crohn's colitis

Name of Clinical Care Pathway

Primary Sclerosing Cholangitis (PSC)

Objective

Provide direction regarding the screening, management and follow-up for patients with primary sclerosing cholangitis (PSC)

Patient Population

Adult patients (≥18years) with a possible or established diagnosis of PSC

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*These clinical decision support tools were developed by Canadian experts in PSC, based on their interpretation of current evidence and considerations specific to Canadian healthcare. International guidelines from Europe and the United States are available. However, these may reflect regional factors that might not directly be applicable in Canada.*

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## Abbreviations

| | |
|---|---|
| AIH | Autoimmune hepatitis |
| ALP | Alkaline phosphatase |
| AST | Aspartate aminotransferase |
| Ca 19.9 | Carbohydrate antigen 19-9 |
| CCA | Cholangiocarcinoma |
| DEXA | Dual-energy X-ray absorptiometry |
| ERC | Endoscopic retrograde cholangiography |
| GGT | γ-glutamyl transferase |
| Hb | Hemoglobin |
| HbA1c | Hemoglobin A1c |
| HCC | Hepatocellular carcinoma |
| IBD | Inflammatory bowel disease |
| IgG4 | Immunoglobulin G4 |
| INR | International normalized ratio |
| LFTs | Liver function tests |
| LSM | Liver stiffness measurement |
| LT | Liver transplant (or transplantation) |
| MELD | Model for end-stage liver disease |
| MRC | Magnetic resonance cholangiography |
| MRCP | Magnetic resonance cholangiopancreatography |
| MRI | Magnetic resonance imaging |
| MRS | Mayo risk score |
| PSC | Primary sclerosing cholangitis |
| UC | Ulcerative colitis |
| UDCA | Ursodeoxycholic acid |
| ULN | Upper limit of normal |
| VCTE | Vibration-controlled transient elastography |

## Highlight Box

- Patients with IBD should have routine liver function tests, and those with chronic cholestasis (ALP > 1.5 X ULN) should be investigated for PSC with magnetic resonance cholangiography (MRC).
- Approximately 60% to 80% of people with PSC also have IBD, most often ulcerative colitis. Patients might be asymptomatic at diagnosis, which often occurs in their 30s or 40s after routine blood tests show abnormal liver function.
- PSC progresses slowly and unpredictably and increases the risk of cholangiocarcinoma, gallbladder cancer, and, in patients with coexisting IBD, colorectal cancer.
- Patients with high-grade strictures defined as biliary stenosis on MRC with >75% reduction of duct diameter in the common bile duct or hepatic ducts warrant further endoscopic investigation, and those with relevant stricture (cholangitis, pruritus) warrants endoscopic ballon dilation.
- Currently, there is no medical treatment proven to stop or slow the progression of PSC; a liver transplant is the only curative option for advanced disease and liver failure.

## Introduction

PSC is a rare chronic bile duct disease, characterized by multifocal bile duct strictures and progressive liver disease. The current incidence is 0.87 per 100 000 and prevalence 13.53 per 100 000, and it can affect all age groups and both sexes, but is more common in men (>70%). The median age at diagnosis is 30 to 40 years. Inflammatory bowel disease coexists in most patients (~70%), mainly ulcerative colitis (UC).

A major challenge in the clinical management of PSC is a highly increased and unpredictable risk of hepatobiliary and colonic malignancy.

Diagnosis

The diagnosis of PSC is frequently incidental, with 50% of patients being asymptomatic; however, after 5 years of diagnosis, 20% of asymptomatic patients develop clinical symptoms, and 75% exhibit evidence of disease progression, as indicated by biochemical or radiographic changes. The most frequent symptoms are fatigue, abdominal pain, jaundice, pruritus, and fever.

The presence of symptoms has clinical significance, as patients with symptoms at diagnosis have a median survival until death or liver transplant of 9 years, compared to 12-22 years in all patients with PSC.

