15.23.3 Primary biliary cholangitis 3127

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15.23.3 Primary biliary cholangitis 3127 Acknowledgements Prof Stefan Hübscher, Pathology, University Hospitals Birmingham, and Dr Abid Karim, Clinical Immunology, University Hospitals Birmingham, United Kingdom. FURTHER READING de Boer YS, et al. (2014). Genome-wide association study identifies vari- ants associated with autoimmune hepatitis type 1. Gastroenterology, 147, 443–52.e5. Hennes EM, et al. (2008). Simplified criteria for the diagnosis of auto- immune hepatitis. Hepatology, 48, 169–76. Kirstein MM, et al. (2015). Prediction of short- and long-term outcome in patients with autoimmune hepatitis. Hepatology, 62, 1524–35. Manns MP, et al. (2010). Budesonide induces remission more effect- ively than prednisone in a controlled trial of patients with auto- immune hepatitis. Gastroenterology, 139, 1198–206. Obermayer-Straub P, et al. (2001). Hepatic autoantigens in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Gastroenterology, 121, 668–77. Trivedi PJ, et al. (2018). Grand round: Autoimmune hepatitis. J Hepatol, doi: 10.1016/j.jhep.2018.11.006. van Gerven NM, et al. (2015). HLA-DRB1*03:01 and HLA-DRB1* 04:01 modify the presentation and outcome in autoimmune hepa- titis type-1. Genes Immun, 16, 247–52. Webb GJ, Hirschfield GM, Krawitt EL, Gershwin ME (2018). Cellular and molecular mechanisms of autoimmune hepatitis. Annual Review of Pathology: Mechanisms of Disease, 13(1), 247–92. 15.23.3 Primary biliary cholangitis Jessica K. Dyson and David E.J. Jones ESSENTIALS Primary biliary cholangitis (PBC), previously known as primary bil- iary cirrhosis, is a chronic, cholestatic liver disease in which the biliary epithelial cells lining the small intrahepatic bile ducts are the target for immune-mediated damage, leading to progressive ductopenia and cholestasis. The cause is unknown but presumed to be autoimmune. The disorder affects women (>90% of cases) and usually has an in- sidious onset in middle age. Younger patients are less common but have a more aggressive disease course. Fatigue and pruritus are the most common presenting symptoms. Findings on examination vary widely, ranging from no abnormality to jaundice with hyperpigmen- tation, scratch marks, and rarely the features of advanced liver disease. Diagnosis of PBC is based on three criteria: (1) cholestatic liver function tests, with increases in serum alkaline phosphatase and γ-glutamyl transferase, (2) presence of serum antimitochondrial antibodies (found in more than 95% of cases), and (3) compatible liver histology. Many asymptomatic patients are recognized fol-

