Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease characterised by inflammation and fibrosis of the intra- and extrahepatic bile ducts. Although the clinical course varies, most patients develop irregularity of the bile ducts that progresses to biliary cirrhosis (Angulo and Lindor, 1999). The incidence and prevalence of PSC range from 0–1.3 per 100,000 inhabitants per year and from 0–16.2 per 100,000 inhabitants per year respectively. It is more common in males, with a peak incidence at around 40 years of age (Boonstra et al, 2012). Only 6% of irritable bowel disease (IBD) patients will have a defined liver disease, of which 4.6% will have PSC. Conversely, 70% of PSC patients will have associated IBD (predominantly ulcerative colitis (UC)) (Mowat et al, 2011). The outcome of PSC is unrelated to colitis disease activity and is not influenced by colectomy. Between 10% and 20% of PSC patients will develop hepatobiliary malignancy in their lifetime, most commonly cholangiocarcinoma, which is often advanced with no curative options available at the time of diagnosis. Understandably, this is a major source of anxiety for PSC patients. There is the additional concern that patients with PSC and colitis are at an increased risk of colorectal carcinoma, compared with patients with colitis alone (Boonstra et al, 2012).

Symptoms

PSC is a progressive disease characterised as either symptomatic or asymptomatic. Patients often may be asymptomatic for prolonged periods of time, and only 50% will be symptomatic at first presentation (European Association for the Study of the Liver (EASL), 2009). The incidence and prevalence of PSC range from 0–1.3 per 100,000 inhabitants per year and from 0–16.2 per 100,000 inhabitants per year respectively. It is more common in males, with a peak incidence at around 40 years of age (Boonstra et al, 2012). Only 6% of irritable bowel disease (IBD) patients will have a defined liver disease, of which 4.6% will have PSC. Conversely, 70% of PSC patients will have associated IBD (predominantly ulcerative colitis (UC)) (Mowat et al, 2011).

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic disease of the intra- and extra-hepatic bile ducts of the liver, often leading to hepatobiliary malignancy, cirrhosis, end-stage liver disease and a need for liver transplantation. Between 60% and 80% of PSC patients have associated inflammatory bowel disease (IBD) and 4.6% of patients with IBD have PSC. Understanding this disease and its diagnosis, treatment and implications for the patient is essential. This article highlights the gap between the needs of patients with PSC and what medicine can offer them. The aim is to increase awareness of the disease and the issues that health professionals working with PSC patients should be aware of in order to improve the patient experience of living with both these debilitating diseases.
**Fatigue**
Fatigue is difficult to manage, particularly if the patient in addition has IBD, which is also known to cause fatigue. There can be many other underlying causes of fatigue, including anaemia, depression or thyroid problems, and these should be investigated. Lack of evidence to support management of fatigue contributes to it being largely ignored or overlooked by health professionals (Czuber-Dochan et al, 2013).

**Pruritus**
Despite medication being available to help with this symptom, many patients are not aware and try to tolerate the itch (PSC Support, 2015). They may not be offered medication or may not realise that alternatives are available if first-line treatment is ineffective.

**Bacterial cholangitis**
Bacterial cholangitis flares in PSC (with a combination of fever, abdominal pain and jaundice) can occur and are a real problem for patients, especially newly diagnosed patients and those unfamiliar with the symptoms. Often, it does not present with the classic symptoms of high fever, severe pain and high white blood cell count, and can involve a spectrum of less specific symptoms. This means that inexperienced or non-specialist clinicians (and patients themselves) may not recognise the symptoms as being due to cholangitis. A true flare requires antibiotics. Nursing staff working with PSC patients are key to educating about symptoms and understanding what to do in the event of a cholangitis attack, helping patients understand the signs, and supporting those who feel they are having an attack by expediting antibiotic treatment and expert follow-up. For example, a bout of cholangitis justifies repeat magnetic resonance cholangiopancreatography (MRCP), to look for evidence of a dominant stricture (Chapman, 2010).

