Autoimmune liver disease for the non-specialist

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Cite this as: *BMJ* 2009;339:b3305
doi: 10.1136/bmj.b3305

Autoimmune hepatitis, primary biliary cirrhosis, and sclerosing cholangitis represent perhaps 5% of all liver diseases, although no registries exist to estimate the true prevalence. They are presumed autoimmune conditions, usually considered as a diagnosis after viral, metabolic, and drug induced liver injuries have been excluded. The combination of medical and surgical treatments means that, if appropriately diagnosed and managed, these diseases overall have an excellent prognosis. We review these conditions for non-specialists and refer to available guidelines and clinical trial data.[1-3]

What are the epidemiological and clinical features of autoimmune liver disease?

Autoimmune liver diseases are chronic, slowly progressive, inflammatory liver diseases that may have overlapping features.[4] (fig 1, table 1).

Autoimmune hepatitis

Autoimmune hepatitis is a relapsing idiopathic hepatitis, encountered more often in women than men across all ages and ethnicities. Ascertainment biases limit available epidemiology; a Swedish study put the annual incidence as 8.5 per 1 000 000 population and point prevalence as 107 per 1 000 000.[5] Patients present clinically with arthralgias and fatigue if symptomatic, and a third of patients present with cirrhosis.[w1] Raised liver enzymes (transaminases) characterise initial laboratory abnormalities.

SUMMARY POINTS

- Autoimmune liver diseases are chronic diseases, each with a long natural course
- Disease need not be symptomatic, but symptoms when present can be challenging to manage
- Autoimmune hepatitis is a parenchymal disease, whereas primary biliary cirrhosis and primary sclerosing cholangitis are biliary diseases
- Medical management of primary biliary cirrhosis (with ursodeoxycholic acid) and autoimmune hepatitis (with prednisolone and azathioprine) is very successful and transplantation is rarely needed
- Primary sclerosing cholangitis lacks effective medical interventions, but transplantation when indicated is highly successful

Primary biliary cirrhosis

Primary biliary cirrhosis is a slowly progressive, chronic cholestatic disease affecting primarily middle aged women (female:male ratio 9 to 1) and is characterised by small duct granulomatous cholangitis and biochemical cholestasis (raised alkaline phosphatase). One robust UK estimate of annual incidence was 32.2 per million population per year, with an estimated prevalence of 334.6 per million.[6] Currently 60% of patients diagnosed with primary biliary cirrhosis have no symptoms, and most have non-cirrhotic disease.[w2] When symptoms are present, fatigue, pruritus, and right upper quadrant discomfort are common, but do not indicate severity of disease. Autoimmune diseases such as Sjögren's syndrome, coeliac disease, scleroderma, and thyroid disease are common in patients and their family members, consistent with a genetic predisposition to disease.[7]

Sclerosing cholangitis

Sclerosing cholangitis is a chronic cholestatic liver disease characterised by fibrosing inflammatory destruction of the intrahepatic and extrahepatic biliary tree. If no aetiologies are identified—for example, portal vein thrombosis, autoimmune pancreatitis, or recurrent pyogenic cholangitis—the prefix primary is used. Primary sclerosing cholangitis affects more men than women (ratio 7 to 3; mean age about 40 at diagnosis). Almost 75% of patients have coexisting inflammatory bowel disease, usually ulcerative colitis. The UK general practice research database estimates annual incidence as 4.1 per 1 000 000 population and prevalence as 38.5 per 1 000 000.[8] The corresponding US estimates are about 10 per 1 000 000 population and 140 per 1 000 000 respectively.[2]

How should patients be investigated and how is a diagnosis reached?

Investigations focus on the pattern of liver biochemistry, the presence of autoantibodies, imaging findings, and liver histology (fig 2).

Autoimmune hepatitis

Raised transaminase levels are usually accompanied by raised IgG levels, which range from slightly raised to extremely high (in the thousands) but are commonly 1.2-3.0 higher than the upper limit of normal.

