncertain or a sudden rise in the serum bilirubin takes place, cholangiography may be necessary, but this should not be a first-line investigation.<sup>4</sup>

### AMA Testing

The major hallmark of PBC is the presence of AMA in serum.<sup>5,6</sup> The simplest and most economical test is immuno-

Abbreviations: PBC, primary biliary cirrhosis; AMA, antimitochondrial antibodies; ALP, alkaline phosphatase;  $\gamma$ GT,  $\gamma$  glutamyl transpeptidase; IF, immunofluorescence; ANA, antinuclear antibodies; SMA, smooth muscle antibodies; UDCA, ursodeoxycholic acid; HRT, hormone replacement therapy.

From the Division of Gastroenterology, University of Toronto, The Toronto Hospital, Toronto, Ontario, Canada.

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Address reprint requests to: Jenny Heathcote, M.D., Division of Gastroenterology, University of Toronto, University Health Network, The Toronto Western Hospital, WW 4-828, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8. E-mail: jheathcote@msn.com; fax: 416-603-9195.

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TABLE 1. Quality of Evidence on Which Recommendation Is Based

Grade	Definition
I	Evidence from multiple well-designed randomized controlled trials each involving a number of participants to be of sufficient statistical power.
II	Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis.
III	Evidence based on clinical experience, descriptive studies, or reports of expert committees.
IV	Not rated

NOTE. These standardized guidelines of the Practice Guideline Committee of the American Association for The Study of Liver Diseases have been modified from the Categories of the Infectious Diseases Society of America's Quality Standards.<sup>1</sup>

fluorescence (IF) using rat stomach and kidney.<sup>5</sup> In PBC patients, AMA is generally present in high titer. Low-titer AMA (<1:40) may not be specific and may disappear on retesting.<sup>7</sup> In addition, false-positive tests may occur due to misreading of the localization of the fluorescence pattern or failing to dilute the sera prior to testing.<sup>8</sup> Because the specific substrates for AMA have been identified as being the inner mitochondrial enzymes of the 2-oxo-acid dehydrogenase family, more specific and sensitive tests for AMA using the enzyme-liked immunosorbent assay technique and immunoblotting have been developed.<sup>6</sup> The sensitivity and specificity of AMA for PBC are both greater than 95%, although there is a report that if all immunoglobulin fractions are examined for antibodies to the several different members of 2 oxo-acid dehydrogenase family of mitochondrial enzymes, all PBC sera test positive.<sup>9</sup> There have been varying reports on prevalence of AMA in family members of index cases,<sup>10,11</sup> some of which suggest that the figures are higher than in the blood donor population where AMA are rarely found.<sup>12</sup> Antinuclear antibodies (ANA) and/or smooth muscle antibodies (SMA) are found in the serum of one third of patients with otherwise clear-cut PBC.<sup>13</sup>

#### AMA Positive With Normal Liver Biochemistry

There is one small study of the liver pathology in 29 asymptomatic AMA-positive subjects (all  $\geq$ 1:40 by IF) with normal alkaline phosphatase values.<sup>14</sup> All but 2 had abnormal liver histology, and in 12 the findings were diagnostic. A 10-year follow-up of these patients reported that 24 of the surviving 29 subjects remained AMA positive. All 24 developed biochemical evidence of cholestasis and 22 became symptomatic.<sup>15</sup>

TABLE 2. Categories Reflecting the Evidence to Support the Use of a Guideline Recommendation

Category	Definition
A	Survival benefit
B	Improved diagnosis
C	Improvement in quality of life
D	Relevant pathophysiologic parameters improved
E	Impacts cost of health care

NOTE. These standardized guidelines of the Practice Guideline Committee of the American Association for the Study of Liver Diseases have been modified from the categories of the Infectious Diseases Society of America's Quality Standards.<sup>1</sup>

#### AMA-Negative PBC

Several investigators have reported patients who clinically, biochemically, and histologically have all the features of primary biliary cirrhosis but their sera consistently tested negative for AMA both by IF and with the most specific immunoblotting techniques.<sup>16-20</sup> These patients have been described as having "immune cholangitis" or "autoimmune cholangitis." Most likely they are cases of PBC, except their non-organ-specific antibody profile is more in keeping with that of autoimmune hepatitis; *i.e.*, they have high titer ANA and/or SMA. The natural history and associated autoimmune conditions in AMA-positive and AMA-negative PBC appear to be exactly the same. However, because the autoantibody profile of AMA-negative PBC is like that of autoimmune hepatitis, confusion as to the correct diagnosis may arise and careful review of the liver biochemical pattern (ALP and  $\gamma$ GT) and the histology (bile duct injury) is necessary. It is extremely unusual for a truly positive AMA test to be found in a patient with otherwise obvious autoimmune hepatitis.<sup>21</sup> A retrospective chart review of 200 patients diagnosed histologically as having the typical findings of PBC on liver biopsy showed that 12% had no autoantibody markers.<sup>22</sup>