**Cancer risk**
Between 8% and 18% of patients with PSC develop a form of bile duct cancer (cholangiocarcinoma). It is often diagnosed at an advanced stage and has a very poor prognosis, with an average survival of less than 1 year (Björnsson and Angulo, 2007). Age, bilirubin, albumin and transaminase levels, variceal bleeding, advanced histological stage and the presence of IBD, particularly UC, have been associated with a poor prognosis (Parés, 2011). Other hepatobiliary and pancreatic malignancies are also more common in PSC (Björnsson and Angulo, 2007).

**Psychological issues**
This is poorly studied, but the unpredictable course of the disease and possible need for liver transplantation, the lack of effective medical therapy and the significant cancer risk associated with the condition creates a significant burden for PSC patients (Boonstra et al, 2012). As a consequence, there is a need to be aware of these issues and be positioned to provide support and signposting for PSC patients in need.

PSC symptoms can become such a normal part of a patient’s life that they become resigned to them, not mentioning even the most difficult symptoms, unless prompted. This means that they may go uninvestigated and manageable symptoms are overlooked. Nurses can help by proactively asking PSC patients about specific symptoms, and supporting and educating them about symptom management.

**Diagnosis**
The diagnosis of PSC is based on clinical manifestations and abnormal liver function tests with a cholestatic pattern (raised alkaline phosphatase), the latter of which accounts for 15–45% of cases (Chapman et al, 2010). Liver test abnormalities are common in up to one-third of patients with IBD (Mendes et al, 2007), particularly due to drug-induced hepatotoxicity. Further investigation is warranted in the absence of a known cause of biliary obstruction. The diagnosis requires stricturing and dilatation of the intra- and/or extrahepatic bile ducts on imaging in the absence of a cause of secondary sclerosing cholangitis (Mowat et al, 2011). An ultrasound of the liver is required to rule out other causes of biliary obstruction, such as gall stone disease. However, PSC is diagnosed by evidence of dilatation and stricturing on bile ducts, and therefore ultrasonographic assessment may not show abnormal duct patterns (Van Assche et al, 2012).
In the event of a normal ultrasound scan, and when other factors such as drug side-effects and other primary liver diseases have been excluded using serological tests (Box 1), the probability of PSC is significantly increased (Van Assche et al, 2012). The established first-line diagnostic test for PSC is MRCP, which has superseded endoscopic retrograde cholangiopancreatography (ERCP) to make a diagnosis (Mowat et al, 2011). In the event of a normal MRCP, a liver biopsy is generally advised over ERCP, as PSC may only affect the intrahepatic small ducts and biopsy is more diagnostic, particularly when there is no extrahepatic biliary structuring on imaging (Parés, 2011; Van Assche et al, 2012). Despite this, a liver biopsy is often not necessary to diagnose PSC; recent guidelines suggest that a liver biopsy should only be indicated in patients without evidence of fibrosis and/or stenosis of the extrahepatic bile duct (EASL, 2009).

### Box 1. Investigations to diagnose primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Routine blood tests</th>
<th>Liver function tests</th>
<th>Full blood count</th>
<th>Urea and electrolytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver screen</td>
<td>Auto-antibodies (antinuclear, anti-smooth muscle, antineutrophil cytoplasmic, antimitochondrial)</td>
<td>HCV and hepatitis B serology</td>
<td>International normalised ratio (INR)</td>
</tr>
<tr>
<td></td>
<td>Immunoglobulins (IgG, IgM, IgG4)</td>
<td>Tumour markers (alpha-fetoprotein, Ca19-9, carinoembryonic antigen)</td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>Liver ultrasound</td>
<td>Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP)</td>
<td>Endoscopic retrograde cholangiopancreatography (ERCP)</td>
</tr>
<tr>
<td></td>
<td>Liver biopsy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Boonstra et al, 2012