Table 1 | Summary features of autoimmune liver disease

	Autoimmune hepatitis	Primary biliary cirrhosis	Primary sclerosing cholangitis
Demographics	Female predominant (4:1) and all ages	Female predominant (9:1); usually post-menopausal at diagnosis	Male predominant (7:3); classically diagnosed in 40s, in association with inflammatory bowel disease
Symptoms	Asymptomatic commonly; alternatively acute jaundice with itch, and upper abdominal pain	Commonly now asymptomatic; traditionally fatigue, pruritus, occasionally xanthoma	Often asymptomatic; may present with cholangitis, pruritus, abdominal pain, or jaundice
Biochemical changes in liver	Raised transaminases (alanine aminotransferase, aspartate aminotransferase)	Cholestatic profile predominates (raised alkaline phosphatase, γ-glutamyl transferase)	Cholestatic profile predominates (raised alkaline phosphatase, γ-glutamyl transferase)
Classic raised serum IgG	IgG	IgM	Non-specific; raised IgG4 may suggest a secondary aetiology
Autoantibodies	Antinuclear antibody, smooth muscle antibody (type 1 autoimmune hepatitis); liver-kidney microsome (type 2)	Anti-mitochondrial antibody (invariably positive for antinuclear antibody in cases that are negative for anti-mitochondrial antibody)	No specific associations; frequently positive for antinuclear antibody and smooth muscle antibody
Classic histology	Interface hepatitis, lobular hepatitis, necrosis/collapse, fibrosis	Granulomatous lymphocytic destruction of interlobular bile ducts in portal triads with ductopenia and fibrosis	Periductal concentric fibrosis, ductopenia, ductular proliferation
Broad treatment	Prednisolone and azathioprine as first line treatment	Ursodeoxycholic acid (13-15 mg/kg)	No proved effective treatment except in secondary IgG4 associated sclerosing cholangitis (steroid responsive)
Usual basis for diagnosis	Combination of liver biochemistry, immunology, and liver biopsy findings	Cholestatic liver tests in presence of anti-mitochondrial antibody	Cholestasis with compatible imaging
Prognosis	Excellent long term survival	Patients whose biochemical status improves with ursodeoxycholic acid have a normal life expectancy	Once symptoms are present, there is about a 50% chance of need for transplantation over 10 years

Of 213 patients at one centre,[w3] aspartate aminotransferase levels at presentation were less than double the upper limit in 12% of patients, two to 10 times the upper limit in 33%, and more than 10 times the upper limit in 54%.

Antinuclear antibodies and anti-smooth muscle antibodies characterise type 1 autoimmune hepatitis, whereas antibodies to liver and kidney microsome mark the rarer, type 2 autoimmune hepatitis, which typically starts in childhood. Usual titres of serum autoantibodies range from ≥1:40 to ≥1:80, but in isolation results have low positive predictive values as the prevalence of autoantibodies in healthy individuals exceeds the prevalence of disease.[w4]

Histological features include lymphoplasmacytic interface hepatitis, lobular hepatitis, and centrolobular necrosis. When a disease scoring system (table 2) based on autoantibody titres, IgG values, histology evaluation, and exclusion of viral hepatitis was applied to a validation cohort it had an 88% sensitivity and 97% specificity (cut-off ≥6) and 81% sensitivity and 99% specificity (cut-off ≥7).[9] Important differential diagnoses include drug induced liver disease (induced by, for example, nitrofurantoin and minocycline) and Wilson's disease.