lowing the incidental discovery of antimitochondrial antibodies or elevated levels of serum alkaline phosphatase. First-line treatment is with ursodeoxycholic acid which can lead to significant improvement in liver biochemical values. Second-line treatment is with obeticholic acid. No immunosuppressive drug regimen has been proven effective. Progression may be slow, but eventually patients can develop cirrhosis. Cholestyramine is used as first line to treat pruritus. There is no recognized treatment for fatigue. Liver transplantation is indicated in some cases. Introduction The term primary biliary cirrhosis was first used in the 1940s before the advent of serological testing and when the disease was recognized in end stage. With current diagnostic approaches, the vast majority of patients are identified early in the disease and are noncirrhotic. This, together with the use of the term cirrhosis with its erroneous implication of an alcohol aetiology among nonexperts, has led a pa- tient-driven move to change the name of the condition to primary biliary cholangitis (PBC), and it has been known as such since 2015. PBC is a chronic inflammatory liver disease characterized by damage to the small intrahepatic bile ducts. There is an autoimmune component to the disease with high titres of characteristic auto- antibodies, portal tract T-cell infiltrates, genetic associations with immunoregulatory gene polymorphisms, and clinical associations with other autoimmune conditions. Bile duct injury is progressive, with a cycle of cholestatic cell damage. The combination of immune and cholestatic injury results in progressive liver injury, fibrosis, and, ultimately, cirrhosis. PBC impact patients through the development of advanced liver disease, and through systemic symptoms that can occur at any point in the disease course. First line therapy is with the hydro- philic bile acid ursodeoxycholic acid (UDCA) which has individual trial and meta-analysis evidence suggesting improvement in prog- nosis. Second line treatment is with the Farnesoid X Receptor agonist Obeticholic Acid (OCA) which has trial evidence to suggest a signifi- cant improvement in surrogate markers of disease severity in patients showing an inadequate response to UDCA. Symptomatic treatment approaches are effective for pruritus. Recent advances in disease patho- genesis are now translating into novel, second-line therapies. Aetiology Genetic basis PBC appears to be typical of autoimmune disease in having a complex aetiology. A genetic component is suggested by familial predisposition (the sibling relative risk is 10.5) and an increased concordance rate in monozygotic twins. Genome-wide association studies have shown remarkably consistent findings internationally, with the strongest as- sociations being within the HLA region (Table 15.23.3.1). Other as- sociations are with pathways regulating antigen presentation, the phenotype of the cellular immune response, and the trafficking of im- mune cells into the liver. No associations at a genome-wide level of sig- nificance have been reported with nonimmune loci. The genetic basis of disease phenotype remains to be explored and genetic approaches currently have no role to play in disease management. Although there is an increased incidence of PBC in family members, absolute risk re- mains low, hence screening of family members is not recommended in the absence of other findings leading to clinical suspicion.

 Environmental factors There is both epidemiological and mechanistic evidence sug- gesting that environmental triggers may be responsible for break- down of immune tolerance in genetically susceptible individuals, but studies looking for the specific trigger are lacking. There is spatial variation in PBC both in terms of worldwide prevalence and within smaller geographical areas, with disease clusters in urban areas. An excess of cases over a limited time-period within limited geographical areas (space-time clustering) also points to a role for transient environmental agents in disease aetiology. Large case–control studies have suggested other factors within the environment and disease associations that may relate to dis- ease risk: history of urinary infections, history of smoking, use of hair dye, eczema, psoriasis, and

shingles. However, study results are conflicting and need further exploration (Table 15.23.3.2). Challenges in identifying environmental risk factors include the time between exposure and onset and the latent period between disease onset and diagnosis. Epidemiology PBC predominantly affects women (90% of patients) with a me- dian age at onset of approximately 60 years. The strong association between female sex and PBC suggests that female sex hormone ef- fects may be important in pathogenesis. Using accepted epidemio- logical criteria, PBC is confirmed as 'definite' by the presence of all three of:

1. elevation of serum alkaline phosphatase of liver origin for at least 6 months
2. presence of antimitochondrial antibodies or PBC-specific anti nuclear antibodies (titre>1:40) in serum
3. diagnostic or compatible liver biopsy (showing characteristic florid bile duct lesions)
   Table 15.23.3.1 Genetic associations in PBC identified in high- quality studies
   Chromosome Position (MB) Probable gene association 1 2.5 67.7 197.5 MMEL1, TNFRSF14 IL12RB2 DENND1B 2 191.8 228.7 STAT1, STAT4 CCL20 3 17.0 119.2 159.7 PLCL2 CD80 IL12A, SCHIP1 4 103.4 NFKB1 5 35.9 158.7 IL7R IL12B 6 26.21–33.74 137.5 MHC (multiple) IL22RA2 7 36.9 128.6 ELMO1 IRF5, TNPO3 9 117.5 TNFSF15 11 64.1 111.2 118.8 RPS6KA4 POU2AF1 CXCR5, DDX6 12 6.4 111.8 TNFRSF1A SH2B3, ATXN2 13 43.1 TNFSF11 (RANKL) 14 68.2 103.6 RAD51L1 TNFAIP2 16 11.3 85.9 CLEC16A, SOCS1 IRF8 17 38.1 44 IKZF3, ZPBP2, GSDMB, ORMDL3 MAPT 19 10.5 50.9 TYK2 SPIB 21 45.6 ICOSLG 22 39.8 MAP3K71P1, SYNGR1 Table 15.23.3.2 Environmental and related associations in PBC identified in high-quality case–control studies Risk factor Howel 2000 (UK) Gershwin 2005 (multivariate analysis) (USA) Prince 2010 (OR compared to epidemiological cases) (UK) OR 95% CI AOR 95% CI OR 95% CI Medical/family history Family history of PBC 4 0.4–44 10.7 4.2–27.2 2.26 1.05–5.21 Psoriasis 4.6 1.2–17.3 1.90 1.21–2.91 Eczema 0.13 0.02–1.0 0.96 0.63–1.46 Urinary infections 1.7 0.96–3.0 1.5 1.19–1.91 2.06 1.56–2.73 Lifestyle Ever smoked 2.4 1.4–4.1 1.57 1.29–1.91 1.63 1.27–2.09 Alcohol consumption 0.7 0.3–1.8 0.57 0.39–0.83 Hair dye 1.29 1.00–1.80 Hair perm 1.13 0.78–1.65 Nail varnish 1.002 1.0–1.003 AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