### Medical treatments

PSC is considered an autoimmune disorder for which there is no curative treatment. The symptomatic treatment of PSC is similar to that of other cholestatic diseases, the primary aim being to treat the complications of the disease. Pruritus, osteopenia and vitamin deficiencies due to malabsorption are the most common. Pruritus is usually managed using colestyramine, although rifampicin can be used as a second-line agent (Parés et al, 2010). Patients who are refractory to drug treatment for pruritus may benefit from a trial of albumin dialysis or plasma exchange (Parés et al, 2010). As prophylaxis against vitamin deficiencies, calcium and vitamin D supplements are routinely prescribed. Patients with severe cholestasis are recommended intramuscular vitamins A and K. Patients with osteoporosis should be treated with agents that improve bone mass, such as bisphosphonates (Parés and Guanabens, 2008).

Recent studies have shown that the use of ursodeoxycholic acid (UDCA), which has been widely used in the past, does not appear to have any effect in preventing PSC progression (Van Assche et al, 2012). However, many specialised centres still use UDCA at a dose of 13–15 mg/kg/day, which appears to be safe. Additionally, many patients have been receiving UDCA at this dose for some years, and withdrawal of a long-term medication can have adverse psychological and biochemical effects, even if the drug has no long-term benefit (Cullen et al, 2008; Chapman, 2010). Clinical trials have shown that UDCA given at a higher dose of 20–30 mg/kg/day has adverse effects and contributes to a worse outcome in PSC, despite improvements in liver function. Therefore, higher doses of UDCA are counterproductive, and should not be administered to PSC patients (Mitchell et al, 2001; Olsson et al, 2005).

Bacterial cholangitis often requires empirical antibiotics, and on occasion it is advisable to use regular and cyclical antibiotics, such as ciprofloxacin, metronidazole or norfloxacin, for periods of 3–4 weeks as prophylaxis against recurrent cholangitis (Parés, 2011). Many other pharmacological treatments, including immunosuppressive agents (corticosteroids, azathioprine, methotrexate, mercaptopurine, tacrolimus, ciclosporin and mycophenolate mofetil) have been used to slow PSC progression.
of PSC, although none of these agents have shown favourable results (Parés, 2011).

New and emerging treatments
Recently, there has been increasing interest in evaluating new treatments that may be effective in preventing the progression of PSC. There are three main targets for new therapies based on the pathology of the disease. These new treatments target the protection of the bile ductular cells (cholangiocytes) that are damaged in PSC, the inflammatory infiltrate into the liver (in particular, around the portal tracts), and biliary-based fibrosis. Consequently, the medical therapies under evaluation are:

- **Bile acids** (obeticholic acid, nor-ursodeoxycholic acid and apical sodium-dependent bile acid transporter inhibitors)
- **Modifiers of the immune response within the liver** (vedoluzimab and VAP-1 inhibition)
- **Anti-fibrotic therapies** (LOXL-2 inhibitors).

All of these agents are currently undergoing multi-centre, early-phase clinical trails to establish safety and efficacy in patients with SC.

Endoscopic treatment
Biliary strictures are found in more than 50% of PSC patients (Weismüller and Lankisch, 2011). The principal symptoms of stenosis in the ducts are jaundice, pruritus, pain and bacterial cholangitis. Endoscopic therapy provides biochemical and clinical improvement. It is important to exclude the diagnosis of cholangiocarcinoma when a PSC patient presents with a dominant bile duct stricture. This usually requires one or several endoscopic procedures, namely ERCP and/or endoscopic ultrasound (EUS) to sample the stricture. The European Liver Society and American Liver Society guidelines recommend the use of ERCP and balloon dilatation over stent insertion to reduce episodes of cholangitis (EASL, 2009). Patients require prophylactic antibiotic therapy prior to endoscopy, and if patients become refractory to endoscopic treatment surgical therapy may be performed (EASL, 2009).