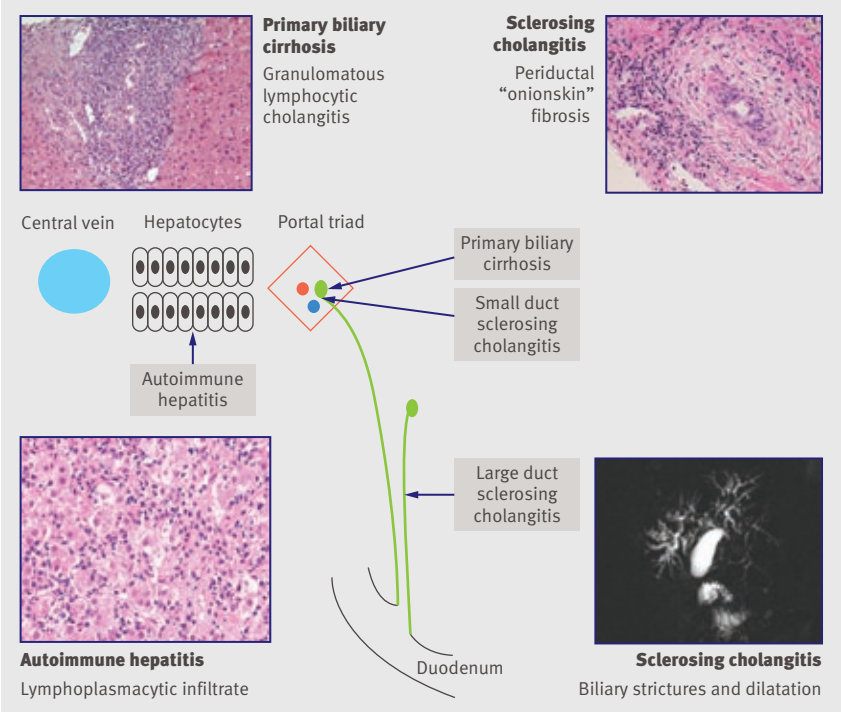

Fig 1 | Characteristic histological and radiological features of autoimmune liver diseases

Primary biliary cirrhosis

The presence of circulating anti-mitochondrial antibodies in 95% of patients is a defining feature.[10] Diagnosis usually rests on the presence of anti-mitochondrial antibodies and persistent cholestatic biochemistry; liver biopsy is generally reserved for anti-mitochondrial antibody negative patients, since the combination of anti-mitochondrial antibody and an alkaline phosphatase level of more than 1.5 times the upper limit and an aspartate aminotransferase level of less than five times the upper limit yields a 98.2% positive predictive value for histological confirmation of disease.[w5]

Sclerosing cholangitis

Diagnosis relies on visualising the biliary tree by magnetic resonance cholangiography, or if not available, by using endoscopic retrograde cholangiopancreatography. Both techniques adequately show the characteristic multifocal strictures and beading of the intrahepatic and/or extrahepatic bile ducts. Once symptoms are present, the clinical course includes episodic cholangitis, with patients variably describing right upper quadrant pain, dark urine, pale stools, and fever. Those with inflammatory bowel