How is PSC diagnosed in adults?

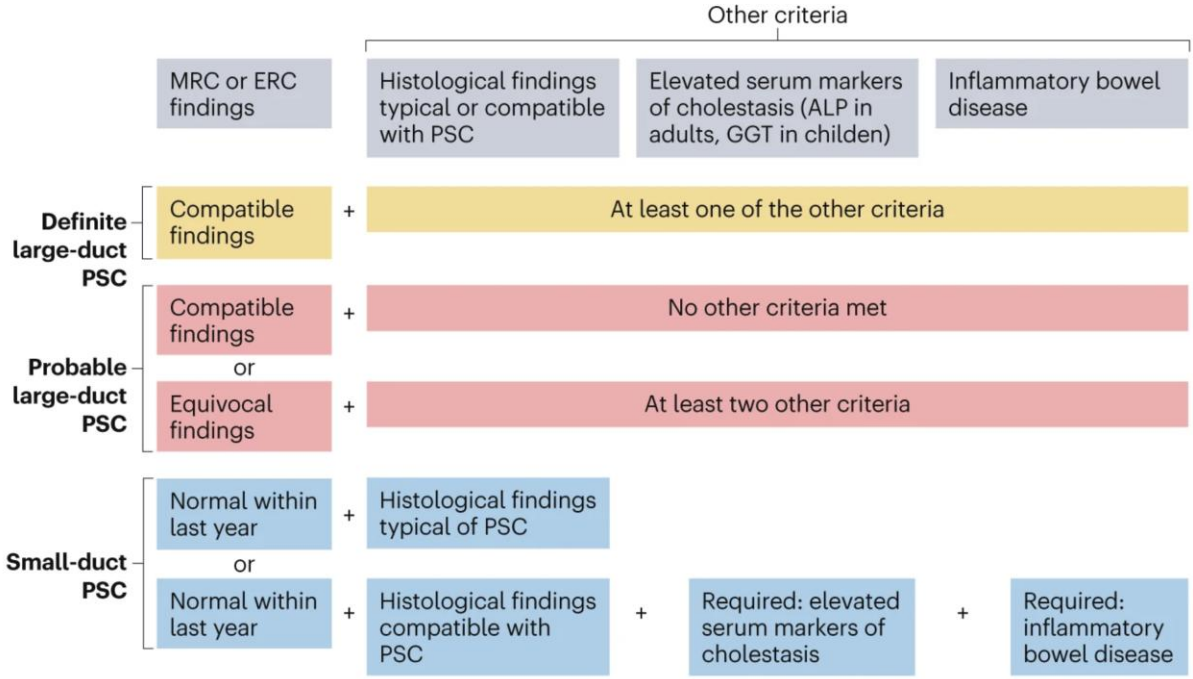
In adult patients presenting with elevated serum markers of cholestasis, a diagnosis of large duct PSC should be made in the presence of typical findings of sclerosing cholangitis on high-quality cholangiography and after exclusion of secondary causes. The preferred diagnostic test is magnetic resonance cholangiography (MRC). A diagnosis of small duct PSC should be considered in patients with elevated serum markers of cholestasis of unknown cause, normal high-quality cholangiography, and compatible histology of PSC, particularly in those with concomitant inflammatory bowel disease (IBD). Autoantibodies should not be used to diagnose or risk-stratify people with PSC.

PSC has been broadly classified into large-duct PSC and small-duct PSC, with large-duct PSCs being further subdivided into extrahepatic disease involving the common ducts or first-order ducts and intrahepatic disease involving second-order and third-order branches.

Patients affected with either form of PSC might present very differently. While many patients with large-duct PSC will present with the classic cholestatic laboratory findings of elevated alkaline phosphatase (ALP) and an abnormal cholangiogram, others can have an atypical presentation that can lead to delays in diagnosis.