Surgical treatment
Liver transplantation is the last therapeutic option for patients diagnosed with PSC. Transplantation is indicated for:

- Persistent jaundice refractory to endoscopic therapy
- Manifestations of decompensated liver disease with complications, such as variceal bleeding, ascites and hepatic encephalopathy
- Recurrent bacterial cholangitis and pruritus that is refractory to conventional medical therapy in the absence of stenosis that can be treated by radiological and/or endoscopy (Campsen et al, 2008).

The expected survival after a liver transplant is 80–90% in the first year and 60–80% at the fifth year (Eksteen, 2014). It is well documented that the recurrence of PSC in a patient with a transplanted liver has an incidence of up to 20% from the first year of the liver transplant (Graziadei et al, 1999). The probability of recurrence of PSC after a liver transplant is related to patient age, sex, the coexistence of IBD, cytomegalovirus infection and whether the liver is coming from a live donor (Campsen et al, 2008).

Outpatient management

Outpatient follow-up models
The outpatient management of PSC is inconsistent throughout the UK, and often depends on the local provision of liver and gastroenterological care, which itself is inconsistent across the UK. Many patients are looked after by gastroenterologists with an interest in IBD but no specific liver interest. There are several tertiary referral hepatology centres in the UK but only seven liver transplant centres, with the transplant centres usually treating PSC cases that are the most complex. PSC, particularly when patients become symptomatic or develop complications or cirrhosis, requires care from clinicians experienced in dealing with the disease.

The impact on patients’ quality of life can be substantial, particularly in view of the fact that many travel for hours for hospital visits, especially from regions such as northwest England. This distance can mean that communication between centres is disjointed, particularly if patients also have IBD and require coordination of care between hepatology and gastroenterology teams. The care of PSC patients requires multidisciplinary coordination between outpatient, endoscopy, radiology and surgical teams and, in the case of those with UC, the gastroenterology team.
An ideal model for patients with PSC and IBD is joint working between key interested consultants and specialist nurses, to ensure adequate information and expert care are provided. Therefore, IBD nurses in particular (and hepatology nurses, where available) have a central role in supporting the care of patients with PSC. Regular audit, maintaining dedicated databases and links to specialist centres to allow participation in clinical trial are key to ensuring better patient experience, outcomes and disease management.

In general, patients with uncomplicated and asymptomatic disease will require review a minimum of once a year, with a surveillance ultrasound to review the appearance of the gallbladder, symptoms, and liver biochemistry. MRI should be undertaken if there has been a change in symptoms, occurrence of cholangitis or if liver biochemistry has deteriorated (EASL, 2009). Patients with symptomatic disease or who exhibit features of advanced or complicated disease will require more frequent liver review. This is best undertaken by a liver clinician, ideally someone with a particular interest in the disease (Mowat et al, 2011; Van Assche et al, 2012). Once cirrhotic, PSC patients should undergo the standard endoscopic and ultrasound surveillance recommended for other aetiologies of cirrhosis (Mowat et al, 2011; Van Assche et al, 2012). The case study highlights the impact of PSC in IBD and the importance of collaborative management and monitoring of this patient group.

**Colorectal cancer risk**

UC patients are known to be at a higher risk of colorectal neoplasia (Soetikno et al, 2002; Jess et al, 2007). The cumulative risk of colorectal cancer is estimated to be 9% after 10 years, 31% after 20 years, and 50% after 25 years of colitis. Screening guidelines (Cairns et al, 2010) recommend annual colonoscopy from diagnosis of UC (Figure 1), and for this to continue following liver transplantation due to the risk of disease recurrence, or following pouch formation.

**The patient’s perspective**

A diagnosis of PSC is often unexpected and devastating. Because PSC is rare, patients can...
feel isolated and lonely. Furthermore, they must deal with the social stigma associated with all liver disease, despite PSC being autoimmune (Boonstra et al, 2012) Thus, newly diagnosed PSC patients can be hungry for information about this poorly understood disease. However, overwhelmed with the life-altering news that their disease is incurable, the use of unfamiliar terms and the whole of the internet to search, they are not always equipped to critically evaluate the content and sources of PSC-related information. Nurses can help by signposting patients to sources of up-to-date, reliable and accurate information, such as the website of the UK’s national PSC charity, PSC Support (www.pssupport.org.uk), which also provides much-needed emotional support for patients.