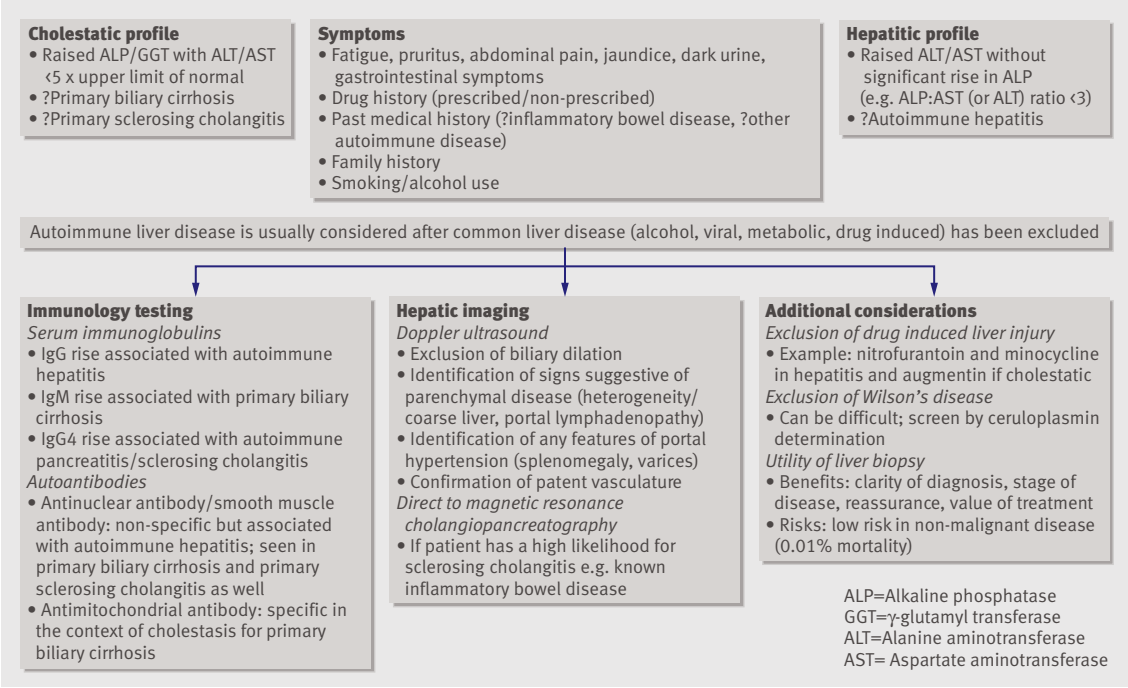

Fig 2 | Evaluating the patient for autoimmune liver disease

disease, notably ulcerative colitis, may be diagnosed when asymptomatic, if screening alkaline phosphatase levels are abnormal, and it seems silent cholangiographic changes may be commoner than thought.[w6] Liver biopsy helps only a subgroup of patients with limited microscopic intra-hepatic bile duct disease.[11]

How should patients with autoimmune liver disease be treated?

Immunosuppression in autoimmune hepatitis

Randomised controlled treatment trials have shown a benefit with steroid treatment[12-14]; maintenance with azathioprine and steroids induces remission—characterised by normal levels of transaminases and IgG, and an inactive histology—in over 90% of patients with type 1 autoimmune hepatitis.[15-17]

Table 2 | Simplified criteria for diagnosing autoimmune hepatitis[9]

Variable	Points*
Antinuclear antibody or smooth muscle antibody†	
Cut-off titre ≥1:40	1
Cut-off titre ≥1:80	2
Liver-kidney microsome†	
Cut-off titre ≥1:40	2
Soluble liver antigen†	
Positive	2
IgG	
Greater than upper limit of normal	1
>1.1 × upper limit of normal	2
Histology‡	
Compatible with autoimmune hepatitis	1
Typical of autoimmune hepatitis	2
Viral hepatitis	
Absent	2

*Probable autoimmune hepatitis, ≥6 points; definite autoimmune hepatitis, ≥7 points.
†Maximum points for all autoantibody categories combined = 2.
‡Typical liver histology: presence of interface hepatitis; lymphocytic/lymphoplasmocytic infiltrates in portal tracts and extending into the lobule; emperipolesis (active penetration by one cell into and through a larger cell); and hepatic rosette formation. Compatible liver histology: presence of chronic hepatitis with lymphocytic infiltration without all the features considered typical. Atypical liver histology: histology showing signs of another diagnosis such as steatohepatitis.

Steroids afford survival benefit according to randomised controlled treatment trials.[12-14] Data from randomised studies support steroid induced remission (normal transaminase and IgG levels and an inactive histology) and maintenance with azathioprine for over 90% of patients with type 1 disease.[15-17] The serological classification of disease does not affect treatment. Initial studies used 15 mg prednisolone daily; others used prednisone monotherapy starting at 60 mg daily or prednisone 30 mg daily with azathioprine 50 mg daily. Our approach is 20 mg prednisolone (or prednisone) daily with azathioprine 1-2 mg/kg a day either from the outset or once treatment response is confirmed. Two to three months of 20 mg prednisolone (or prednisone) daily is followed by treatment for one to two years of 5-10 mg a day. The individual severity of presentation and response to treatment dictate dose adjustments.

Treatment is warranted for symptomatic patients with *(a)* transaminases ≥10× upper limit, *(b)* transaminases ≥5× upper limit with IgG values ≥2× upper limit, or *(c)* active liver histology (bridging necrosis, multiacinar necrosis) as such patients historically had a six month mortality rate of 40% and a 10 year mortality of over 70% if not given steroids. Patients not fulfilling these indications probably benefit from treatment as *(a)* untreated patients with mild hepatitis have a 17% chance of cirrhosis within five years, *(b)* patients with mild to moderate laboratory disturbances have a 49% chance of cirrhosis within 15 years and a 10 year survival of 90%.[w7 w8] No treatment is needed if cirrhosis is identified in the absence of inflammatory activity.