#### Immunoglobulins

The pattern of the immunoglobulin fractions in PBC is characterized by an elevation of IgM in particular.<sup>23</sup> IgA levels are usually normal but PBC has been described in persons with IgA deficiency.<sup>24</sup> However, testing for the pattern of immunoglobulins is probably only necessary in doubtful cases of PBC. In AMA-negative PBC, the IgG fraction is elevated whereas the IgM fraction is less likely to be increased.<sup>18,20</sup>

#### Liver Biopsy

In a patient who has an AMA of  $\geq$ 1:40 and the typical symptoms and biochemical abnormalities, a liver biopsy may not be essential to make the diagnosis of PBC. Nevertheless, the histological features of PBC, particularly in noncirrhotic patients, are very specific. Although different histological stages of the disease (stage 1 through 4) have been well described, it is not unusual to find features typical of several different stages in the one biopsy specimen. Because this disease predominantly affects bile ducts, it is essential that the liver specimen have an adequate number of portal tracts for the pattern of bile duct damage to be accurately assessed.<sup>25</sup> Stage 1 disease is characterized by a portal hepatitis with granulomatous destruction of the bile ducts, although granuloma are often not seen. Stage 2 is characterized by periportal hepatitis and bile duct proliferation. The presence of fibrous septa or bridging necrosis is classified as stage 3 and cirrhosis as stage 4.<sup>26</sup> The presence of fibrosis or cirrhosis does indicate a worse prognosis than if no fibrosis is seen on biopsy.<sup>27</sup>

If the AMA is negative or in low titer (<1:40) or if the patient has a biochemical picture with prominent elevation of transaminase levels, *i.e.* "hepatitic," or has been taking potentially hepatotoxic drugs, a liver biopsy is essential to confirm or refute the diagnosis of PBC. There are many other causes of chronic, intrahepatic cholestasis, mostly due to vanishing intrahepatic bile ducts (some may involve the larger ducts as well, *i.e.*, primary sclerosing cholangitis).<sup>28</sup> In late stage cirrhosis, it may be impossible to make a confident histological diagnosis of PBC.

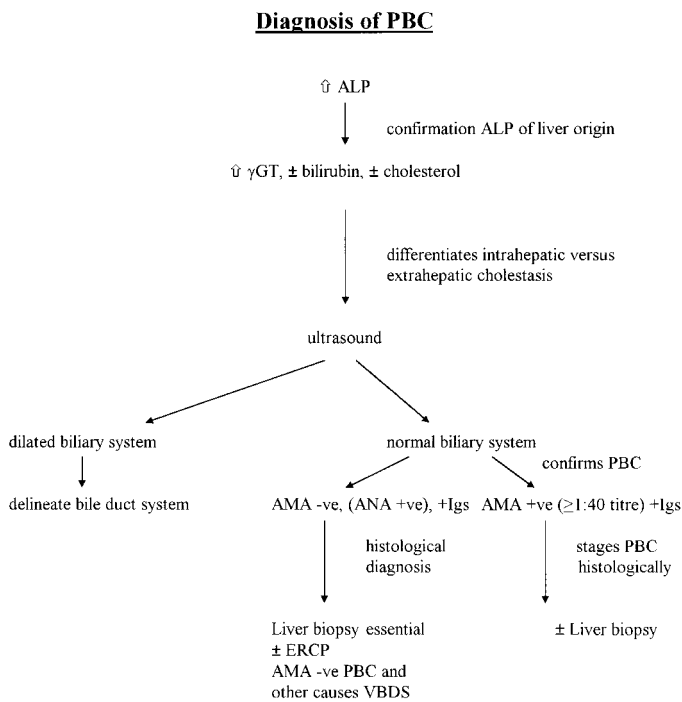


FIG. 1. Diagnosis of PBC. Abbreviations: Igs, immunoglobulins; VBDS, vanishing bile duct syndromes.

