Cholestatic Liver Disease

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), previously termed primary biliary cirrhosis, is an autoimmune disease affecting the small and medium bile ducts. The female-to-male predominance is 9 to 1. PBC is often asymptomatic but can present with fatigue and pruritus. Liver chemistry tests usually demonstrate a cholestatic pattern of injury, and the alkaline phosphatase may be significantly elevated. Diagnosis of PBC does not require liver biopsy when the ALP level is at least 1.5 times the upper limit of normal and antimitochondrial antibody results are positive or, if results are negative, other PBC-specific autoantibodies, including sp100 or gp210, are present. In patients with negative antibody results and strong suspicion for PBC, liver biopsy is necessary. Elastography can be used for fibrosis staging.

Initial treatment is ursodeoxycholic acid, which results in histologic improvement, improves survival rates, and diminishes the need for liver transplantation. Response to treatment is defined by improvement of the ALP level to less than 1.67 times the upper limit of normal. Patients who present with normal bilirubin and albumin levels and respond to treatment have a life expectancy similar to that of individuals without PBC. Patients whose disease does not respond to ursodeoxycholic acid should receive fibrates (off label) or obeticholic acid.

PBC is associated with other autoimmune conditions, particularly autoimmune thyroid disease. Thus, thyroid-stimulating hormone level should be checked yearly. In patients with cirrhosis and a PBC score of 4.1 or greater (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/updated-natural-history-model-for-primary-biliary-cirrhosis) or transient elastography results of 17 kPa or greater, upper endoscopy is indicated to assess for esophageal varices.

Patients with advanced disease should be managed like other patients with cirrhosis and portal hypertension (see Complications of Advanced Liver Disease). In addition, men with PBC and all patients with PBC and cirrhosis should be screened for hepatocellular carcinoma (see Hepatocellular Carcinoma for recommendations on screening and surveillance). Patients with PBC have increased risk for osteoporosis and should ensure daily intake of 1000 to 1500 mg of calcium and 1000 IU of vitamin D. Bone mineral density should be assessed every 2 years, and bisphosphonate therapy should be considered if the result is in the osteoporotic range. Patients with elevated lipid levels may be at risk for cardiovascular disease and can be considered for lipid-lowering therapy. Fat-soluble vitamin deficiencies should be treated with parenteral or water-soluble supplements. Liver transplant outcomes for patients with PBC are excellent, with a 1-year survival rate greater than 90% and a recurrence rate of approximately 20% at 5 years after liver transplantation. First-degree relatives of patients with PBC, especially women, should be screened by periodically checking ALP level.

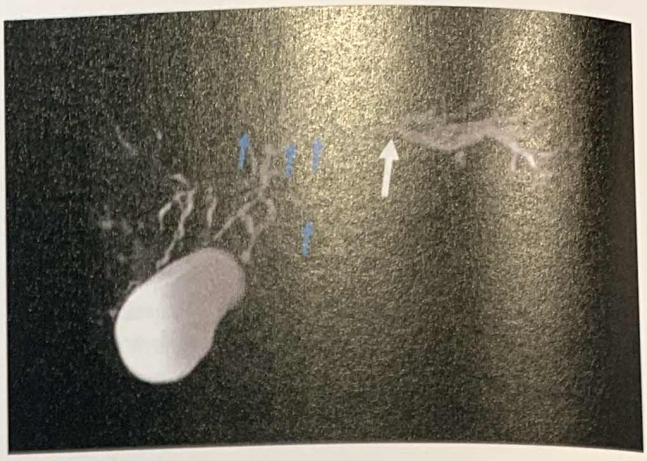

FIGURE 32. Magnetic resonance cholangiopancreatogram showing multifocal intrahepatic and extrahepatic bile duct stricturing (*blue arrows*) with a dominant left-lobe stricture (*white arrow*) and upstream bile duct dilation consistent with the diagnosis of primary sclerosing cholangitis.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is an autoimmune fibroinflammatory disease of the large bile ducts, but it can also affect the small bile ducts (small-duct PSC). It is more common in men than women, which is unique among the autoimmune liver diseases. PSC often presents without symptoms with a cholestatic pattern of liver enzyme abnormalities; pruritus may also be the presenting feature.

PSC can be diagnosed noninvasively through magnetic resonance cholangiopancreatography (MRCP) (**Figure 32**). Diagnosis does not usually require liver biopsy; small-duct PSC, which cannot be diagnosed by MRCP, is an exception. Endoscopic retrograde cholangiopancreatography (ERCP) should be considered in patients with jaundice, worsening pruritus, bacterial cholangitis, or a dominant stricture or bile duct mass on MRCP.