15.23.3 Primary biliary cholangitis 3129 The presence of two features is defined as 'probable' PBC. The com- bination of antimitochondrial antibodies at diagnostic titres and ele- vated alkaline phosphatase is over 95% accurate for diagnosing PBC, an observation which has led to a dramatic reduction in the need for liver biopsy for diagnosis (it is now mainly reserved for prognostic and treatment assessment). Although these criteria were developed to standardize diagnosis in the context of epidemiological studies, they have entered widespread clinical use. PBC is a rare disease (prevalence <50/100 000 population), with higher prevalence in Northern Europe and much lower prevalence in Asia and Africa, although there is a paucity of good epidemio- logical studies from these areas (Table 15.23.3.3). Some studies have suggested that the prevalence of PBC is increasing over time, but this may be due to improved case finding, increased dis- ease awareness, differences in study populations, and methods of identifying cases. There are an increasing number of patients being identified with antimitochondrial antibodies (or other PBC-specific auto-antibodies) but normal liver function tests, and they are at risk of developing overt clinical PBC during follow-up. Current advice is that these patients undergo regular monitoring, but not be treated until a serum liver biochemical abnormality is seen. Large-scale patient cohorts such as the 6000-patient UK-PBC cohort have allowed identification of male sex and younger age at diagnosis

as risk factors for inadequate response to therapy. Young age of disease onset is also strongly associated with high symptom burden, particularly fatigue. Pathogenesis/pathology The pathogenetic process in PBC is one of sequential immune and cholestatic cytopathic injury to biliary epithelial cells lining small intrahepatic bile ducts, followed by ductopenia, progressive biliary fibrosis, and ultimately cirrhosis (Fig. 15.23.3.1). Autoimmune phenomena are almost universal with high-titre autoantibodies and liver infiltrating autoreactive T-cell responses directed most Table 15.23.3.3 Prevalence of PBC in well-designed epidemiology studies Study Country Prevalence Kim, 2000 USA 65.4 per 100 000 (95% CI 43.0–87.9) for women 12.1 per 100 000 (95% CI 1.1–23.1) for men 40.2 per 100 000 (95% CI 27.2–53.1) overall Witt-Sullivan, 1990 Canada 23 per 100 000 Metcalf, 1997 England 24 per 100 000 overall 90 per 100 000 women ≥40 years Kingham, 1998 England 20 per 100 000 James, 1999 England 25 per 100 000 Rautiainen, 2007 Finland 18 per 100 000 overall 29 per 100 000 women Lofgren, 1985 Sweden 13 per 100 000 Danielsson, 1990 Sweden 15 per 100 000 Inoue, 1995 Japan 3 per 100 000 Mori, 1997 Japan 5 per 100 000 Liu, 2010 China 49 per 100 000 Watson, 1995 Australia 1.9 per 100 000 overall 5.1 per 100 000 women >24 years CI, confidence interval. Cholestasis Immune injury Ductopaenia Fibrosis Immunotherapy Bile acid therapy Antifibrotic therapy Transplantation Fig. 15.23.3.1 Pathogenetic pathway for PBC and implications for potential approaches to therapy: proposed model for the pathogenesis of PBC. An initial autoimmune response leads to injury to small intrahepatic bile ducts and retention of toxic hydrophobic bile acids. These cause a secondary cycle of bile duct injury and, cumulatively with immune injury, progressive ductopenia and secondary hepatocyte injury, fibrosis, and cirrhosis. In an alternative proposed model, the ‘upstream’ immune injury is itself a consequence of primary cholestasis leading to altered self-antigen processing. The concept of a cumulative impact of immune and cholestatic injury remains valid in both models. Potential approaches to therapy are to target the initial immune response, the cholestatic cycle, the downstream fibrotic reaction, and, in the context of advanced disease, organ replacement through transplantation.