**Recommendations Regarding the Diagnosis of PBC (Fig. 1)**

1. In patients with otherwise unexplained elevation in alkaline phosphatase (normal bile ducts on ultrasound), serum testing for AMA is appropriate (III B).
2. The diagnosis of PBC can be made with confidence in a patient with high-titer AMA ( $\geq 1:40$ ) and a cholestatic pattern of liver biochemistry in the absence of an alternative explanation. A liver biopsy may also be considered (III B).
3. Patients who are AMA positive ( $\geq 1:40$ ) with a normal serum alkaline phosphatase, should be followed prospectively with annual reassessment of biochemical testing (III B).
4. In patients with otherwise unexplained elevation in alkaline phosphatase (normal bile ducts on ultrasound) and a negative AMA test, ANA, SMA, and immunoglobulins should be tested and a liver biopsy should be performed (III B).

**MANIFESTATIONS OF PBC (Fig. 2)**

1. *Fatigue* is present in up to 70% of PBC patients.<sup>29,30</sup> It does not correlate with the severity of the liver disease but

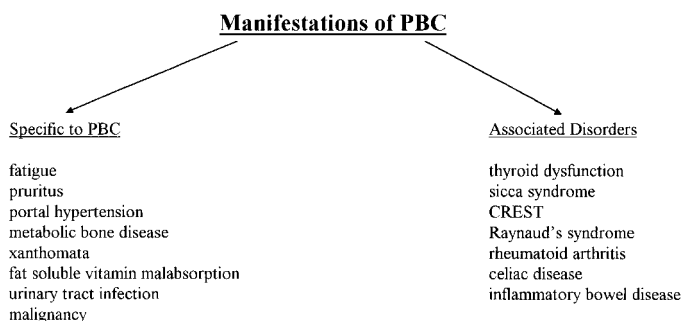


FIG. 2. Manifestations of PBC.

there is an association with sleep disorder and depression. However, which symptom leads to the other remains unknown.

2. *Pruritus*. The pathogenesis of pruritus in cholestasis remains unknown. Objective studies indicate there is a circadian rhythm to pruritus due to cholestasis.<sup>31</sup> The symptom diminishes with time from diagnosis.<sup>32</sup> When present, pruritus may be so severe as to cause sleep deprivation and even severe emotional disturbance sufficient to necessitate liver transplantation. This may be seen in a patient who otherwise has good liver function.

3. *Portal hypertension*. Patients may, on occasion, present *de novo* with a variceal hemorrhage. This may be caused by noncirrhotic portal hypertension<sup>33</sup> or secondary to cirrhosis. Complications of variceal hemorrhage are not predicted by standard prognostic indices.

4. *Metabolic bone disease*. Both decreased osteoblastic activity and increased osteoclastic activity contribute to the development of osteoporosis in PBC patients.<sup>34</sup> Patients may present with osteoporosis and yet be asymptomatic from their liver disease. The relative risk of osteopenia, *i.e.*, osteoporosis greater than expected for gender and age, is 4.4.<sup>35</sup> Because patients with osteoporosis without fractures have a normal ALP, the presence of an increased ALP in patients with osteoporosis should raise a suspicion of PBC. Genetic factors may also play a role in the pathogenesis of osteoporosis in PBC.<sup>35,36</sup> Metabolism of vitamin D is normal in PBC, but malabsorption of both calcium and vitamin D may occur. Pancreatic insufficiency and celiac disease, which are also seen in PBC<sup>37-39</sup> may further aggravate malabsorption.

5. *Xanthomata* are much more common in PBC than with any other chronic cholestatic disease in adults. They predominantly occur around the eyes (called xanthelasma), although they may be found on the palms (often painful), buttocks, and heels. They are not uniquely associated with hypercholesterolemia although hypercholesterolemia is common in PBC. They generally spontaneously disappear with progression of disease.

6. *Fat soluble vitamin malabsorption*. When biliary secretion of bile acids is insufficient, *i.e.*, below the critical micellar volume in the duodenum, malabsorption of both fat and fat soluble vitamins will take place. Serum values for vitamin A and E have been shown to be low in a minority of patients with primary biliary cirrhosis prior to jaundice.<sup>40</sup> Night blindness is infrequently documented. Neurological impairment secondary to vitamin E deficiency is much more common in children than adults with chronic cholestasis, although electromyograph changes have been found in PBC patients with low serum tocopherol levels.<sup>41</sup> Osteomalacia is now very rarely seen in PBC as a liver transplant is performed in most patients before the development of this complication of prolonged deep jaundice.