The foundation of PSC diagnosis is a magnetic resonance cholangiography (MRC) or endoscopic retrograde cholangiography (ERC) that detects bile duct changes with multifocal strictures or segmental dilatations in the intrahepatic or extrahepatic biliary tree. Patients with small-duct PSC should have had a normal cholangiogram within the preceding year. Small-duct PSC is generally thought to represent an earlier stage of PSC, with rates of progression to large-duct PSC of 33 to 55% reported in observational studies.

Flowchart 1: International Primary Sclerosing Cholangitis study group diagnostic criteria for PSC (Adapted from Manns MP et al.)




Diagnosis of PSC requires assessment of multiple clinical components. In 2021, the International PSC Study Group published their diagnostic criteria for PSC. These criteria initially categorize patients according to the bile duct changes observed with MRC or ERC. Other supportive criteria include histological findings if liver biopsy has been performed, elevated ALP and diagnosis of IBD. By combining the assessment of these criteria, patients can then be categorized into definite large-duct PSC, probable large-duct PSC or small-duct PSC (Flowchart 1).

*For details on differentiating IgG4-SC from PSC, see the Supplementary Resources section.*

Prognosis

Approaches to simple risk stratification of PSC at initial work-up using non-invasive tools.

"Low risk" of events:

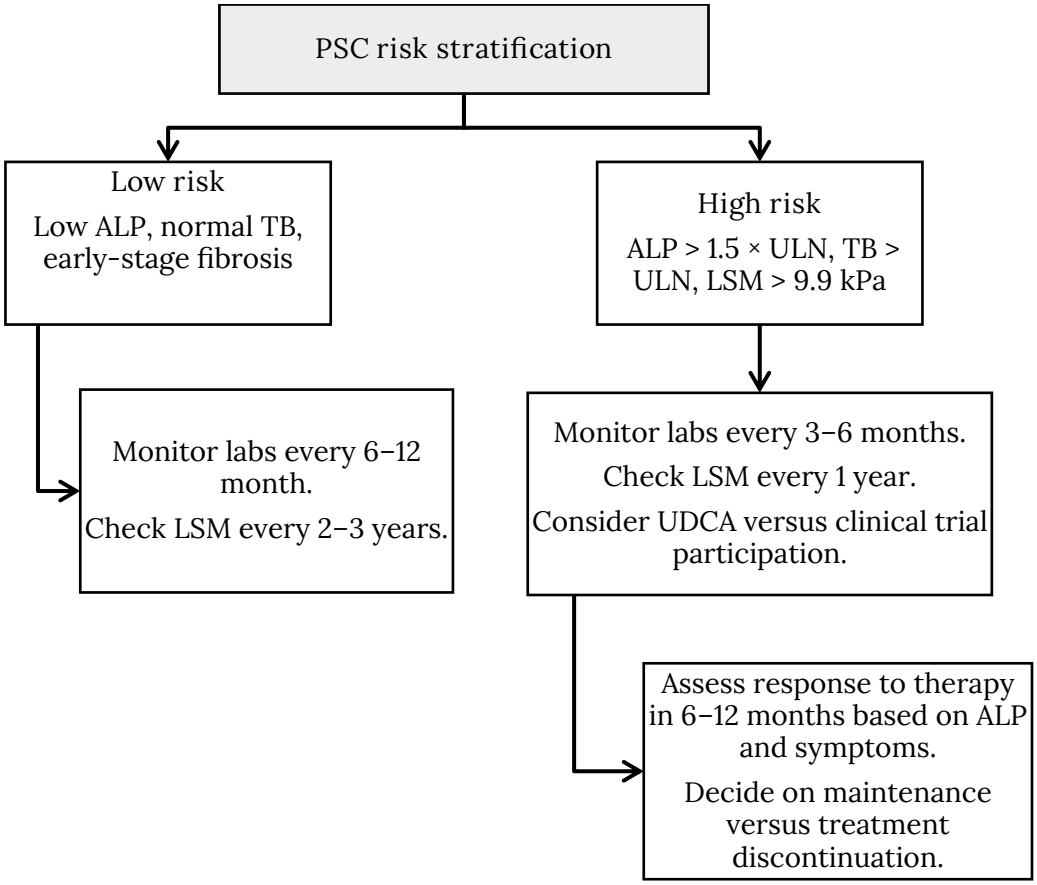
- Small duct PSC and no evidence of cirrhosis
- Classical PSC and (all to be present): asymptomatic with normal bilirubin, albumin, platelets, and INR, ALP <1.5 ULN
- LSM (VCTE) <6.5 kPa, limited biliary changes on MRI/MRCP

