CLASSIC DISEASES REVISITED

Primary biliary cirrhosis: new perspectives in diagnosis and treatment

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Abstract

Primary biliary cirrhosis (PBC) is a chronic autoimmune disease characterised by cholestatic liver function tests, antimitochondrial antibodies, and abnormal liver histology. Early descriptions of a rare rapidly progressive disease no longer reflect the more indolent progress often seen today. Many patients have significant long term morbidity through symptoms such as fatigue and itch with a minority progressing to liver failure and need for transplantation. The current data on the diagnosis, clinical progression, and treatment of PBC are reviewed.

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Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with a probable autoimmune aetiology. Increasing awareness of PBC among doctors, and the availability and more widespread use of diagnostic tests such as autoantibody screens, has led to an increasing rate of diagnosis. PBC has traditionally been regarded as a severe but rare disorder with a high probability of progression to cirrhosis with the complications of portal hypertension and, ultimately, liver failure. Wider diagnosis has, however, led to an increased recognition of milder forms of the disease where the risk of death from liver related complications is markedly lower. The impact of PBC related symptoms on quality of life, however, remains significant in these patients. Changes in diagnosis, disease severity spectrum and, therefore, goals for treatment have thus forced us to reassess our approach to disease management.

Here we present a review of recent changes in our understanding of the clinical features of and management options in PBC, with particular emphasis on their impact for patients and the doctors caring for them.

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Diagnosis

Early reports and case series of patients with PBC described an almost universally severe condition, usually with jaundice present at the time of diagnosis, and a survival of less than six years after diagnosis.[1–3] In the absence of the serological and radiological tools now available, the diagnosis in these patients was based on characteristic findings on liver biopsy obtained at laparotomy performed to exclude other obstructive causes for cholestasis. The discovery of antimitochondrial antibodies (AMA) in the 1960s,[4] and their subsequent inclusion in "routine" autoantibody profiles, has led to the diagnosis of PBC being made more frequently and, usually at a much earlier stage in the disease process. Jaundice at the time of diagnosis is now the exception rather than the norm.[5–8]

PBC is classically diagnosed on the basis of the triad of AMA, abnormal liver function tests (LFTs) that are typically cholestatic (with raised alkaline phosphatase levels being the most frequently seen abnormality), and characteristic histological changes[9] in the absence of extrahepatic biliary obstruction.[10] Liver biopsy, although desirable, may not be possible in some patients because of infirmity or clotting abnormalities. The very strong association between the presence of AMA and PBC means, however, that in the presence of cholestatic LFTs and AMA, and the absence of other aetiological factors these patients can be regarded as having "probable" PBC. We currently exclude obstruction with transabdominal ultrasound examination and use endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography only when the distinction between PBC and extrahepatic obstruction is in doubt (for example where there is a dilated common bile duct or the biopsy suggests coexisting obstruction).

AMA are both the most specific and the most sensitive marker of disease presence and are found in over 95% of patients with PBC.[11–14] Nine staining patterns for AMA on immunofluorescence have been described, of which the M2 distribution is the best associated with PBC. Other immunofluorescence staining patterns are also seen (rarely) in other non-autoimmune diseases.[15] AMA with an M2 distribution have been reported in patients with autoimmune hepatitis[16] emphasising the importance of obtaining histological confirmation of the diagnosis if possible.

The association between the presence of AMA, particularly in an M2 pattern, and the histological features of PBC appears to be stronger than many of the associations to autoantibodies reported in other autoimmune diseases. Mitchison *et al* reported a series of 29 patients with serum AMA but normal LFTs who underwent liver biopsy.[17] Liver histology was diagnostic of PBC in 12 patients, suggestive of PBC in a further 12, and normal in just two. Furthermore, follow up of these patients after 10 years showed that 24 had developed

persistently abnormal serum LFTs.[18] The clear implication of these studies is that when AMA is persistently present patients should, even in the absence of clinical features suggestive of the disease or cholestatic LFTs, be considered to have an early ("pre-disease") form of PBC and should undergo regular monitoring to detect the development of overt "classical" PBC.