7. *Urinary tract infections*. Recurrent, but often asymptomatic, urinary tract infections may be found in up to 19% of women with primary biliary cirrhosis.<sup>42</sup>

8. *Malignancy in PBC*. There have been two reports that suggest that the rate of carcinoma of the breast is increased in

women with PBC,<sup>43,44</sup> but this has not been confirmed in two other studies.<sup>45,46</sup> It is likely that the perceived increased prevalence of breast cancer in PBC patients is due to an increase in the rate of detection, because patients are regularly undergoing medical examination. In contrast, two recent studies both indicated that hepatocellular carcinoma complicates late-stage PBC just as it does other causes of cirrhosis.<sup>47,48</sup> One report suggests that this complication is more common in men with PBC. The overall incidence of hepatocellular carcinoma in a sample of 273 PBC patients with stage III/IV disease was found in one study to be 5.9% (4.1% in women but 20% in men with advanced disease).<sup>47</sup>

#### MANIFESTATIONS OF PBC— ASSOCIATED DISORDERS (Fig. 2)

The prevalence of autoimmune disorders found in association with PBC is reported in several large series.<sup>49-51</sup>

1. *Thyroid dysfunction* is a common autoimmune disorder associated with PBC and its presentation often predates the diagnosis of PBC.<sup>52</sup>

2. If *sicca symptoms* are sought by direct questioning, they are present in up to 70% of PBC patients.<sup>53</sup> Symptoms related to the sicca syndrome include xerophthalmia, xerostomia, dental caries, dysphagia, tracheobronchitis, and dyspareunia. If a superimposed motility problem is also present, asymptomatic or symptomatic reflux causing esophagitis and possible stricture formation may develop. This is more common in patients with the CREST syndrome.

3. *CREST* (calcinosis cutis, Raynaud's phenomena, esophageal dysmotility, and telangiectasia) in its complete form is rarely seen in PBC patients.<sup>54</sup>

4. *Raynaud's syndrome* alone is more common and is particularly troublesome for patients living in cold climates.

5. *Rheumatoid factor* is present in the serum in 25% of patients with PBC, but symptomatic arthritis is less common.<sup>55</sup>

6. *Celiac disease*, often asymptomatic, is present in 6% of PBC patients.<sup>40</sup>

7. *Inflammatory bowel disease*, namely ulcerative colitis may be uncommonly seen in association with PBC.<sup>56</sup>

#### SPECIFIC THERAPY FOR PRIMARY BILIARY CIRRHOSIS

All PBC patients with abnormal liver biochemistry should be considered for specific therapy.

##### *Ursodeoxycholic Acid Therapy*

Bile duct destruction leads to the retention of hydrophobic bile acids within the liver cell, and this most likely contributes to the gradual deterioration in liver function observed in patients with primary biliary cirrhosis. Ursodeoxycholic acid (UDCA) increases the rate of transport of intracellular bile acids across the liver cell and into the canaliculus in patients with both primary sclerosing cholangitis and PBC.<sup>57</sup> UDCA treatment reduces intracellular hydrophobic bile acid levels and thereby may have a cytoprotective effect on cell membranes.<sup>58,59</sup> UDCA may also act as an immunomodulatory agent.<sup>60</sup>

There have been many randomized controlled trials of UDCA in PBC and all included both asymptomatic and

symptomatic patients. There have been 4 large trials,<sup>32,61-63</sup> and the raw data from 3 of these trials have been combined as each used the same formulation of UDCA in the same dose, *i.e.*, 13 to 15 mg/kg/d.<sup>64</sup> The analysis of these data collected from 548 patients shows that UDCA therapy leads to a significant increase in survival after up to 4 years of therapy, as judged by time to liver transplantation.

In the fourth large randomized controlled study in PBC patients using a slightly lower dose of UDCA (10 mg/kg/d), the investigators suggest that UDCA is less effective in patients whose bilirubin is greater than 2 mg/dL at baseline.<sup>63</sup> However, the combined analysis of the other 3 large studies does not suggest that this is the case.<sup>64</sup> In fact, the greatest benefit is seen in those with the most severe disease, because predictably, more events were observed in patients with severe rather than with mild disease.