"Significant risk" of events, if any present:

- Symptomatic
- ALP >1.5 ULN, abnormal bilirubin, albumin, platelets or INR

LSM (VCTE) >9.9 kPa, extensive biliary changes (especially intrahepatic biliary dilatation) on MRI/MRCP

Flowchart 2: PSC risk stratification



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Risk stratification should be performed at diagnosis of PSC be revisited over time. Variables associated with low risk for disease progression include low ALP, normal total bilirubin level and early-stage fibrosis. For patients at such low risk, monitoring laboratory tests every 6–12 months and repeating non-invasive fibrosis assessment with liver stiffness measurement (LSM) every 2–3 years is recommended.

By contrast, patients with elevated ALP levels, elevated bilirubin and/or increased liver stiffness are at high risk for progression to cirrhosis, clinical liver decompensation, liver transplant or death. Liver chemistries of these patients should be monitored every 3–6 months and liver stiffness be rechecked annually.

In addition, they would benefit from a trial of treatment with ursodeoxycholic acid (UDCA) or consideration for clinical trial participation. If UDCA is initiated, response to therapy should be assessed in 6–12 months based on symptoms and laboratory tests. If significant improvement is not observed, the drug should be discontinued.

*Validated prognostic models are summarized in Supplementary Table S1.*

Medical treatment

There is no effective medical treatment. ursodeoxycholic acid (UDCA) at doses of 15 mg/kg/d can be given since it may improve serum liver tests and surrogate markers of prognosis; however, available data do not allow for a firmer recommendation. UDCA at doses of 28-30 mg/kg/d should not be given.

A multicentric study was stopped early since UDCA at high dose (28 to 30 mg/kg/day) increased the risk of disease progression and worse outcomes, defined as cirrhosis development, varices, CCA, LT, or death, mainly in patients with early-stage.

In addition, high-dose UDCA was also associated with an increased risk of colorectal neoplasias among patients with UC.

Long-term use of antibiotics is not recommended for the treatment of PSC in the absence of recurrent bacterial cholangitis.

High-grade strictures in PSC

In PSC, high-grade strictures, previously known as dominant strictures, develop in a significant portion of patients, ranging from 36% to 56%.

These strictures, which are narrowed areas in the bile ducts, can lead to impaired bile drainage, causing symptoms like jaundice, pruritus, and recurrent cholangitis.

Recommendations:

Abandon the term “Dominant stricture”

High-grade stricture: A biliary stricture on MRI/MRCP with >75% reduction of duct diameter in the common bile duct or hepatic ducts. This warrants diagnostic work-up, with endoscopic retrograde cholangiopancreatography (ERCP), with brush cytology, or cholangioscopy with targeted directed biopsies if available (Refer to Figure 1).

Relevant stricture: A high-grade biliary stricture on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis, warrants endoscopic therapy with balloon dilation.