AMA are directed against highly conserved antigens present on the inner mitochondrial membrane. These antigens have been identified as members of the 2-oxoacid dehydrogenase family of multienzyme complexes (in particular the pyruvate dehydrogenase complex, PDC), all of which play fundamental parts in cell metabolism.[19 20] Intriguingly, the PDC is remarkably conserved throughout evolution, being found in a highly homologous form in all eukaryotic and prokaryotic organisms from rickettsia to man. The pathway leading to breakdown of immune tolerance to such a highly conserved self antigen, the mechanism by which autoreactive T cell responses to PDC and/or AMA result in the characteristic liver damage seen in PBC, and the reason why inflammatory damage in PBC is largely limited to the liver when every cell in the body contains the PDC remain, however, largely unclear.

A small minority of patients have all the histological, biochemical, and clinical signs of PBC but are persistently AMA negative. The term "autoimmune cholangitis" has recently been coined to describe these patients (who are typically antinuclear antibody or antismooth muscle antibody positive[12]), and has largely replaced the term "AMA negative PBC".[11 12 21 22] Autoimmune cholangitis appears to run a similar clinical course to "classical" PBC.

The histological changes seen in the liver in PBC are well defined and are traditionally graded into four stages of severity as defined by Scheuer.[9] These changes are summarised in table 1. The biliary epithelial cells lining the small intrahepatic bile ducts are the primary target for immunological damage, and thus the majority of early changes are seen in the portal and periportal regions. As only patients in stage IV have a "true" histological cirrhosis, the term primary biliary cirrhosis may be considered a misnomer. The recognition of this, combined with the stigma felt by many patients at being diagnosed with "cirrhosis" has led to recent calls for the term PBC to be replaced. There is, at present, no consensus with regard to suitable alternative terms.

Biochemical testing of patients with PBC typically reveals a cholestatic pattern of LFTs together with raised immunoglobulin IgM concentrations.[6 7] Very early disease may be associated with normal LFTs,[17] and LFTs may also occasionally normalise over time, particularly when patients are treated with ursodeoxycholic acid (UDCA; see below).[23] Individuals with PBC and a more hepatitic picture of LFTs are well described. In some cases these patients may have a crossover syndrome between PBC and autoimmune hepatitis.[16] This possibility should be particularly born in mind when patients also have raised immunoglobulin IgG concentrations and/or antinuclear or smooth muscle antibodies. Such patients may show an excellent response to combination treatment with UDCA and corticosteroids.[16] The degree of interface hepatitis seen on liver biopsy in such patients is, in our experience, predictive of the response to corticosteroid therapy.

Epidemiology

Ninety per cent of patients with PBC are female and the majority are diagnosed after the age of 40.[7] Only one case of paediatric PBC has been reported. Although this girl fulfilled the diagnostic triad for PBC as above, she also had atypical liver immunohistochemical staining patterns and autoantibodies.[24] There remains debate as to whether this was truly PBC.

The incidence and prevalence of PBC appears to be significantly higher in the family members of PBC patients than in the general population; the sibling relative risk (λ_s) for PBC has recently been calculated as 10.5 in a population based study.[25] The familial risk of disease development is not, we feel, high enough to warrant screening of relatives. It does, however, provide important clues regarding the aetiology of the disease suggesting there to be a genetic component to disease.[26]

Wide variations in the population prevalence and incidence of PBC have been reported,[27] although some of the lower estimates may have resulted from incomplete methods of case finding. Two recent studies from the UK have estimated the incidence of PBC at between 204 and 251 per million in the general population and at 954 per million in the group most at risk of disease (women over the age of 40).[28 29] Furthermore, the incidence of PBC appears to be rising.[27 30] Such apparent increases may result

Table 1 Histological staging of PBC on liver biopsy (after Scheuer[9])