Resolution of inflammatory activity on liver biopsy

TIPS FOR NON-SPECIALISTS

- Diagnosis of autoimmune liver disease requires the exclusion of common viral, drug induced, and metabolic liver disease first
- Liver imaging and histology testing are important tools in making an accurate diagnosis
- Acknowledging the importance of the symptoms to the patient, particularly fatigue and pruritus, is important
- Care is invariably shared with secondary and tertiary care as expertise is often focused in specialist centres
- Routine monitoring usually consists of liver biochemistry and blood count tests every three to six months; identification of complications of cirrhosis and side effects of medications is also sought, as for any other chronic liver disease

is one clinical end point, but interim evaluation relies on measurement of serum transaminases and immunoglobulins, as this reliably monitors activity and response to treatment.[w9] If treatment is stopped, about 80% of patients will relapse, 50% within six months.[w10] Azathioprine initially at 2 mg/kg has been shown in randomised trials to reduce relapse rate and maintain remission. Factors associated with an increased relapse rate include a slow time to initial remission and failure to have consistently normal transaminase levels thereafter. Black men (when compared with a non-black comparison group of predominantly white men) seem to have worse outcomes.[18] There is no prescribed treatment duration, although relapses while treatment is stopped correlate with the duration of treatment received: relapses are fewer after 48 months of treatment than after 26 months of treatment.[w11] Repeated attempts to stop treatment leads to repeated relapses and greater progression to cirrhosis, death from liver failure, and requirement for transplantation.[w12]

Whereas steroids are usually prescribed for one to two years after diagnosis, azathioprine is given for two to five years, if not indefinitely (for example, if cirrhosis is present at presentation or the patient has experienced a previous relapse). Practice varies, however, with some clinicians withdrawing treatment if a follow-up liver biopsy is reported as showing no inflammatory activity. Appropriate discussion is needed of the possible long term risk of lymphoma with azathioprine.[w13] Disease flare-ups can be seen post-partum, and azathioprine use during pregnancy has not been associated with adverse outcomes.[w14]

Ursodeoxycholic acid in primary biliary cirrhosis and primary sclerosing cholangitis

Primary biliary cirrhosis

Most patients with primary biliary cirrhosis and abnormal liver biochemistry are prescribed lifelong ursodeoxycholic acid, at a daily dose of 13-15 mg/kg. This hydrophilic bile acid is safe, with few side effects (weight gain about 3 kg, hair thinning, and diarrhoea). Overall a combined analysis of three controlled trials showed a reduction of a third in the risk of death or transplantation for treated patients with moderate to severe disease.[19] The Cochrane group, however, found no effect on the incidence of death and/or transplantation despite improvements in serum bilirubin, jaundice, and ascites for treated patients.[20] Another meta-analysis found that ursodeoxycholic acid improved survival without transplantation; the authors suggested that the difference between their finding and the Cochrane group's finding was their study's restriction to trials with optimal dosing.[21] Falling mortality and transplantation trends have also been taken to confirm an effect of treatment.[w15 w16]

Primary sclerosing cholangitis

Ursodeoxycholic acid has been evaluated in primary sclerosing cholangitis, but studies repeatedly fail to show benefit despite improvements in liver biochemistry. Encouraging results were seen in a two year, double blind, placebo controlled study of 26 patients with primary sclerosing cholangitis randomised to 20 mg/kg a day of ursodeoxycholic acid or placebo.[22] A randomised, placebo controlled study (ursodeoxycholic acid at 17-23 mg/kg a day) found significantly improved liver biochemistry but no difference for the end point of death or liver transplantation.[23] Most recently a randomised, placebo controlled study of high dose ursodeoxycholic acid (28-30 mg/kg a day), in 150 patients, reported no benefit but more importantly potential harm.[24] Liver transplantation, when indicated, represents the only potentially curative option, although recurrence in the new graft is common (occurring in about one in five patients). Colectomy before or after transplantation for those with colitis may reduce recurrence.[w17]

Alternative agents

A randomised trial of newly diagnosed non-cirrhotic patients with autoimmune hepatitis found that budesonide, a steroid with high first pass metabolism, was

AREAS FOR FUTURE RESEARCH

Biology

- Probe the genetic variants associated with disease risk as an unbiased means to better understand the pathology
- Develop more realistic animal models of disease
- Identify early markers of poor outcome