UDCA treatment is associated with a marked improvement in serum biochemical markers of cholestasis, *i.e.*, bilirubin, ALP, and  $\gamma$ GT, including a fall in serum cholesterol levels. Treatment does not seem to benefit the symptom of fatigue and has a variable effect on pruritus,<sup>32</sup> no benefit on osteoporosis,<sup>65</sup> but some benefit on the development of portal hypertension.<sup>66</sup> Side effects from UDCA use are rare, the most common being diarrhea; it is an extremely safe drug. The biliary enrichment with UDCA is the same whether it is taken in divided doses or as a single dose.<sup>67</sup> Compliance is likely better with the latter regime. However, although UDCA slows the progression of PBC in treated patients, its use does not lead to resolution of the disease. Progressive disease continues to require liver transplantation.

Treatment with UDCA reduces the rate of development of esophageal varices, but it does not reduce the rate of bleeding from varices.<sup>68</sup>

Small trials of combination therapy using UDCA with methotrexate, colchicine, or prednisolone, have been reported but have not shown any increased efficacy over UDCA therapy. The sample sizes of these studies were too small to adequately evaluate efficacy.<sup>69-71</sup>

**Recommendations.** Appropriately selected patients with PBC with abnormal liver biochemistry should be advised to take UDCA, 13 to 15 mg/kg daily in either divided doses or as a single daily dose. If cholestyramine is used, 4 hours should elapse between cholestyramine intake and UDCA administration (I, A, D, E).

##### *Immunosuppressive Therapy*

As primary biliary cirrhosis appears to be an autoimmune disease, several immunosuppressive drugs have been tested in randomized controlled trials and none have been shown to be of great benefit. However, only two of the trials were sufficiently large to accurately evaluate an effect on survival. One trial was of azathioprine and the other of cyclosporine.<sup>72,73</sup> Despite sample sizes of 248 and 349, neither trial showed a beneficial effect of therapy on survival. Neither of these drugs is without side effects. Cyclosporine use was associated with a high withdrawal rate because of significant effects on renal function and systemic blood pressure. There has been one small randomized controlled trial of prednisolone in which a beneficial effect on the biochemical markers of PBC was observed, but there was some deterioration in bone mineral density.<sup>74</sup>

Methotrexate, used in pilot studies only, has been said to have beneficial effects on the symptoms and biochemical and



histological features of PBC.<sup>75</sup> However, one randomized controlled trial of methotrexate therapy, suggested that even at low doses (2.5 mg 3 times per week) methotrexate may be toxic over a 6-year period.<sup>76</sup> Hence at the present time, there is insufficient data to support the use of immunosuppressive therapy in PBC.

**Liver Transplantation**

PBC is a common indication for transplant.<sup>77</sup> There is some evidence that PBC may recur in the allograft.<sup>78,79</sup> When it does so, it is certainly a rare event, progresses only very slowly, and is no reason for not recommending liver transplantation.

**Timing of Liver Transplantation.** The most reliable determinants of prognosis in PBC are the height of the serum bilirubin<sup>3</sup> and the Mayo risk score.<sup>80</sup>

The Mayo risk score is calculated as  $R = 0.871 \log_e(\text{bilirubin in mg/dL}) + -2.53 \log_e(\text{albumin in g/dL}) + 0.039 \text{ age in years} + 2.38 \log_e(\text{prothrombin time in seconds}) + 0.859(\text{edema score of 0, 0.5, or 1}).$ <sup>80</sup>

A recent report has reassessed the Mayo risk score taking into consideration other factors found to be important in the timing of transplantation in patients with chronic cholestatic liver disease.<sup>81</sup> Neither the height of the serum bilirubin nor Mayo risk score are invalidated by UDCA therapy.<sup>82</sup> Treatment with UDCA before liver transplantation does not alter the posttransplantation outcome.<sup>83</sup>

**Recommendation.** Liver transplantation in PBC is recommended for liver failure (II A, C, D). Liver transplantation may be recommended in appropriately selected patients for (1) uncontrollable pruritus (IV C); and (2) severe osteoporosis (IV C).