Stage	*Key histological features*
I: The florid duct lesion	Expansion of some, but often not all, portal tracts around septal and interlobular bile ducts by aggregates of lymhocytes and plasma cells. Formation of often poorly defined granulomas within or close to affected tracts Irregularities or rupture of biliary epithelium, often with relative preservation of remaining portal architecture Histological evidence of cholestasis usually absent
II: Ductular proliferation	Changes in all portal tracts. Expansion of portal tracts by immature connective tissue, mononuclear and neutrophil aggregates and, to a lesser extent than in stage I, by lymphocyte aggregates Bile ducts scanty with proliferation of biliary ductules. Occasional biliary plugging Mild piecemeal necrosis at limiting plate
III: Septal stage	Inflammation less severe, although the sites of bile ducts may be marked by lymphocyte collections Formation of dense fibrous tissue extending from portal tracts, but the absence of regeneration nodules Cholestasis frequent
IV: Cirrhosis	Formation of regenrative nodules and a "true" cirrhosis Gross reduction in number of bile ducts

to a significant degree from improved diagnosis and awareness of the disease and the increased use of autoantibody screens in primary care. It is impossible, however, to exclude a genuine rise in the frequency of disease.

Geographical clusters of disease have been reported. The most prominent of these was that found by Triger in Sheffield where 75% of all cases of PBC obtained their drinking water from a single reservoir which supplied only 20% of the town's population.[31] No causative environmental agents were, however, identified in the water supply. Observations such as this, together with the presence of the PDC with significant homology to that seen in humans in all bacteria, has led to the suggestion that exposure to bacterial PDC might, through the process of molecular mimicry, contribute to the breakdown of immune tolerance to self PDC and the induction of AMA.[32] Given the rarity of AMA and PBC in the population, and the universal exposure to bacterial PDC experienced by the population, additional factors are likely to be required for AMA induction and the development of PBC. One additional factor is likely to be the apparent genetic susceptibility to the disease. Other postulated suggestions have included a putative viral trigger[33 34] and mycobacteria.[35] A recently described mouse model of PBC (experimental autoimmune cholangitis) may provide us with further important insights into the immunopathogenesis of the disease.[36 37]

Symptoms and associated conditions

Early reports described PBC as a severe progressive disorder, presenting with itch, with patients often developing the complications of jaundice, liver failure, and premature death.[1] However, earlier and more widespread diagnosis, possibly together with the introduction of prognosis modifying drugs, has meant that many, if not most, patients present with a milder, more indolent form of disease. Increasingly, case series comprise patients with early stage disease, a significant minority of whom are asymptomatic at diagnosis.[3 6–8 38 39]

As the symptoms of liver failure become rarer other symptoms are predominating, the two most frequently seen being persistent fatigue and itch. Persistent fatigue is the commonest symptom in PBC occurring in up to 80% of patients. Furthermore, this troubling symptom interferes with normal daily activity in the majority of these patients.[8] This symptom occurs independently of other problems (for example, anaemia or hypothyroidism)[40 41] and is not related to sleep disturbance.[42] Fatigue severity does not correlate with other clinical, biochemical, and histological markers of PBC severity.[40 41 43] Although fatigue levels correlate weakly with depression inventory scales, the majority of patients with PBC and fatigue are not clinically depressed.[41] This apparent association may result from items within depression inventories attributing symptoms of chronic liver disease as markers of depression (for example, weight loss, appearance change). The mechanism responsible for fatigue in PBC is poorly understood.[44] Studies using cholestatic rat models have implicated a central neurochemical process, possibly through hippocampal control of endogenous corticosteroids.[45 46] Such work has not been repeated in humans.

Itch is the second commonest symptom in PBC occurring in 50%–60% of patients.[8] Itch is characteristically worse on the palms and soles and is not associated with cutaneous changes (apart from those due to repeated scratching such as lichenification or localised hyperpigmentation), making it distinguishable from other dermatological conditions. Pruritus was classically thought to result from the retention of irritant bile salts which accumulated in the skin. However, itch severity shows only a weak correlation with the degree of cholestasis. Animal models of cholestasis have suggested that pruritus actually results from the accumulation of endogenous opioid agonists and up-regulation of central opioid receptors.[47] This has led to trials of opiate antagonists for symptomatic therapy (see below).[48 49]