section 15 Gastroenterological disorders 3130 typically at highly conserved mitochondrial self-antigens (2-oxoacid dehydrogenase enzymes, in particular the E2 component of pyru- vate dehydrogenase complex (PDC-E2)). Autoreactive T-cell re- sponses are most marked in early disease leading to the view that cytotoxic T-cell responses directed at biliary epithelial cells might be an early aspect of the disease process. There is no evidence to suggest that autoantibody responses are pathogenetic. In addition to biliary epithelial cell apoptosis, senescence is also seen, sug- gesting that the pathway to injury is more complex than a simple immune ‘hit’. The bile acid pool is abnormal in PBC, with increased levels of toxic hydrophobic secondary bile acids that can also cause bil- iary epithelial cell apoptosis and give rise to a secondary cycle of cholestasis following initial immune injury. This interplay of processes has implications for the sequencing of therapy, in particular the applicability and timing of immunotherapeutics. A component of bile acid-driven biliary epithelial cell injury may be a defect in a normal protective process of active transport of bicarbonate into the bile duct. Normalization of this ‘bicarbonate umbrella’ represents a novel potential approach to treatment (Fig. 15.23.3.2). Interface hepatitis can accompany the characteristic granu- lomatous portal tract inflammation and duct injury, and has been associated with more severe, and less treatment-responsive forms of the disease (Fig. 15.23.3.3). One area of controversy has been the extent to which interface hepatitis represents an overlap process with autoimmune hepatitis. Whereas true overlap pa- tients do exist, patients meeting diagnostic criteria for both PBC and autoimmune hepatitis are uncommon, and most patients exhibiting

interface hepatitis probably have a more aggressive form of PBC. Conventional disease staging uses four-stage scores such as the Scheuer score (Table 15.23.3.4) that focus on ductopenia, portal tract change, and fibrosis, but underplay interface hepatitis. Appreciation of the importance of interface hepatitis followed the development of the scores and all underplay its significance. Newer scoring systems are needed to more accurately reflect cur- rent understanding of disease pathogenesis. Liver biopsy is likely to play an increasing role in treatment stratification as molecular pathology markers associated with higher-risk disease are recog- nized, but the patchy nature of the disease in the liver must be borne in mind when considering liver biopsy findings. A few patients have an aggressively ductopenic form of disease characterized by profound cholestasis. Prognosis is poor, pruritus is prominent, and treatment resistance is the norm. These patients typically come to transplantation. Apoptosis Apoptosis Senescence (1) (2) (3) Cytotoxic T-cell Natural killer (NK) cell Pyruvate dehydrogenase (PDH) component/epitope Anti-PDH antibody Bicarbonate transporter (AE2 etc) Bicarbonate ‘umbrella’ Hydrophobic bile acid Reactive oxygen species (ROS) Latent TGF-β Active TGF-β Fig. 15.23.3.2 Proposed mechanisms for biliary epithelial cell injury in PBC. Three mechanisms, which are not mutually exclusive, have been postulated for biliary epithelial cell (BEC) injury: (1) direct and indirect immune injury related to B-cell and T-cell autoreactivity; (2) apoptotic injury to BEC through the actions of retained hydrophobic bile acids. Susceptibility to such injury is increased by loss of a protective ‘bicarbonate umbrella’; (3) BEC senescence driven by oxidative stress and the activation of latent transforming growth factor (TGF)-β.