**THE PROGRESSION OF PBC**

The progression of PBC is extremely variable. Studies of asymptomatic patients suggest that their survival is reduced when compared with an age- and gender-matched population.<sup>84,85</sup> The response to UDCA therapy is not uniform. Those patients whose liver biochemistry returns to normal may have a better outcome than those patients where treatment has a less beneficial effect on serum biochemistry.<sup>86</sup>

**HYPERBILIRUBINEMIA IN PBC**

Serum bilirubin level is a useful guide to subsequent outcome and may be used to indicate time for transplantation. However, there are situations in which elevation in the serum bilirubin may not be caused by progression of PBC. They include Gilbert's syndrome, sepsis, pregnancy/hormone replacement therapy (HRT)/oral contraceptive pill, common duct stones, untreated thyroid disease, hemolysis, and toxic liver injury. Hence, a rise in bilirubin that does not appear to be associated with other signs of deterioration in liver function should prompt further investigation.

Once signs of liver failure are present, *i.e.*, ascites, hepatic encephalopathy, and/or a coagulopathy that cannot be corrected by supplemental vitamin K, deterioration in liver function tends to be rapid. It is unusual, but not unknown, for ascites to develop before the onset of jaundice.

**HYPERCHOLESTEROLEMIA IN PBC**

The total serum cholesterol may be elevated in patients with PBC. It tends to decrease with disease progression and is significantly reduced by treatment with UDCA. High chole-

sterol levels may cause unnecessary anxiety, but retrospective studies do not suggest an increase in atherosclerotic heart disease in PBC.<sup>87</sup> Fractionation of the triglyceride fractions show high-density lipoprotein levels to be greater than low-density lipoprotein, and treatment with UDCA further lowers low-density lipoprotein and raises high-density lipoprotein values.<sup>88</sup>

**MANAGEMENT OF COMPLICATIONS OF PBC (Fig. 3)**

**Symptomatic Treatment**

**Pruritus.** There is no evidence that standard topical therapies for the pruritus of PBC are effective. The oral anion exchange resin, cholestyramine, has been the mainstay of therapy for pruritus associated with cholestasis. The original study indicated that this anion-binding resin led to marked improvement of the symptom of pruritus.<sup>89</sup> It may be that this drug is most effective in those patients with an intact gallbladder when taken before and after breakfast,<sup>90</sup> because the greatest amount of bile is likely to be available for binding at this time. Many patients find cholestyramine unpleasant to take and constipating, and they often request other therapy. Because this drug not only binds bile acids but also oral medications, notably UDCA, thyroxin, digoxin, and oral contraceptive hormones, it is advisable that at least 4 hours should lapse between the taking of cholestyramine and any other medication. This drug is effective within a few days of starting treatment. Doses of cholestyramine should start at 4 g daily and be increased, if the effect is not sufficient, to a maximum of 16 g. It needs to be made clear to the patient that the treatment should be taken daily for the best effect.

**Rifampicin** is an enzyme-inducing antibiotic that was fortuitously identified as an agent that improved pruritus in cholestasis. A subsequent crossover trial indicated that the drug caused good control of pruritus in PBC patients at doses

**Management of the Complications of PBC**

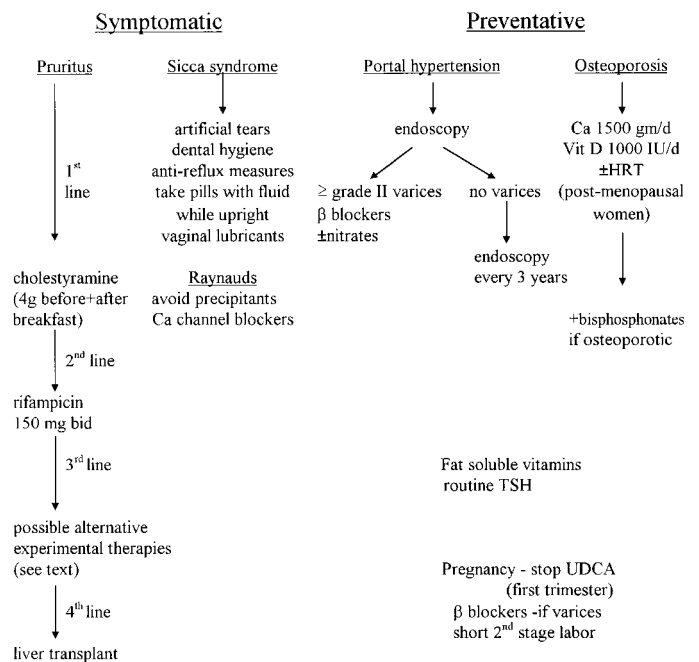


FIG. 3. Management of the complications of PBC.