PBC is associated with the cutaneous changes of generalised hyperpigmentation and facial xanthelasmata. The latter changes result from raised total cholesterol concentrations.[3] There does not, however, appear to be an increased incidence of atherosclerotic disease in patients with PBC, presumably as much of the cholesterol rise is due to increases in the high density lipoprotein fraction.[50]

PBC is frequently associated with other autoimmune conditions. The most common of these are Sjögren's syndrome (found in 31% of patients) and thyroid disease (7%),[51] although there are case reports of almost every other autoimmune disease occurring in patients with PBC. The incidence of coeliac disease is increased in PBC.[29] Steatorrhoea is rare in the absence of coeliac disease.[7]

Osteoporosis is commoner in women with PBC than age and sex matched controls.[52] The presumed mechanism for this is low grade fat malabsorbtion reducing vitamin D concentrations and hence inhibiting calcium uptake. Supplementation with parenteral vitamin D does not, however, prevent bone loss.[53] The true prevalence of osteopenia (bone mineral density more than two standard deviations below age and sex matched norms, without fragility fractures) is unknown. Unpublished data from our own unit suggest that ostoepenia in best assessed by a single screening densitometry measurement at diagnosis followed by a repeat scan either after five years or when liver transplantation is considered. Audit of our patients suggests that this regimen will identify all clinically relevant cases of osteopenia at a much lower cost than annual screening. Coeliac disease should be excluded in all patients with severe osteoporosis.[29]

Concerns have been raised regarding possible associations between PBC and malignant disease, particularly breast and hepatocellular carcinoma. Early reports of an increased risk of breast cancer[54 55] have not been confirmed in later studies, particularly when the effects of increased surveillance are accounted for.[56 57]

Hepatocellular carcinoma is markedly increased in PBC (relative risk = 26.5).[56] However, this risk is very highly concentrated in the relatively small group of male patients with stage IV (that is cirrhotic) disease.[58] As hepatocellular carcinoma is now the second commonest cause of death in male PBC patients,[58] we advocate routine monitoring with ultrasound and serum α-fetoprotein levels in men with known cirrhosis who are young enough to considered for transplantation.

Prognosis

The prognosis for patients with PBC is heterogeneous. Prognostic models have been studied in some detail with the aim of counselling patients and allowing for optimal timing of liver transplantation. Serum bilirubin was the first variable shown to be related to prognosis.[59] It is, however, only raised in a minority of patients and then only in "late stage" disease, with the result that it is of limited usefulness in planning treatment. Several groups have subsequently developed complex prognostic indices producing scores based on clinical variables which can then be used to predict survival over a variety of periods.[60–64] Three of these models are summarised in table 2. The European model requires recent histology which may not be available in the presence of a coagulopathy and hence the Mayo risk score is perhaps the most widely used of these. The Mayo score has been modified to assess short term (that is less than two year) survival[65] and has been validated in several centres.[66–68] Although highly useful in advanced disease, the Mayo score remains relatively insensitive to early disease advancement before the development of severe biochemical abnormalities. Furthermore, the Mayo score is strongly influenced by bilirubin concentrations and was devised before the widespread introduction of treatment with UDCA (which reduces bilirubin concentrations[69–73]). Concerns have been raised as to whether the Mayo score remains valid after UDCA treatment. Two recent studies have addressed this question and reported no significant variation between actual survival and that predicted by the Mayo score in patients treated with UDCA.[74 75]

The prognosis for patients with early and asymptomatic disease is uncertain with most reports being limited to a single centre and therefore subject to Berkson's bias. The prognosis of asymptomatic disease appears to be better than symptomatic.[76–78] However, asymptomatic patients with PBC still have higher death rates than the age and sex adjusted norm[79] and, furthermore, between 40% and 100% of these patients will subsequently develop symptoms of PBC.[18 79 80] Since increasing numbers of patients are being diagnosed at an asymptomatic stage more information is required on the prognosis in early disease, both to counsel the patient and to weigh the risks and benefits of treatment. AMA subtype,[81] tumour necrosis factor promoter polymorphisms,[82] and tests of hepatic metabolic reserve[83–87] have all been shown to predict the course of disease at an early stage. However, none of these are readily available in the majority of clinical centres.