PSC is complicated, and effective clinical care requires specialist understanding and experience. As nearly 80% of PSC patients also have IBD (and/or another autoimmune condition), they are faced with managing a plethora of symptoms and diverse medications under the care of multiple specialities. A recent survey conducted by PSC Support (2015) found that 81% of PSC patients had suffered with fatigue in the previous month, 49% with itching and 47% with upper-right quadrant pain. Living with pain, itching and fatigue is a daily reality for many PSC patients.

One of the most difficult aspects of living with PSC for patients can be the fear and anxiety around an uncertain future, especially considering the increased cancer risks and lack of curative treatment. Patients desperately want a cure. Research conducted by PSC Support (2015) found that patients have a strong willingness to help and positive attitude towards PSC research, with many stating they would be happy to participate in clinical trials requiring invasive procedures, such as liver biopsy (53%), ERCP (54%) and colonoscopy (57%), if it meant advancing the knowledge and understanding of this disease. Nurses can help by being informed about the latest clinical research and trials, sharing that information with interested patients and helping them access the trials.

PSC Support (2015) found that most PSC patients with IBD do not have access to an IBD nurse. However, those patients that do share feel that their nurses are a valuable asset, supporting their care in important ways. It is difficult for PSC patients to know when and who to contact when their symptoms are exacerbated or new ones appear; they frequently complain of being unable to easily access timely expertise when it is genuinely needed. IBD nurses are an important point of access to support and help, and the resulting prompt management and action can avoid a hospital stay or the need for a consultant appointment.

During a recent patient focus group arranged by PSC Support, a patient commented about IBD nurse specialists:

‘Any queries/worries were answered over the phone on the same day, which was fantastic. They also dealt with getting new

Case study: primary sclerosing cholangitis
A 20-year-old non-smoking woman who did not drink alcohol was referred to the liver clinic for evaluation. She was diagnosed in another hospital with pan-ulcerative colitis (UC) on colonoscopy 10 months earlier. Magnetic resonance enteroclysis was normal, but revealed features of intra- and extrahepatic primary sclerosing cholangitis (PSC). Liver biochemistry was compatible with this diagnosis, with an elevated alkaline phosphatase and a normal bilirubin. She complained of pruritus, intermittent upper-right quadrant pain, fatigue, diarrhoea 8 times in 24 hours (with night rising), and arthralgia affecting the knees, back and hands. She was taking high-dose long-acting mesalazine. Prednisolone had been discontinued 3 months earlier (due to severe side effects), and azathioprine had been noted to worsen her liver function tests and hence had been discontinued a month beforehand. Examination was unremarkable. An opinion was sought as to whether there was any contraindication to golimumab treatment for UC in a clinical trial.

In summary, she had PSC with active UC and was intolerant to standard first-line therapies. Her main symptoms referable to the liver were itch and fatigue. She was commenced on cholestyramine for itch and simple analgesics for arthralgia. Her magnetic resonance cholangiopancreatography was reviewed, with features compatible with PSC found, but no evidence of a dominant stricture.

On review at 6 weeks, she continued to complain of itch and diarrhoea. She had not tolerated cholestyramine for itch, and rifampicin was commenced. She had been established on adalimumab in the irritable bowel disease clinic. She thereafter missed some appointments at the liver clinic, until she made contact 5 months later, complaining of worsening upper abdominal pain. Liver function tests were unchanged. She was admitted to hospital for further evaluation.