of 150 mg 2 times a day or 3 times a day.<sup>91</sup> However, it is not effective in all patients; if effective, the benefit will become apparent within 1 month of the start of treatment. Side effects of treatment include unconjugated hyperbilirubinemia, dark staining urine, and on occasion, a hepatitis, thrombocytopenia, and sometimes renal tubular damage. Rifampicin has also been shown to improve the biochemical pattern of patients with primary biliary cirrhosis (when given long term).<sup>92</sup> The mechanism of action of rifampicin as an antipruritic in PBC remains unknown, but it may alter the intracellular bile acid milieu.<sup>93</sup>

There have been studies using *opioid antagonists*, given both intravenously and orally, in the treatment of the pruritus associated with chronic cholestasis. The first study used the oral drug nalmephe, which showed an overall benefit when given for up to 9 months, but treatment was associated with the symptoms of narcotic "withdrawal" in some patients.<sup>94</sup> Currently, this drug is not licensed for the treatment for pruritus from cholestasis. An excellent crossover study showed that intravenous naloxone led to a significant reduction in pruritus, measured using a highly objective system.<sup>31</sup> However, it is inappropriate for long-term use because it has to be given intravenously. Recently, naltrexone has been assessed in a short-term randomized controlled trial and was reported not to give rise to withdrawal symptoms but to cure pruritus in half of the patients treated. Its use also improved the symptoms of fatigue and depression.<sup>95</sup> Longer and larger studies are needed to fully assess the value of naltrexone in controlling the pruritus of PBC in the long term, to assess whether tolerance develops, and to provide a more complete understanding of its side effects.

There have been many other drugs, as well as *ultraviolet light exposure* (without sunblock) and *plasmapheresis*, tried in the treatment of pruritus associated with PBC, but none have been assessed in any formal manner. In some patients, pruritus cannot be controlled, and life becomes intolerable; in these circumstances, liver transplantation may be the only solution.

#### *Recommendations for the treatment of pruritus.*

1. Cholestyramine is the drug of first choice (III C).
2. In patients who fail or are intolerant to the side effects of cholestyramine, rifampicin should be used as a second line therapy (III C).
3. Opioid antagonists can be considered in resistant cases (III C).
4. Liver transplantation is indicated for uncontrollable pruritus (IV).

#### *Sicca Syndrome.*

1. Eyes: Complications of chronic xerophthalmia include corneal ulceration, hence artificial false tears without preservatives need to be prescribed.
2. Mouth: Those patients with chronic xerostomia should be advised to have regular visits to the dentist/dental hygienist checking for caries. Various moisturizers are available to facilitate speech.
3. Esophagus: Food may need to be consumed with liquid to facilitate swallowing. It is wise for patients to make sure all medications are swallowed with an adequate amount of fluid and affected patients should remain in the upright position

after swallowing any pills. Sleeping with the head of the bed elevated and all the other standard antireflux measures are advised.

4. Vagina: Lubricating jelly is recommended to avoid dyspareunia. In post menopausal women, estrogen creams are recommended.

#### *Recommendations for the Management of the Sicca Syndrome.*

1. All patients should be asked directly about dry eyes, dry mouth, dysphagia, and a dry vagina in women, because patients often do not volunteer these symptoms (III C).
2. If symptoms are present, appropriate therapy should be offered.

*Raynaud's Syndrome.* This is particularly troublesome for patients living in colder climates. Patients should be advised to prevent exposure of their hands and feet to the cold and to stop smoking if they are smokers. Calcium channel blockers may relieve symptoms in the extremities but worsen esophageal dysmotility.

#### *Preventative Treatment*

Regular periodic follow-up with focused assessment of the liver disease and associated conditions affords the opportunity to introduce preventative therapy when appropriate.

*Portal Hypertension.* Patients with PBC may develop presinusoidal portal hypertension before becoming cirrhotic. The management of portal hypertension in patients with cirrhosis should be as for all cirrhotic patients.<sup>96</sup> However, the effectiveness of  $\beta$ -blockade in those patients with noncirrhotic presinusoidal portal hypertension has not been proven, and failure of medical management in patients with such early disease may be well managed with shunt surgery.<sup>97</sup>

#### *Recommendations.*

1. PBC patients should be screened for the presence of varices when first diagnosed and every 3 years until found (III B, C).
2. If and when varices are found, standard prophylactic measures should be taken.