Treatment

There are two aims of medical treatment in PBC. The first is to slow progression of the disease to cirrhosis with its attendant complications thereby increasing patient survival (or at least prolonging the time to transplantation). The second is to treat the symptoms of the disease thereby, hopefully, improving quality of life. Liver transplantation in PBC is highly effective in both prolonging life and in eliminating symptoms.

(A) TREATMENTS AIMED AT SLOWING DISEASE PROGRESSION

Many drugs have used in an attempt to improve prognosis in PBC. These can be broadly divided into two groups of agent, namely exogenous hydrophilic bile acids and immunosupressants. The best studied and most successful of these has been UDCA.

UDCA is a strongly hydrophilic bile acid which is absorbed in the terminal ileum as part of the physiological enterohepatic recirculation. Prolonged treatment results in UDCA replacing a significant proportion (42%) of bil-

Table 2 Prognostic indices in PBC

Model	*Variables included*	*Formula for calculation of index*	*Method of application of index*
European[60]	Bilirubin (μmol/l) Age (years) Albumin (g/l) Prothrombin time (sec) Central cholestasis* Cirrhosis† Azathioprine‡	R = (2.51 × Log_e serum bilirubin) + (0.00069 × exp (age-20)/10) − (0.05 × albumin) + (0.88 × cirrhosis) + (0.68 × central cholestasis) + (0.52 × azathiopirine) + 3.09	Cross reference to graph
Mayo[62]	Bilirubin (mg/dl) Age (years) Albumin (g/dl) Prorthrombin time (sec) Oedema§	R = (0.871 × log_e serum bilirubin) − (2.53 × log_e albumin) + (0.039 × age) + (0.859 × oedema) [e]	Probability of survival of time t = $S^{exp\ (R—4..07)}$ where S = 0.970 at 1 year 0.941 at 2 years 0.774 at 5 years
Japanese[63]	Age (years) Bilirubin (mg/dl) Albumin (g/dl) Cholesterol (mg/dl)	PI = (0.0409 × age) + (0.7801 × log_e serum bilirubin) − (0.8016 × log_e albumin) + (0.3217 × log total serum cholesterol)	Cross reference to graph

*0 if central cholestasis absent on histology, 1 if present.
†0 if non-cirrhotic on histology, 1 if cirrhotic.
‡0 if no azathioprine treatment, 1 if treated.
§0 if no oedema, 0.5 if oedema repsonsive to diuretics, 1 if non-resposive oedema.
PI=prognostic index.

iary bile acids.[88] The exact mechanism for the action of UDCA is unknown but it is thought to act both by replacing more hepatotoxic hydrophobic bile acids in the bile acid pool and as a choloretic agent stimulating increased biliary flow and reducing stagnation.[89 90] In addition, UDCA has been reported to modify biliary epithelial HLA expression[91] and may therefore have a local immunosuppressant action.

There have been four large double blind randomised controlled trials of UDCA treatment in PBC.[69 71 72 92] These trials used UDCA at doses of 10–15 mg/kg and monitored patients over two to four years. The results of three of these have been subjected to a combined analysis.[89] Although LFTs (particularly bilirubin) improved in all trials, the overall effect on liver transplant free survival was small and no significant differences were found. A small improvement in survival was reported in the combined analysis[89] with 25 of 273 patients dying in the treatment arm compared with 34 out of 275 in the control arm (with 22 and 32 needing liver transplants respectively). However, this combined analysis did not use preset criteria for selecting studies and may therefore be subject to considerable selection bias. Bateson and Gedling recently described 10 years of clinical experience of prescribing UDCA and reported an improved survival compared to historical controls.[93]

There has been debate as to whether the biochemical improvement predicts a true improvement in survival (see above). This controversy has recently been highlighted by the publication of the preliminary results of a thorough meta-analysis which failed to find any survival benefit for UDCA.[94]

UDCA has a small beneficial effect on pruritus (with 39% of patients reporting a improvement), but little effect on fatigue.[95] A small number of patients suffer a paradoxical increase in pruritus with UDCA (up to 10% of patients in one study[95]) which may necessitate stopping treatment. UDCA does not modify the course of associated autoimmune diseases.[51]

In view of the above data it remains controversial as to whether UDCA should be prescribed to all or just a subgroup of patients. Our current practice is to use UDCA in all patients with troubling pruritus and those with a higher probability of developing complications of disease (that is patients who are younger at diagnosis, male, have a raised bilirubin or have a liver biopsy specimen showing active inflammation or development of fibrosis).