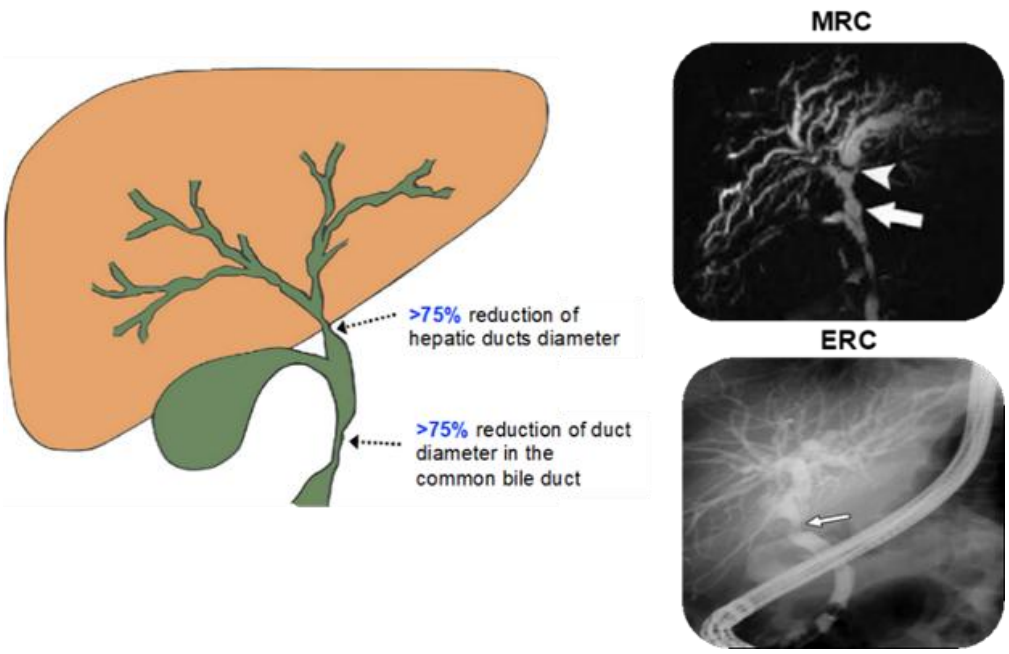


Figure 1: High-grade biliary strictures in primary sclerosing cholangitis.
Diagram and imaging examples showing >75% reduction in duct diameter involving the hepatic ducts (top) and the common bile duct (bottom). *Adapted from Fung BM et al.*, 2019