*Osteoporosis.* Osteoporosis is often insidious and can only be detected accurately using dual X-ray absorptiometry, which measures bone mineral density. It remains uncertain whether osteoporosis can either be prevented or satisfactorily treated. Prospective clinical trials are in progress. One retrospective study indicated that postmenopausal women with PBC who had taken HRT had less osteoporosis than those who had not taken HRT.<sup>98</sup> The new natural estrogens, which can be administered transdermally, may be less cholestatic than oral estrogens and may be more appropriate in postmenopausal women with chronic cholestasis.

In randomized controlled trials, neither UDCA nor calcitonin have been shown to benefit the osteoporosis associated with PBC.<sup>65,99</sup> Therapy with biphosphonate has been shown to prevent steroid-induced osteoporosis in PBC.<sup>100</sup> A dietary intake of 1,500 mg/d of calcium and 1,000 IU/d of vitamin D may be of some benefit.<sup>101</sup> One small study using sodium fluoride suggested some benefit in preventing osteoporosis in PBC.<sup>102</sup> Severe osteoporosis is an indication for liver transplantation even in the absence of liver failure. Although the osteoporosis may increase during the first 6 months posttransplantation, it improves quite markedly thereafter.<sup>103</sup>

**Recommendations for the Management of Osteoporosis.**

1. Bone mineral density should be assessed with dual X-ray absorptiometry when the diagnosis of PBC is first made and every 2 years thereafter.

2. Education regarding the importance of lifestyle changes (e.g., regular exercise, smoking cessation) and vitamin D and calcium supplementation should be given (III C).

3. HRT, best via the transdermal route, is recommended where appropriate (III C).

4. If osteoporosis is evident, therapy with a biphosphonate is advised (III D).

**Fat Soluble Vitamin Deficiency.** Hyperbilirubinemia may be complicated by fat soluble vitamin deficiency and calcium malabsorption. In the nonjaundiced patient, little is known about fat soluble vitamin status or the effectiveness of oral supplementation. Parenteral vitamin K (10 mg) is available and can easily be given by the subcutaneous route monthly to counteract a coagulopathy secondary to vitamin K deficiency.

**Recommendation.** In patients with hyperbilirubinemia, fat soluble vitamin replacement is likely best given using the water soluble form of the fat soluble vitamins (III C).

**Thyroid Disease.** Thyroid disease affects 15% to 25% of PBC patients. It often, but not always, antedates the clinical presentation of PBC by many years.

**Recommendation.** Serum thyroid stimulating hormone should be checked at diagnosis of PBC and periodically thereafter (III C).

**Pregnancy.** Few reports on the outcome of pregnancy in women with underlying PBC have been made. In most cases, pregnancy has caused pruritus either to begin or to become worse, presumably because of the additional cholestatic effect of higher estrogen levels. Whereas reports suggest increased fetal loss in women with cholestasis of pregnancy,<sup>104,105</sup> there are no good data on the outcome of pregnancy in women with PBC.

**Recommendations.**

1. It is currently recommended that any specific therapy (e.g., UDCA) be withheld in women with PBC contemplating pregnancy because its safety during the first trimester has not been proven. UDCA therapy during the last trimester of pregnancy appears to be safe and may be beneficial in mothers with cholestasis (III C, D).

2. Patients who are pregnant should undergo an esophago-gastroduodenoscopy to check for varices and given nonselective  $\beta$ -blocker therapy if varices are found. The obstetrician should be advised to minimize the duration of the second stage of labor (III C).

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**APPENDIX**


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These guidelines were developed under the auspices of, and approved by, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases. They are intended to suggest preferable approaches to the clinical management of liver diseases. They are flexible and are not intended as the only acceptable approach to treatment. As the appropriate level of skill or course of treatment will vary in light of the relevant facts and circumstances surrounding each individual case, these guidelines are not intended to

define the applicable standard of medical care and may be updated periodically as new information becomes available.

**Practice Guidelines Committee Members:** Thomas D. Boyer, M.D. (Council Liaison), Henry C. Bodenheimer, M.D. (Chair), David E. Bernstein, M.D., Melissa Palmer, M.D., Jan M. Novak, M.D., James R. Spivey, M.D., Gary L. Davis, M.D., Stuart C. Gordon, M.D., Donald M. Jensen, M.D., F. Blaine Hollinger, M.D., Jacob Korula, M.D., Eve A. Roberts, M.D., and Thomas Shaw-Stiffel, M.D.

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