15.23.3 Primary biliary cholangitis 3131 Clinical features Hepatological PBC is characterized by cholestatic liver biochemistry (elevated al- kaline phosphatase and γ-glutamyl transferase) and PBC-specific autoantibodies. Serum autoantibodies specific for mitochon- drial, nuclear, and centromere antigens are present in approxi- mately 95% and 30% of patients, respectively (Table 15.23.3.5). A titre of 1/80 or greater for any autoantibody linked to PBC is regarded as positive, and an elevated IgM level is characteristic. Screening ultrasonography should be performed to exclude alter- native diagnoses. Magnetic resonance cholangiopancreatography should be considered in patients with negative autoantibodies and cholestatic liver biochemistry to exclude primary sclerosing chol- angitis. Gallstones are common in PBC patients but often asymp- tomatic. Periportal lymphadenopathy is frequent and related to the underlying disease process. Elevated bilirubin and decreasing serum albumin levels are features of advanced disease and suggest poor prognosis. Risk scores, each including serum bilirubin, have been designed to predict prognosis in patients with PBC. The Mayo risk score (age, serum bilirubin and albumin, coagulation time, and the pres- ence of fluid retention and/or use of diuretics) predicts outcome in advanced disease but does not identify high-risk patients in early disease. More recently, simple assessments of the biochemical re- sponse to treatment have been shown to accurately identify high- risk patients who may have reduced survival or increased need for liver transplantation (Table 15.23.3.6). It is unclear which risk/response criteria are optimal for use in clinical practice. (a) (b) (c) Fig. 15.23.3.3 The histology of PBC. (a) Interface hepatitis in PBC. A feature which can lead to suspicion of overlap with AIH, this is increasingly recognized as a manifestation of aggressive PBC. (b) Bile duct lesion in PBV. There is granulomatous destruction of a medium- sized bile duct radicle in which the epithelium appears hyperplastic. Epithelioid macrophages are surrounded by a chronic inflammatory cell infiltrate. Haematoxylin and eosin. (c) Stage 4 PBC: an established micronodular cirrhosis; the halo effect seen around the nodules is a characteristic feature of primary biliary cholangitis. Haematoxylin and eosin. Images (b) and (c) courtesy of A.D. Burt. Table 15.23.3.4

Scheuer score for staging PBC Stage Histological features 1 Florid duct lesions and portal inflammation without interface activity 2 Interface hepatitis, ductular proliferation, and periportal fibrosis 3 Bridging necrosis or bridging fibrosis 4 Cirrhosis

section 15 Gastroenterological disorders 3132 Symptomatic Cirrhotic PBC patients experience the typical problems of ad- vanced liver disease, including encephalopathy, ascites, and weight loss, albeit typically in a less marked form than in cirrhosis of other aetiologies. In addition, patients frequently experience character- istic symptoms that can occur at any point in the disease course, in particular pruritus and fatigue (Table 15.23.3.7). Up to 80% of patients experience pruritus at some point in the disease course. In its severest form it can be life-altering, with scratching leading to deep excoriations. PBC pruritus shares characteristics with other forms of cholestatic pruritus, including typical scalp, hands, and feet involvement. Conventionally thought of as being caused by irritant, retained bile acids, recent studies have highlighted the role played by the autotoxin pathway in cholestatic itch, which can improve in end-stage disease. Fatigue in PBC is complex and affects over 50% of patients (20% severely). Large cohort studies using a disease-specific quality of life measure (the PBC-40) have suggested that fatigue is the major con- tributor to poor life quality and can be exacerbated by social isola- tion. The aetiology of PBC fatigue remains unclear.
Table 15.23.3.5 Autoantibody associations of PBC: the archetypal antimitochondrial antibodies are diagnostic for PBC but their presence or titre has no prognostic significance. Where present, the characteristic antinuclear antibodies (which need to be distinguished from the diffusely staining antinuclear antibody seen in autoimmune hepatitis) are both diagnostic and associated with worse prognosis. Detection can be either by immunofluorescence or enzyme- linked immunosorbent assay for specific antigens Cellular location Antigen Frequency (%) Clinical significance Mitochondrial Pyruvate dehydrogenase (PDH) E2 component PDH-E1α PDH-E1β 2-Oxoglutarate dehydrogenase complex-E2 Branch-chain 2-oxo acid dehydrogenase complex-E2 95+ 40–66 2–10 39–88 53–89 Diagnosis Diagnosis Diagnosis Diagnosis Diagnosis Nuclear Gp210 Nucleoporin p62 Sp100 10–47 32 20 Diagnosis and prognosis Diagnosis Diagnosis and prognosis Table 15.23.3.6 Criteria for assessing treatment response in PBC Criteria Treatment response criteria Sample size Results Barcelona criteria Response to treatment defined by ALP decrease >40% of baseline values or normal levels after 1 year of treatment 192 patients (181 women) 8.9% died or fulfilled criteria for liver transplantation Observed survival higher than that predicted by Mayo model and lower than control population (p <0.001) 61% responded to treatment Survival of responders was significantly higher than that predicted by Mayo model and similar to that estimated for control population (p = 0.15) Paris I criteria Treatment response defined as:

1. ALP <3× ULN and
2. AST <2× ULN and
3. Bilirubin <1× ULN 292 patients 10-year transplant-free survival rate of 90% (95% CI, 81–95%), compared to 51% (95% CI, 38–64%) for those who did not (p <0.001) Paris II criteria Early-stage PBC defined by normal bilirubin and albumin at baseline Response treatment criteria: ALP and AST ≤1.5× ULN with normal bilirubin level 165 patients Average follow-up 7 years All adverse events observed in nonresponders (p <0.001) Toronto criteria ALP <1.67× ULN at 2 years of treatment
with UDCA 69 patients with follow-up liver biopsy performed approximately 10 years after initial histological diagnosis Histological progression in stage of fibrosis observed in paired liver biopsies was associated with absence of biochemical response at 2 years: ALP

>1.67× ULN, p = 0.001; OR 12.14;
95% CI 2.69–54.74 when defined as an increase in one stage ALP >1.76× ULN, p = 0.03; OR 5.07; 95% CI 1.17–21.95 when defined as an increase in two stages Ductopenia (>50% loss) predicted histological progression (p = 0.012) and biochemical response to UDCA (p = 0.002) Rotterdam criteria PBC classified as early (pretreatment bilirubin and albumin levels normal), moderately advanced (one level abnormal), or advanced (both levels abnormal) Biochemical response defined by normalization of abnormal bilirubin and/or albumin levels 375 patients Median follow-up time 9.7 years Prognosis for early PBC comparable to Dutch population and better than predicted by Mayo risk score Survival of responders better than that of nonresponders (according to Paris and Rotterdam criteria (p <0.001)). Prognosis of early PBC comparable for responders and nonresponders Prognosis of responders significantly better in those with (moderately) advanced disease
ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; OR, odds ratio; ULN, upper limit of normal.