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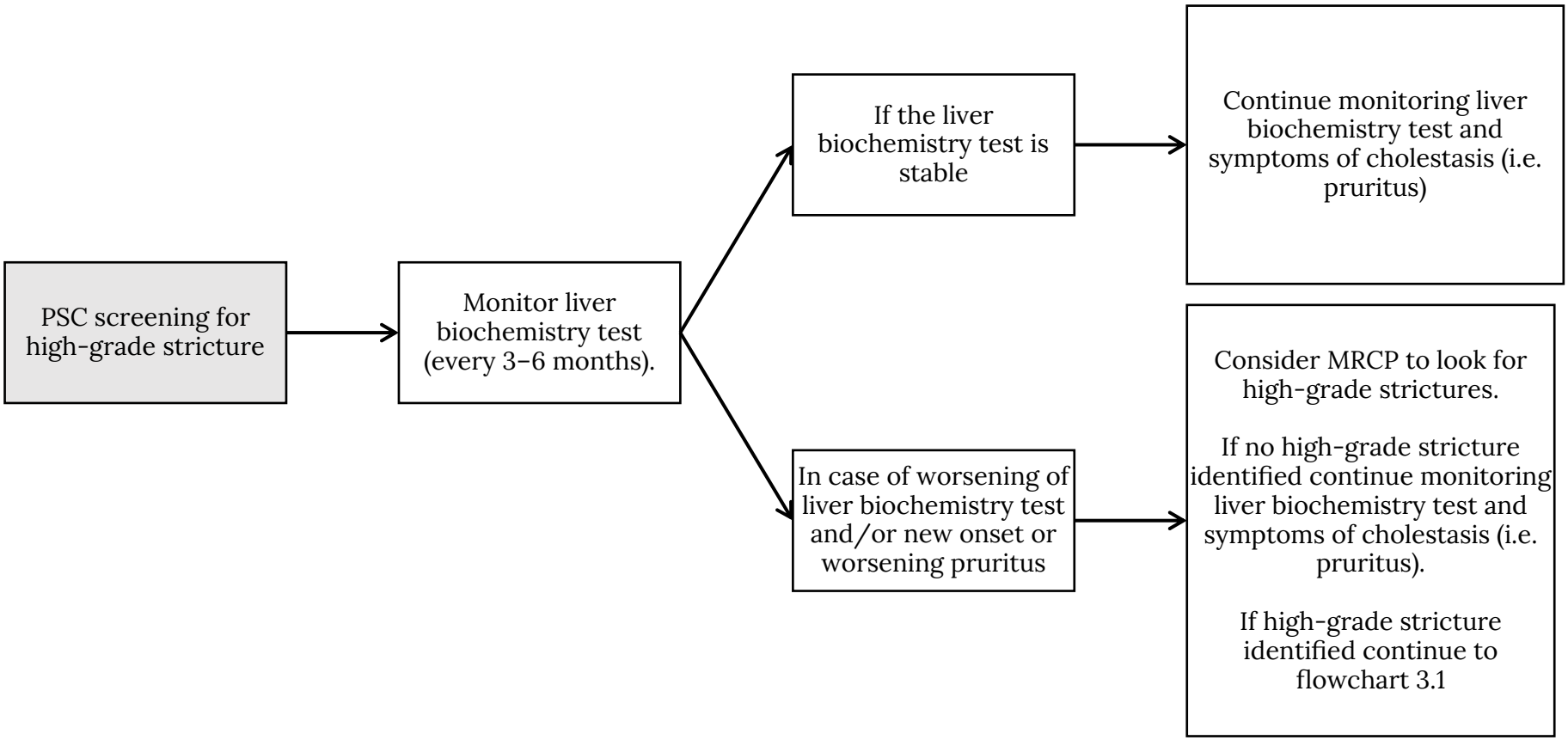
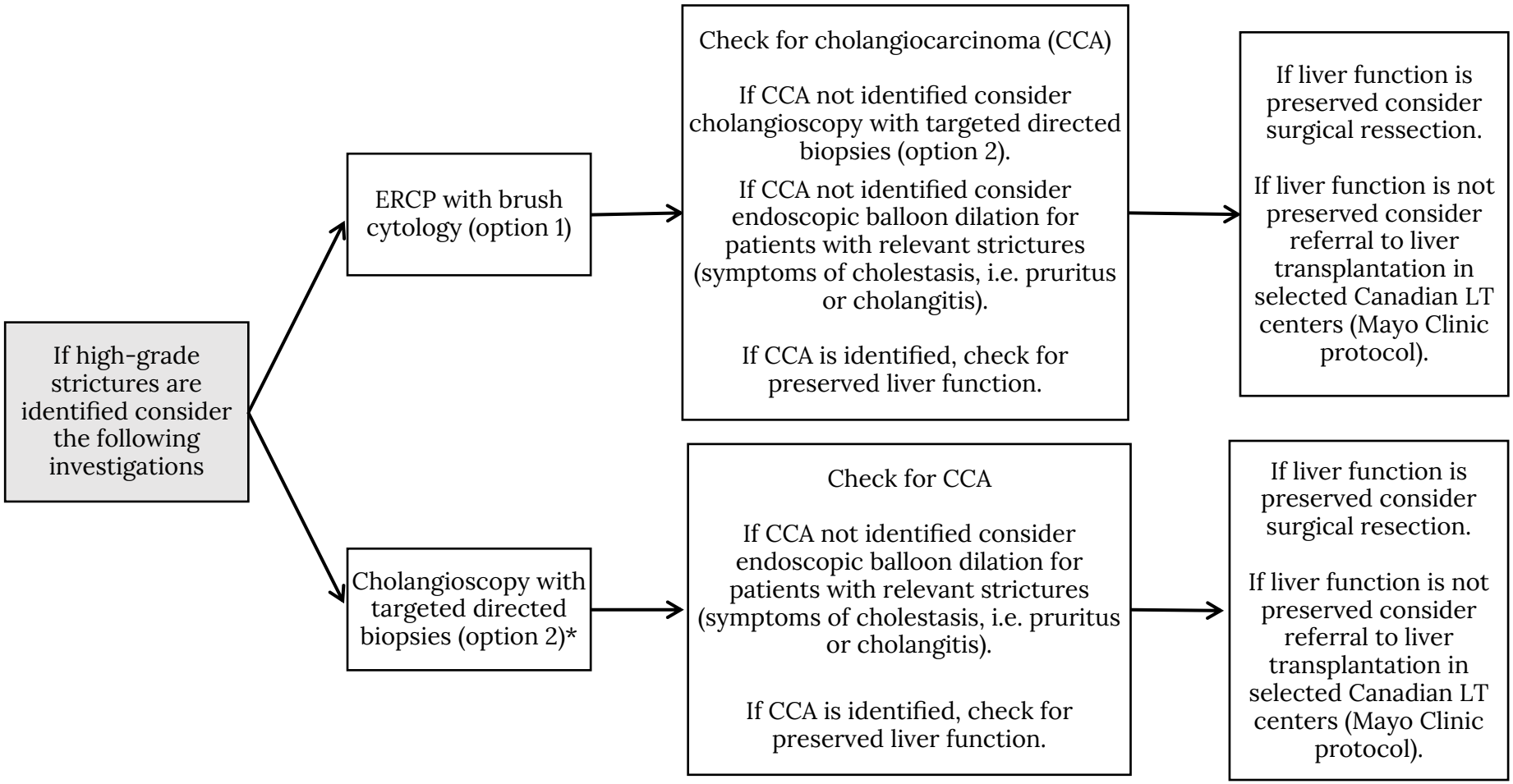
Flowchart 3.0: PSC screening for high-grade strictures



