PBC & PSC

Two cholestatic diseases that behave nothing alike · one has effective drugs, the other has surveillance and transplant

Cholestatic ALP
splits two ways

TELL THEM APART *the antibody and the duct anatomy do most of the work*

Feature	Primary biliary cholangitis	Primary sclerosing cholangitis
Who	**Women, middle-aged**, around 90% female	**Men, younger**, often 30s to 40s
Duct affected	**Small intrahepatic** ducts, destroyed by lymphocytic cholangitis	**Large intra- and extrahepatic** ducts, with fibrosing strictures
Serology	**Anti-mitochondrial antibody (AMA) in about 95%**, plus raised IgM. **AMA plus a cholestatic ALP is enough to diagnose without biopsy**	**No diagnostic antibody.** p-ANCA is often positive but is not specific and does not make the diagnosis
Imaging	Usually normal, since the affected ducts are too small to see	**MRCP is diagnostic**: multifocal strictures with intervening dilatation, the **"beaded" appearance**
The association	Other autoimmune disease, especially **Sjogren, thyroid disease and scleroderma**	**Inflammatory bowel disease in most patients, usually ulcerative colitis.** The bowel disease is often mild and can be silent, so **colonoscopy is indicated even without symptoms**
Cancer risk	Hepatocellular carcinoma once cirrhotic	**Cholangiocarcinoma, gallbladder cancer, and colorectal cancer** when IBD is present. This risk defines much of the management

PBC MANAGEMENT *the one place where treatment genuinely changes outcome*

Step	Detail
1. Ursodeoxycholic acid first-line, everyone	**13 to 15 mg/kg/day**, split with food. Improves biochemistry, slows progression and delays transplant. **Start it in every patient with abnormal enzymes regardless of histologic stage**, and continue it lifelong even when second-line therapy is added
2. Assess response at 12 months	Judged on **alkaline phosphatase and bilirubin**. A widely used threshold for inadequate response is **ALP above 1.67 times the upper limit of normal, or a raised bilirubin**. **Roughly 40% respond inadequately**, which is exactly why this scheduled reassessment matters rather than assuming the drug is working
3. Add a PPAR agonist current second-line	**Elafibranor (Iqirvo) 80 mg daily**, a dual PPAR-alpha/delta agonist, or **seladelpar (Livdelzi) 10 mg daily**, a PPAR-delta agonist. Both are given **with UDCA**, or alone if UDCA is not tolerated. Fibrates such as bezafibrate are an off-label alternative and also help pruritus
⚠ Obeticholic acid is no longer an option in the US	It was the original second-line agent, but was **withdrawn from the US market at FDA request over a risk of serious liver injury, including in patients without cirrhosis**, with the approval formally withdrawn in November 2025. **Do not prescribe it**, and update any protocol or teaching that still lists it

PSC MANAGEMENT *no drug alters the disease, so surveillance is the treatment*

Issue	Detail
⚠ No effective medical therapy	Nothing has been shown to change the natural history. **High-dose UDCA is harmful**: it was associated with worse outcomes in trial, so it should not be used. Low-dose UDCA improves the numbers without proven clinical benefit
Dominant stricture	A new stricture with rising bilirubin, jaundice, pruritus or cholangitis needs **ERCP with brush cytology and, where indicated, FISH**, then dilatation. **Never assume a dominant stricture is benign**: cholangiocarcinoma hides there, so get tissue before dilating
Cholangiocarcinoma surveillance	**MRI or MRCP with CA 19-9, usually every 6 to 12 months.** Risk is lifelong and does not track disease duration predictably, so a short history is no reassurance
Colonoscopy	**Full colonoscopy at diagnosis in everyone**, because IBD is frequently present and silent. If IBD is found, **annual surveillance colonoscopy**, since PSC with colitis carries a markedly higher colorectal cancer risk than colitis alone
Cholangitis and transplant	Treat bacterial cholangitis promptly, and note recurrent episodes are an indication to reconsider transplant. **Liver transplantation is the only definitive treatment**, with excellent outcomes, though PSC can recur in the graft

THE MIMICS *one of them is steroid-responsive, so it must not be missed*

Mimic	How it differs, and why it matters
IgG4-related sclerosing cholangitis treatable	**The one you cannot afford to miss.** It looks like PSC on MRCP but **responds dramatically to glucocorticoids**. Suspect it with a raised **serum IgG4**, an associated **autoimmune pancreatitis** or a pancreatic mass, other organ involvement, and an older male patient. **Check IgG4 in every new "PSC"**, because labelling it PSC condemns a treatable disease to surveillance alone
Secondary sclerosing cholangitis	Identical imaging from a known insult: **prolonged critical illness**, ischemia, recurrent bacterial cholangitis, prior biliary surgery, choledocholithiasis, or HIV cholangiopathy. **PSC is a diagnosis of exclusion**, so take the history before accepting the label
AMA-negative PBC	Behaves like PBC but the antibody is absent in around 5%. Diagnosed on **anti-sp100 or anti-gp210** with a compatible biopsy. **Treat it as PBC**, since it responds to UDCA the same way
Drug-induced cholestasis	Common and reversible. Usual culprits include **amoxicillin-clavulanate**, antistaphylococcal penicillins such as oxacillin and nafcillin, anabolic steroids and herbal supplements. **Take a full medication and supplement history before any invasive workup**

SYMPTOMS, COMPLICATIONS & PEARLS

- **Pruritus has a ladder, and it is worth knowing in order: cholestyramine** first (4 g, and **separate it from other drugs by 4 hours** or it binds them), then **rifampin**, then **naltrexone**, then sertraline. Itch is often the symptom that most damages quality of life, and it does not track disease severity.
- **Fatigue is the other dominant symptom** and responds to none of the above. Exclude the treatable contributors, hypothyroidism, anemia and depression, rather than attributing it to the liver by default.
- **Chronic cholestasis causes fat-soluble vitamin deficiency and metabolic bone disease.** Check **vitamins A, D, E and K**, and screen for **osteoporosis with DEXA**, which is common and often overlooked in a young patient who otherwise feels well.
- **A cholestatic ALP with a normal AMA is not automatically PSC.** Confirm the ALP is hepatic with a **GGT**, then think about drugs, infiltration, IgG4-related disease, and **AMA-negative PBC**, which behaves like PBC and is diagnosed on antibodies such as sp100 or gp210 with a compatible biopsy.

References: AASLD practice guidance on primary biliary cholangitis and on primary sclerosing cholangitis · FDA and manufacturer communications on the withdrawal of obeticholic acid (2025) · FDA labeling for elafibranor and seladelpar.

Educational aid; verify against current guidance, local formulary and patient factors.