15.23.3 Primary biliary cholangitis 3133 Associated conditions The strongest disease associations are with other autoimmune con- ditions, reflecting shared immunogenetic risk (Table 15.23.3.8). The presence of associated autoimmune disease should be con- sidered in fatigued patients as a number of these associated condi- tions are themselves potentially treatable causes of fatigue. Cholestatic disease associations include fat-soluble vitamin deficiency and associated osteoporosis. The specific impact of osteoporosis in PBC has been overstated with the relatively high rates seen reflecting more disease demographics than specific risk. Increased falls risk is also seen in PBC due to an association with autonomic dysfunction contributing to the osteoporotic fracture risk. Atherosclerotic cardiac risk does not appear to be increased in PBC despite cholesterol elevation and an increased smoking rate identified in epidemiological studies. This reflects the fact that the cholesterol elevation is typically of high-density lipoprotein/ lipoprotein X. Anecdotal reports suggested an association with breast cancer but there is no increase in cancer risk in PBC in well-designed studies, with the exception of hepatocellular carcinoma in ad- vanced disease. Differential diagnosis The specificity and sensitivity of the PBC-associated autoantibodies usually prevents diagnostic uncertainty. Approximately 5% of PBC patients are negative for antimitochondrial antibodies, but most of these will be positive for the PBC-specific nuclear antibodies and do not require liver biopsy for diagnosis. However, liver biopsy is required for the diagnosis of true autoantibody-negative PBC. This ensures that the main differential diagnoses of small-duct PSC, sarcoidosis, graft-versus-host disease (in the appropriate context), idiopathic ductopenia, and genetic cholestasis syndromes are not overlooked. Management Prognostic therapy The licensed first line therapy for PBC is the hydrophilic bile acid UDCA (13–15 mg/kg), which has been demonstrated in phase III trials subjected to meta-analysis to reduce the risk of death or need for liver transplantation (Table 15.23.3.9). UDCA is well tolerated and recommended for use in all patients. Its mode of action remains unclear, although effects include choleresis (increase in volume of bile secretion), antiapoptotic actions, and a diluting effect, with UDCA displacing toxic hydrophobic bile acids in the bile pool. Patients who are under-responsive to UDCA should be considered for second-line treatment with obeticholic acid, which has shown benefit in terms of liver biochemistry in a phase III trial. This is a semisynthetic bile acid analogue and agonist for the farnesoid X re- ceptor, which suppresses bile acid production and alters excretion. It can be used in combination with UDCA when the response to UDCA has been inadequate, or as monotherapy in patients intolerant of UDCA. Bezafibrate, a Peroxisome Proliferator-Activated Receptor Alpha

(PPARa) agonist, also significantly improves liver biochemistry in UDCA-under-responsive patients but, in contrast to Obeticholic Acid, is not currently licensed for this indication. There is no evidence to support the nonselective use of immuno- suppressive drugs. Stratified approaches to therapy utilizing second- line therapeutics in the subgroup of patients who show an inadequate response to UDCA are now being developed. There are also ongoing studies exploring the impact on bile acid biology and cholestasis of fibrates (acting through the PPARα pathway). Although the stratified approach has been explored for novel immunotherapeutic agents, re- sults have been disappointing. This may reflect the challenge of therapy sequencing (Fig. 15.23.3.1). Studies to identify molecular markers of stratification for enhanced risk in PBC are now being undertaken with the aim of allowing earlier targeted use of second-line therapy. Symptomatic therapy Effective treatment is available for pruritus (Table 15.23.3.10). First- line treatment is with the bile acid sequestrant cholestyramine. Tolerability can be an issue and the drug can be made more accept- able by the addition of fruit juice. Second-line agents include rifam- picin (a good evidence base with meta-analysis confirming efficacy), which probably works through pregnane X receptor agonism, and oral opiate antagonists including naltrexone, which probably target opiate neurotransmission in the pruritus pathway. Other therapy approaches such as gabapentin, apical sodium-dependent bile acid transporter inhibitors, and physical methods such as nasobiliary Table 15.23.3.7 Symptom associations of PBC: data are from the UK-PBC cohort of over 2000 patients. Features of severe/advanced disease are uncommon in the patient population as a whole. Systemic symptoms such as fatigue are common and, with the exception of the small subgroup of patients with very advanced disease, unrelated to disease severity. PBC-40 is a validated PBC-specific quality of life tool widely used in clinical and trials practice Symptom Prevalence (%) Disease severity association? Fatigue (PBC-40 domain) 55 No (other than end stage) Vasomotor autonomic (OGS) 40 No (other than end stage) Emotional (PBC-40 domain) 45 No Social (PBC-40 domain) 33 No Cognitive (PBC-40 domain) 33 No (other than end stage) Sleep disturbance 30 No Pruritus (PBC-40) 28 Cholestasis not severity Depression (HADS) 10 No Jaundice <5 Yes Ascites <5 Yes HADS, Hospital Anxiety and Depression Scale; OGS, Orthostatic Grading Scale. Table 15.23.3.8 Autoimmune associations of PBC Condition Reported prevalence (%) Sjögren’s syndrome 3.5–47 Raynaud’s syndrome 12–24 Autoimmune thyroid disease 9–23 Scleroderma 8–17 Rheumatoid arthritis 1.8–17 Type 1 diabetes mellitus <1 Coeliac disease 3 Systemic lupus erythematosus 1.8–3