Clinical

- Improve the epidemiological evaluation of autoimmune liver disease to better define the aetiology
- Clarify the role of alternative agents to prednisolone in managing autoimmune hepatitis
- Identify alternatives to ursodeoxycholic acid for non-responders in primary biliary cirrhosis
- Validate diagnostic criteria of disease in widespread practice
- Define the basis of overlap syndromes
- Develop treatments that alter the natural course of primary sclerosing cholangitis
- Identify secondary aetiologies of sclerosing cholangitis early to allow treatment
- Identify markers of future cholangiocarcinoma to prevent disease

Symptoms

- Learn why patients complain of fatigue in order to intervene more successfully
- Improve the understanding of itch, a distressing and difficult symptom

Table 3 | Management of symptoms of autoimmune liver disease in general practice

Symptom	Management suggestions
Pruritus:	
First line treatment	Daily cholestyramine (4 g before and after breakfast; other medication 1 h before or 4 h after cholestyramine)
Second line treatment	Oral rifampicin 150-300 mg twice daily (monitor for drug toxicity by blood counts as well as renal and liver biochemistry)
Third line treatment	Sertraline 50-100 mg once daily
Fourth line treatment	Naltrexone (maximum 100 mg a day; usually after a trial of infusion naloxone)
For urgent relief	Plasmapheresis or albumin dialysis
Supportive relief	Ultraviolet light therapy
Definitive	Rarely liver transplant
Sicca complex*	Dental hygiene, artificial tears (lubricant eye drops); if symptoms are severe refer to ophthalmologist
Dyspareunia	Vaginal lubricants
Raynaud's phenomenon	Advise patients to avoid precipitants, wear gloves, and consider calcium channel blockers
Fatigue	Consider alternative aetiologies (anaemia, depression, side effects of drugs, Addison's disease, autonomic dysfunction) and recommend exercise; no evidence for drug intervention
Non-specific abdominal pain	Exclude alternative aetiologies (gallstones, cholangitis) ; reassure and manage symptomatically

*Xerostomia plus xerophthalmia.

an alternative for inducing and maintaining remission with fewer side effects than prednisolone.[25] If treatment fails in autoimmune hepatitis (with particular risk groups being younger patients with more acute, severe disease) a review of the diagnosis and evaluation for non-compliance is an essential first step. There are no established second line treatments, although several immunosuppressants—for example, ciclosporin A, tacrolimus, and mycophenolate mofetil—are described in non-randomised reports.

In a Spanish cohort of 192 patients with primary biliary cirrhosis, a biochemical response to ursodeoxycholic acid defined as normalisation of alkaline phosphatase or a >40% fall after one year, predicted an outcome equal to that of healthy individuals.[26] Similarly a French cohort (n=292) found a treatment response defined as an alkaline phosphatase level of ≤3× upper limit, an aspartate aminotransferase level of ≤2× upper limit, and bilirubin level ≤17.1 µmol/l after one year, predicted a 10 year transplantation-free survival rate of 90% compared with 51% for non-responders.[27] Definitive trial data for non-responders to ursodeoxycholic acid for agents such as farnesoid X receptor agonists, antiretroviral drugs, and fibrates are awaited.

The lack of any effective treatment for primary sclerosing cholangitis is evidenced by the numerous uncontrolled studies of other treatments, particularly antibiotics (such as vancomycin, metronidazole, minocycline). A Cochrane review of steroid treatment found no benefit.[28] A derivative of ursodeoxycholic acid, nor-ursodeoxycholic acid, showed promising efficacy in an animal model of disease, but data for humans are awaited.[w18]

Symptoms and surveillance

A combined approach by family physicians and specialists (including nurses) facilitates patient education, compliance, and monitoring for treatment side effects (see the box on nurse specialists and the patient's perspective box). Fatigue and pruritus are multifactorial in aetiology and challenging to treat (table 3).