Immunosupressant treatments used in PBC have included penicillamine,[96 97] azathioprine,[60] methotrexate,[98 99] cyclosporin,[100] and colchicine.[101–103] Although methotrexate is still used in some American centres, none of these drugs remain in regular clinical usage in the UK because limited effectiveness and/or the risk of side effects. Prednisolone has been shown to be effective in improving the biochemical markers of PBC,[104] its use has, however, been limited by concerns regarding its detrimental effects on osteoporosis. We currently use steroids only in patients whom we feel may have several features to suggest a hepatitis crossover picture (that is unusually high transaminase level, high IgG levels, high titre of antinuclear antibodies, and/or severe interface hepatitis on liver biopsy) or those with a poor medium term prognosis in whom transplantation is not an option or could usefully be delayed (for example for personal reasons). Our standard regimen is to start patients on 30 mg of prednisolone daily for two to four weeks to assess respones and then tail the dose down to between 5 and 10 mg daily maintainance provided side effects remain acceptable.

(B) TREATMENTS AIMED AT REDUCING THE SYMPTOMS OF PBC

Pruritus may be treated with a number of agents. Of these the bile acid sequestrants are the most widely used. Most units now use cholestyramine as a first line agent, although the development of (usually gastrointestinal) side effects often limits treatment. These side effects can be minimised by starting at very low dosages (for example, half a sachet once daily) and gradually titrating upwards to a level where itch is controlled at an acceptable level of palatability. Colestipol may be tried in patients who cannot tolerate cholestyramine. UDCA improves itch in up to 40% of patient.[95]

A number of third line options exist for patients for whom the above treatments are either unsuitable or ineffective. Rifampicin relieves itch in up to 89% of patients.[105 106] The actions of rifampicin do not appear to related to its liver enzyme inducing capacity as other enzyme inducers (with the possible exception of phenobarbitone) are ineffective in controlling pruritus in PBC. Rifampicin can, however, induce hepatitis in its own right and its use must therefore be closely monitored with serial liver function testing. Our current practice is to start rifampicin at a dose of 150 mg daily and increase the dose in increments of 150 mg to a maximum of 450 mg daily or until itch is relieved. We monitor LFTs monthly, although drug induced hepatitis has been rare in our experience. We have safely continued the drug long term where symptoms have necessitated this.

Phenobarbitone is less effective than rifampicin at relieving itching and its neurological side effects usually preclude its use for this indication.[106] Antihistamines are not recommended for itch because of concerns regarding accumulation in cholestasis and fatigue induction. A case series of five patients reported itch relief with grapefruit juice (at a dose of 400 ml/day),[107] although this has never been subject to a controlled trial. Early reports of ondansetron being effective for this symptom have not been supported by clinical trials.[108]

Opiate antagonists may be tried as a last line to prevent itch before consideration for liver transplantation.[48 49] Our current protocol for using opiate antagonists is to offer an in patient overnight trial of intravenous naloxone at a dose of 0.2 μg/kg/min (both to assess responsiveness and side effects) and, if appropriate, to

Questions (correct answers at end of article)

1. Which of the following are thought to be responsible for the itch associated with PBC?

a. Raised serum bilirubin
b. Bile salts retained in the skin
c. Endogenous opioid agonists
d. Raised cholesterol
e. Autoantibodies

2. The AMA seen in PBC react against which autoantigen:

a. The outer mitochondrial membrane
b. The pyruvate dehydrogenase complex
c. Mitochondrial DNA
d. Bilirubin
e. Mitochondrial cytochrome systems

3. The commonest symptom in PBC is:

a. Jaundice
b. Fatigue
c. Itch
d. Right upper quadrant pain
e. Bone pain

4. Which of the following medications have not been used in trials of prognostic benefit in PBC?

a. Cyclosporin A
b. Ursodeoxycholic acid
c. Colchicine
d. Methotrexate
e. Rifampicin

5. Which of following are not seen at an increased frequency in patients with PBC?

a. Ischaemic heart disease
b. Hepatocellular carcinoma
c. Osteoporosis
d. Rheumatoid arthritis
e. Hypercholesterolemia

follow this with the long acting oral antagonist naltrexone. This is a non-licensed indication and should be used with caution as there are no long term data regarding its use in PBC.