 drainage and albumin dialysis are experimental. Patients failing first- and second-line therapy should be referred to specialist centres. There are no specific therapies for fatigue. The possibility of as- sociated conditions that are contributing should be considered. Pruritus, particularly if prominent at night, can be associated with significant fatigue and should be treated. Reducing autonomic dys- function, addressing daytime somnolence, and treating depression (all associated features) can also reduce the impact of fatigue. Coping strategies are critical, as are addressing issues such as social isolation. UDCA is not effective at treating PBC symptoms. Liver transplantation Liver transplantation is an effective treatment for end-stage PBC, increasing life expectancy. In the United Kingdom, patients must Table 15.23.3.9 Therapy in primary biliary cirrhosis Agent All patients or stratified use Notes Licensed therapy Obeticholic acid (5–10 mg/day) Stratified Second-line bile acid therapy licensed for use in patients showing an inadequate response to UDCA or who are intolerant of UDCA UDCA (13–15 mg/kg) All Second-line bile acid therapy licensed for use in patients showing an inadequate response to UDCA or who are intolerant of UDCA Emerging therapy with an evidence base Fibrate (various) Stratified Addition in UDCA nonresponders improves biochemistry. Phase III trial evidence. Potential safety

concerns and label precludes use in some jurisdictions Budesonide (6 mg/day) Stratified Some evidence that addition to UDCA improves efficacy. Trial base weak. Contraindicated in patients with perihepatic shunting Therapy with unclear utility Prednisolone ± azathioprine/ mycophenolate mofetil Both Ineffective in broad-based use with substantial side effects. Wide experience of use in patients deemed to have overlap but no structured evidence. Unclear role in new paradigms of second-line therapy in UDCA nonresponders Ineffective therapies Ciclosporin 2.5–4 mg/kg/day All Limited efficacy. Renal toxicity and hypertension May be value in exploring again in the setting of stratified therapeutics Methotrexate 15 mg/week All Some benefit but outweighed by toxicity (in particular pulmonary). May be value in exploring again in the setting of stratified therapeutics Chlorambucil 0.5–4 mg/day All Potentially toxic Colchicine 0.6–1.2 mg/day All Minor benefits but insufficient evidence to support use d-Penicillamine 250–100 mg/day All No convincing benefit. Excessive toxicity Azathioprine 1–2 mg/kg per day All Limited efficacy. May be value in exploring again in the setting of stratified therapeutics Mycophenolate mofetil 1 g/day All Some efficacy in pilot study. May be value in exploring again in the setting of stratified therapeutics
Table 15.23.3.10 Stepwise approach to the management of pruritus in PBC Agent Dose Additional notes

1. Cholestyramine 4 g/day to a maximum of 16 g/day as tolerated Must be given 2–4 h before or after UDCA (usually give UDCA at night) Pharmacy advice to avoid interactions with concomitant medications Suggest give at breakfast time (1 h before or after eating) if gallbladder in situ Mixing with orange squash and leaving in fridge overnight improves palatability
2. Rifampicin 300–600 mg/day Risk of hepatotoxicity—need regular monitoring of liver function tests (LFT)s; start at 150 mg daily then titrate upwards if LFT not elevated, repeating LFTs 2 weeks after dose increment
3. Naltrexone 50 mg/day (normal maximum dose, although higher doses have been used in the specialist clinic setting) Start at 12.5 mg/day to avoid withdrawal symptoms
4. Sertraline 100 mg/day Titrate dose to symptoms and as tolerated Needs interaction at the primary/secondary care interface—change over if on alternative antidepressant. Note: in widespread use
5. Physical approaches Albumin dialysis (and related approaches) Nasobiliary drainage Salvage procedures which should be considered in specialist centres only Limited trial evidence Significant morbidity and cost
6. Transplantation Highly effective High cost Limited organ availability raises questions of prioritization for a symptomatic indication

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Revision #1
Created 2026-01-22 16:38:46 UTC by Omar Ayman
Updated 2026-01-22 16:38:46 UTC by Omar Ayman