Cholangitis (right upper quadrant pain, jaundice, fevers, dark urine, pale stools) requires prompt antibiotics (such as ciprofloxacin) and sometimes hospital admission. Cross sectional and case-control evidence exists for greater prevalence of osteoporosis in cholestatic disease, and guidelines suggest baseline bone densitometry and treatment if indicated.[29] In cirrhotic patients, surveillance for oesophageal varices and screening for hepatocellular carcinoma are indicated; portal hypertension may also occur in precirrhotic cholestatic liver disease.[w19]

Primary sclerosing cholangitis is a premalignant condition, and the annual incidence of cholangiocarcinoma is about 1%; in one cohort study, cholangicarcinoma was diagnosed within the first year after

The role of nurse specialists in autoimmune liver disease management

- Patients may have varying presentations, from asymptomatic through to liver failure, making patient education varied and difficult. Treatment is often beneficial, but the diseases are chronic, and a particular role for the nurse is to educate patients about the causes and consequences of their disease
- Many patients are young and do not feel ill but nevertheless need regular blood tests and treatment. As with other chronic diseases, the relationship built between the medical team and the patient often correlates with treatment compliance, and the continuity offered by nurse specialists can be pivotal in this regard
- In pregnancy the nurse specialist can support and monitor the patient, providing reassurance and advice
- A nurse specialist for an uncommon disease such as autoimmune liver disease acts as a go-between for the patient, the general practitioner, and the specialist and can significantly help to coordinate care, which would ideally be delivered close to the patient's home

A patient's perspective

Thirty four years ago, when I was 19, my doctor found a small mass in my thorax area. A non-malignant cyst was to be removed. Blood tests, though, indicated jaundice and abnormal clotting. After a month I was told that I had autoimmune hepatitis and should not engage in sports and not have children. I had a splenectomy and a radical tubal ligation. I was fortunate that the doctor had become aware of azathioprine. I thus took azathioprine, along with prednisone, and today I am on maintenance therapy. This is, from my perspective, the only indication that I have disease.

I chose to believe that since I did not feel or look sick I would not limit myself. I have an advanced university degree and have worked in business all my life. I travel the world and have been active in competitive rowing, beach volleyball, and golf. I do meditation and yoga. So what have I learnt? The key for health professionals is to listen to their patients. At 19 I believed if I didn't look sick I wasn't sick and I could do anything I wanted. It seems to have worked for me at least.

Christine Maxwell, Toronto

SOURCES AND SELECTION CRITERIA

We used a combination of professional body consensus, personal practice, and a PubMed search using the terms primary biliary cirrhosis, autoimmune hepatitis, and sclerosing cholangitis

ADDITIONAL EDUCATIONAL RESOURCES

For healthcare professionals

- Liver Centre, Toronto Western Hospital (www.torontoliver.ca)—Clinical and educational resources for those interested in chronic liver disease
- British Association for the Study of Liver (www.basl.org.uk/)—National site for British liver disease specialists with relevant links across the specialty
- NHS Evidence—Gastroenterology and Liver Diseases (www.library.nhs.uk/Gastroliver/)—Specialist collection of the NHS Evidence resource that aims to provide access to the best available evidence in gastroenterology and liver diseases

For patients

- British Liver Trust (www.britishlivertrust.org.uk/)—National charity working to reduce the impact of liver disease in the UK through support, information, and research
- AIH Support Group (www.autoimmunehepatitis.co.uk/)—Provides information and support groups for people with autoimmune hepatitis
- PBC Foundation (www.pbcfoundation.org.uk/)—Charity providing support and information to people with primary biliary cirrhosis and to their families and friends
- PSC Support UK (www.psc-support.demon.co.uk/)—Information and forums for people with primary sclerosing cholangitis

diagnosis of primary sclerosing cholangitis in 24 (50%) cases as well as in 13 (27%) patients for whom liver transplantation was planned.[30 w20] Median survival is less than one year, and in most patients the diagnosis involves advanced unresectable disease. Transplantation is contraindicated except in research settings. One meta-analysis of observational studies showed that patients with primary sclerosing cholangitis and ulcerative colitis were four times more likely to develop colonic dysplasia than patients with ulcerative colitis alone,[w21] and this finding has driven the practice of colonoscopy and serial biopsies for all patients followed by surveillance.[w22] Unblinded follow-up of a randomised placebo controlled treatment trial suggests ursodeoxycholic acid reduces colorectal dysplasia in those with colitis.[w23]

Contributors: GMH and SD contributed equally to the preparation of this article, and both are guarantors. PMcG contributed to the section on symptoms and surveillance, including the text, table, and box.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent obtained.

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