A computerised tomography (CT) scan revealed a large tumour in the liver hilum replacing the left lobe of liver. There was gross ascites. A drain was inserted, and cytology of the ascites revealed adenocarcinoma. Review in the hepatobiliary multidisciplinary team meeting concluded that she had an inoperable cholangiocarcinoma with malignant ascites on a background of PSC and UC, and was suitable only for palliative chemotherapy. Despite pursuing this course of treatment, her condition progressed rapidly and she died in hospital approximately 6 weeks later.

During a recent patient focus group arranged by PSC Support, a patient commented about IBD nurse specialists:

‘Any queries/worries were answered over the phone on the same day, which was fantastic. They also dealt with getting new...
prescriptions/changes without the need to see a consultant where possible (and over the phone if symptoms changed rapidly, in the hope of avoiding another admission).’

‘The real value of IBD nurses to PSC patients lies in a deep understanding of IBD and the complexities of PSC. This offers an opportunity for a patient to experience empathic care from medical professionals more able to treat them holistically, rather than just as a discrete set of symptoms.

As well as the help and advice that IBD nurses directly deliver, they can further help patients by signposting them to quality online sources of information and support such as PSC Support (http://tinyurl.com/ok2da2u), the British Liver Trust (http://tinyurl.com/2z8srn), the Children’s Liver Disease Foundation (http://tinyurl.com/y2zoe599), and LIVErNORTH (http://tinyurl.com/oun6ok6), in addition to sharing information about local hospital support groups.

Research

There remain many unanswered questions regarding PSC, including whether it is a single disease or a collection of phenotypically similar diseases with differing mechanisms of disease which require differing therapies. There is the need to better stage the disease and improve prediction of prognosis for individual patients, and also to evaluate whether new treatments are effective in changing the natural history of the disease. There is the need to understand and quantify the impairment of quality of life experienced by PSC patients using validated tools, which will help in the evaluation of treatments aimed at tackling the symptoms of the disease, if not the underlying cause. Most importantly, there is the need to identify, evaluate and demonstrate the efficacy of new treatments that are effective in altering the prognosis of the disease.

Due to the relative rarity of the disease, multi-centre collaborative research is required to create large enough cohorts of patients to address many of these unanswered questions about PSC. The UK has been at the forefront of such collaborative research, with the UK-PSC consortium established in 2009. The main aim of this was to establish a large cohort of PSC patients for a genetic association study to identify genetic factors that contribute to the development of PSC. To date, 221 hospitals in the UK have recruited more than 2400 patients. This has provided the platform for a successful application for funding from the National Institute for Health Research (NIHR) in 2014. This will enable more detailed phenotyping and bio-banking of samples, including urine and faeces, and samples taken from colonoscopy and ERCP, from patients from 5 sites in the UK acting as research hubs (Royal Free, London, University College Hospital, Oxford, Birmingham, Newcastle and Cambridge). If you have any patients who you feel would be suitable for this study (for criteria, see Box 2), please contact the UK-PSC Consortium Administrator, Claire Barrett, on 01223 746771 or at clb200@medschl.cam.ac.uk, or visit http://tinyurl.com/qefmsxs or http://tinyurl.com/pjgjk7.

Conclusion

PSC is a debilitating condition affecting people of working age who often have busy lives with young families and work commitments. Many patients develop progressive disease, and, unfortunately, treatment options are limited, except for liver transplant in those with advanced disease. Consequently, patients with PSC have many unmet needs, with the large physical and psychological burden of disease. Increased awareness of the symptoms, investigations, ongoing management and research opportunities for these patients will improve their experience and hopefully ensure access to an appropriate level of specialist input, when required. Close communication between hepatology and gastroenterology services is essential for PSC patients. The specialist nurse has a crucial role in this regard, offering pastoral support, coordinating and escalating care where necessary, and signposting patients to support groups when required.

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**Box 2. UK-PSC consortium study inclusion criteria**

- Diagnosis of PSC confirmed by MRCP/ERCP
- Over 16 years of age
- Previous orthotopic liver transplant considered
- Patients with or without IBD

Source: (UK PSC, 2015)
Declaration of interest  The authors have no conflicts of interest to declare.


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