Flowchart 3.1: Recommendations if high-grade strictures are identified




*Use cholangioscopy where available or ERCP remains acceptable.



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Suggested algorithm for follow-up in PSC

Routine surveillance
Regular surveillance in patients with PSC is essential for the early detection of disease progression and associated malignancies, including cholangiocarcinoma, gallbladder carcinoma, and colorectal cancer. Early identification through structured monitoring can significantly impact management decisions and long-term outcomes.

Every 12 months for all, every 6 months for patients with high risk.

- Serum liver tests
- Clinical evaluation
- Every 12 months (even in patients with low risk)
- MRC
- US with special attention to gallbladder wall abnormalities. Gallbladder polyps of >8 mm is an indication for cholecystectomy, as it can lead to gallbladder cancer in PSC, and <8 mm warrants a close follow-up with US (3-6 months).
- Colonoscopy (Every 5 years in those without IBD at initial staging). If IBD is present, a colonoscopy should be done annually in accordance with Dysplasia CCP. *Refer to the CCP here*: *Colon Dysplasia Surveillance.*
- LSM by VCTE (Every 2 to 4 years)
- Assessment of bone mineral density is recommended for all individuals with PSC at the time of diagnosis, using dual-energy X-ray absorptiometry (DEXA). Follow-up and treatment of osteopenia and osteoporosis should follow the current practice guidelines.
- Vitamin D levels.

Additional workup when clinically indicated (new symptoms or new or worsening abnormalities in routine investigations, i.e. increasing ALP or bilirubin)

- Suspected CCA: Ca 19.9 and MRC.
- Suspected AIH or drug toxicity (autoantibodies, liver biopsy).
- Suspected clinically significant portal hypertension (Baveno VII criteria): gastroscopy, non-selective beta blockers.

How should pruritus be managed in people with PSC?

- Exclude relevant bile duct strictures in PSC.
- If present and reachable, relevant strictures should be treated by endoscopic balloon dilatation.