PSC is associated with inflammatory bowel disease (IBD) in about 85% of cases; up to 7.5% of patients with ulcerative colitis have PSC. All patients with PSC without known IBD should have a colonoscopy at the time of PSC diagnosis. Patients with concomitant IBD may have a unique PSC-IBD phenotype, characterized by rectal sparing, mild pancolitis, and backwash ileitis. This carries a higher risk for colon cancer, necessitating colonoscopy with surveillance biopsies every year from the time of diagnosis, as well as a higher risk for pouchitis after total colectomy.

Patients with PSC have a 15% lifetime risk for cholangiocarcinoma. Yearly MRCP and measurement of carbohydrate 19-9 are recommended for cholangiocarcinoma surveillance. The incidence of cholangiocarcinoma is highest in the first 2 years after PSC diagnosis. There is also an increased risk for gallbladder cancer in PSC; regular screening with ultrasonography should be considered. The management of gallbladder polyps is discussed in the Disorders of the Gallbladder and Bile Ducts chapter.

There is no effective medical therapy for PSC; it often requires liver transplantation and has the highest case-based mortality rate among the autoimmune liver diseases. In symptomatic patients, ERCP is used to dilate strictures and remove stones.

Median transplant-free survival for patients with PSC is 12 years. Transplantation should be considered for patients with decompensated cirrhosis, recurrent bacterial cholangitis, and hilar cholangiocarcinoma. Transplant outcomes for patients with PSC are excellent, with 1-year survival rates of at least 90% and recurrence rates of approximately 20% at 5 years after liver transplantation.

KEY POINTS

- For primary biliary cholangitis, ursodeoxycholic acid treatment results in histologic improvement, better survival rates, and diminished need for liver transplantation.
- Primary sclerosing cholangitis is associated with inflammatory bowel disease in about 85% of cases; these patients have an increased risk for colon cancer and require surveillance colonoscopy at diagnosis and every 1 to 2 years.
- Patients with PSC have a 15% lifetime risk for cholangiocarcinoma; annual MRCP and measurement of carbohydrate 19-9 are recommended for cholangiocarcinoma surveillance.

Classification of Liver Disease Severity

The Child-Turcotte-Pugh (CTP) score (**Table 36**) and MELD score (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/) are prognostic in patients with cirrhosis. The 1-year survival rates for CTP class A, B, and C cirrhosis are 100%, 80%, and 45%, respectively.

The MELD formula includes bilirubin level, INR, and creatinine level and is accurate in predicting 3-month mortality. Another version of the MELD score, the MELD-Na (www.mdcalc.com/meldna-meld-na-score-liver-cirrhosis), incorporates the sodium level. The MELD score was the basis for liver transplant allocation until 2016, when the allocation system was changed to include the MELD-Na score because it is a more predictive model of 3-month mortality.

The MELD score can estimate postoperative mortality in patients with cirrhosis (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis).

KEY POINT

- The Model for End-Stage Liver Disease-sodium formula accurately predicts 3-month mortality and is used for liver transplant allocation.

Complications of Advanced Liver Disease

Patients with chronic liver disease from any cause are at risk for cirrhosis. Compensated cirrhosis is uncomplicated and may be asymptomatic or associated with nonspecific symptoms. Patients with decompensated cirrhosis have complications such as ascites, hepatic encephalopathy, and variceal hemorrhage.

Portal Hypertension

Portal venous hypertension develops in the setting of advanced cirrhosis due to obstruction of blood flow caused by intrahepatic fibrosis, regenerating liver nodules, increased intrahepatic vascular resistance, and increased flow via the portal vein. Prehepatic causes, including portal vein thrombosis, and posthepatic causes, such as Budd-Chiari syndrome, can result in portal hypertension in the absence of cirrhosis. Complications of portal hypertension include gastroesophageal varices, ascites, and spontaneous bacterial peritonitis. The presence of these complications heralds a high rate of further complications and mortality and should prompt consideration of liver transplantation. See Vascular Diseases of the Liver for additional discussion of portal vein thrombosis and Budd-Chiari syndrome.

Esophageal Varices

Esophageal varices are enlarged vessels within the lumen of the lower esophagus that provide extrahepatic pathways of blood flow from the portal to the systemic circulation (**Figure 33**).

TABLE 36. Child-Turcotte-Pugh Score[a]

	1 Point	2 Points	3 Points
Encephalopathy	None	Grade I-II	Grade III-IV
Ascites	None	Mild/moderate	Severe
Bilirubin	<2 mg/dL (34.2 µmol/L)	2-3 mg/dL (34.2-51.3 µmol/L)	>3 mg/dL (51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8-3.5 g/dL (28-35 g/L)	<2.8 g/dL (28 g/L)
Prothrombin time above control/INR	<4 s/<1.7	4-6 s/1.7-2.3	>6 s/>2.3

[a]5-6 points = Child-Turcotte-Pugh class A; 7-9 points = Child-Turcotte-Pugh class B; 10-15 points = Child-Turcotte-Pugh class C.