Although fatigue is the most troubling symptom for the majority of patients,[8] there is little one can do to treat it. There have been no reported randomised placebo controlled trials specifically aimed at improving this symptom. This may partly be due to perceived difficulties in quantifying this symptom, although validated measures of its severity do exist.[40] One should always exclude associated conditions such as anaemia, hypothyroidism, or renal impairment. Antidepressants may be tried in view of the association between fatigue and subclinical depression, although this treatment is not supported by trial evidence. Even in patients who attribute their fatigue to poor sleep, hypnotics have no place in the treatment of fatigue.[42] Anecdotal reports have suggested benefit from oral antioxidant medication.[109]

Osteoporosis should be treated as in patients without PBC. We no longer routinely treat all patients with intramuscular vitamin D as its effect is limited in patients without clinical malabsorbtion.[53] Established osteoporosis should be treated with bisphosphonates. Many doctors have concerns about treating postmenopausal women with oestrogen containing hormone replacement therapy in view of possible cholestatic side effects. A recent case series, however, showed these drugs to be safe and effective at improving bone mineral density.[110] It is still probably prudent to monitor LFTs more closely for the first few months of hormonal treatment.

Although in the past it was conventional to give all patients with PBC paraenteral fat soluble vitamins (notably A, D, and K), this is no longer our practice as vitamin deficiency is rare in the absence of frank fat malabsorbtion. As stated above there is little evidence to support regular prophylactic use of vitamin D and calcium supplements to prevent osteoporosis.

(C) LIVER TRANSPLANTATION

Transplantation remains the only effective treatment for advanced disease with complications of liver failure and may also be needed for intractable symptoms.[111] Many patients are precluded from transplantation by age or infirmity at the time of deterioration. PBC currently accounts for approximately 20% of liver transplants performed in the UK (1998 UK Transplant Special Support Authority data, personal communication) and has the best outcome of any indication for this operation. Current survival rates are approximately 80%–90% at one year and 70% at five years. Survival after transplantation is significantly worse for patients who have jaundice, renal impairment, or ascites[112] before surgery. There is therefore a careful balancing act to be undertaken in all patients with advancing disease; delaying operation as long as possible to prevent unnecessary transplants, but operating before transplant associated mortality is significantly increased by any of the above factors. In practice this is best done by regular calculation of prognostic indices such the Mayo score. Patients may be considered for transplantation when their predicted survival falls below that expected after operation. In practice many gastroenterolgists refer any patient under the age of 65 years for monitoring at a transplant centre when their bilirubin exceeds 50 μmol/l without a reversible cause.

Transplantation does not cure patients. Recurrence of AMA is almost universal and some patients will develop histological changes of recurrent PBC.[111] It is unknown whether recurrence can be prevented by differing immunosupression regimens or by deliberate HLA mismatching between donor and recipient. Quality of life is, however, markedly improved by transplantation with a high degree

of patient satisfaction.[113] The efficacy of transplantation in prolonging life improving quality of life means that all patients with advanced disease who do not have physical contraindications should be at least referred for transplant assessment.

Summary

PBC has moved from being a rare but rapidly fatal disease to being an uncommon chronic debilitating, but not necessarily fatal, condition. Increased diagnostic awareness and/or increases in true incidence have led to an increased prevalence of PBC. The chronic morbidity, treatment costs, and transplantation needs of patients with PBC mean that this disease now accounts for a sizeable proportion of clinical hepatology workload. As prognosis is improved by earlier diagnosis and therapy more emphasis needs to be placed on symptomatic treatment.

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Answers: 1c, 2b, 3b, 4e, 5a.