Table 1: Pharmacological treatment of moderate to severe pruritus

| Evidence | Drug | Potential side effect |
|---|---|---|
| 1st line | Bezafibrate (400 mg daily) | Renal insufficiency, myalgia, myopathy, hepatitis |
| 2nd line | Rifampicin (150-300 mg/d) | Hepatitis |
| 3rd line | Naltrexone (12.5-50 mg/d) | Opioid withdrawal syndrome |
| No evidence for PSC | Anion exchange resins (cholestyramine [4 g once to four times daily] | Abdominal discomfort |
| No evidence for PSC | Sertraline (50-75 mg/d) | |

Liver transplantation for PSC

Patients with PSC should be referred for LT when they develop any of the complications listed below:

- Patients progressing to decompensated cirrhosis
- MELD score ≥15
- HCC meeting transplant criteria

Other indications for LT include:

- Intractable pruritus
- Recurrent bacterial cholangitis
- High-grade dysplasia (in some LT centers)
- Hilar CCA (Radial mass <3 cm, in selected Canadian LT centers, Alberta, Montreal and Toronto).

## Resources for Patients

PSC Partners Canada: https://pscpartners.ca/resource/lessons-learned-post-liver-transplant/

## Resources for Providers

EASL Clinical Practice Guidelines on sclerosing cholangitis: https://www.journal-of-hepatology.eu/article/S0168-8278(22)00326-9/fulltext

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Supplementary Resources

## Differentiating IgG4-Related Sclerosing Cholangitis (IgG4-SC) from Primary Sclerosing Cholangitis (PSC)

The detection of serum immunoglobulin-4 (IgG4) levels as part of the initial evaluation of PSC is recommended to rule out the diagnosis of IgG4-related sclerosing cholangitis, for which corticosteroid treatment is beneficial, in contrast to PSC.

Serum IgG4 levels are elevated in up to 15% of patients with PSC, although IgG4 levels greater than four times the upper limit of normal have been reported to have 100% specificity for IgG4-related sclerosing cholangitis. Patients with IgG4-related sclerosing cholangitis may have normal or mildly elevated serum IgG4 levels, and the diagnosis of IgG4-related disease requires additional detection of IgG4-positive plasma cells in biliary epithelium or liver biopsies.

Table S1: Prognostic scores
These models utilize common laboratory studies, age and other clinical assessments, including the presence of varices and cholangiography, to classify patients into high-risk and low-risk groups.

Table 1: Main scores developed to predict the risk of clinical outcomes in PSC

| | Wiesner 1989 | Farrant 1991 | Broome 1996 | Revised Mayo Score 2000 | Boberg 2002 | Ponsioen 2002 | Tischendorf 2007 | Amsterdam-Oxford 2017 | UK-PSC 2019 | PREsTo 2020 |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | Y | Y | Y* | Y | Y* | Y* | Y | Y* | Y | Y(+ PSC duration) |
| Bilirubin | Y | | Y | Y | Y | | Y | Y | Y | Y |
| Albumin | | | | Y | Y | | Y | Y | Y | Y |
| AST | | | | Y | | | | Y | | Y |
| ALP | | Y | | | | | | Y | Y | Y |
| Hb | Y | | | | | | | | Y | Y (+ Na) |
| Platelets | | | | | | | | Y | | Y |
| IBD | Y | | | | | | | | | |
| Histology | Y | Y | Y | | | | | | | |
| Splenomegaly /Hepatomegaly | | Y | | | | | Y | | | |
| Variceal bleed | | | | Y | | | | | Y | |
| Cholangiogram | | | | | | Y | Y | Y (small *vs* large) | Y | |
| Outcome | Death | Liver-related death/ LT | Liver-related death/LT | Death | PSC-related death/LT | Liver-related death/LT | Death/LT | PSC-related death/LT | Death/ LT | Hepatic decomp-ensation |