Key Concepts

- MRCP should be used as the initial investigation to diagnose PSC as it has similar accuracy without the invasiveness of ERCP.
- Patients with a high clinical suspicion of PSC but with normal cholangiogram should undergo liver biopsy to exclude small duct PSC. Likewise, liver biopsy is indicated if an overlap with autoimmune hepatitis is suspected. In this case, treatment with corticosteroids or other immunosuppressants may be beneficial.
- All patients diagnosed with PSC should have serum IgG4 measured, not only to help exclude IgG4-associated cholangitis, but also to identify a subgroup of patients at higher risk for a more aggressive course of PSC.
- Use of ursodeoxycholic acid is not routinely recommended; use of high dose regimens (>25 mg/kg/day) is contraindicated due to increased risk of clinical deterioration. Drugs under investigation include antibiotics, supplements such as docosahexaenoic acid, fibrates, nor-UDCA, retinoic acid and anti-fibrotics.
- Individuals with PSC have increased risk for hepatobiliary and colorectal malignancies. Use of surveillance strategies is highly recommended.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation, fibrosis and destruction of intra and extra hepatic bile ducts, ultimately leading to biliary cirrhosis. Many unanswered questions remain, especially with regards to a unifying concept of pathogenesis, leading to a series of medical controversies and challenges in the management of PSC. The most commonly encountered controversies involve diagnosis, medical management and cancer surveillance.

I- Diagnosis

a. When is ERCP Indicated?

As there are no diagnostic features or classic clinical presentation of PSC, the first challenge is to make the correct diagnosis. Epidemiological data can be used as a guide: two thirds of patients are male and most are young at disease onset (30-40 years of age). An association with inflammatory bowel disease (IBD) occurs in 60-85% of patients with PSC. Thus, the diagnosis needs to be based on a combination of epidemiological data, chronic cholestasis and cholangiographic findings. ERCP used to be the gold standard for cholangiographic evaluation. However, MRCP can now provide similar overall accuracy with sensitivity of 86% and specificity of 94%, without the risk of an invasive procedure or radiation, and at lower cost (1). ERCP has superior sensitivity in detection of subtle peripheral bile duct changes and should be obtained if clinical suspicion is high and the MRCP is unrevealing. Otherwise, ERCP is generally reserved for situations where therapeutic intervention or tissue acquisition is required. Of note, both
AASLD and EASL guidelines now recommend MRCP as first line investigation.

b. What is the Role of Liver Biopsy in PSC?

A liver biopsy is not required for the diagnosis of PSC. In fact, the histological features of PSC are not pathognomonic. Mild portal tract edema and fibrosis, periductal inflammation and subtle ductular reaction are the most common findings and indicate a cholangiopathy. However, the most characteristic fibro-obliterative lesion (onion-skinning) is seen in fewer than 40% of all needle biopsy specimens in PSC (2). The liver biopsy is particularly helpful in two circumstances: small duct PSC and overlap with autoimmune hepatitis.

Small duct PSC is notable for a normal cholangiogram. This is recognized in approximately 10% of patients with PSC, and in these cases a liver biopsy is required for the diagnosis. Epidemiology is similar to that of large duct PSC in terms of age of onset and gender predominance, but it appears that patients with small duct PSC are more likely to have Crohn’s disease comparing to those with large duct PSC. Presence of IBD is not required for the diagnosis of small duct PSC, but the interpretation of liver biopsy findings depends on the IBD status. Thus, in the absence of IBD, typical findings of PSC are required on the liver biopsy, whereas for patients with IBD, histological changes can be merely compatible with PSC.

Studies of small duct PSC suggest that this entity may have a more benign course and better prognosis: over a median follow-up of 13 years (IQR 10-16) for patients with small duct PSC and 10 years (IQR 5.8-14) for those with large duct PSC, mortality (13% vs. 28.7%), liver transplantation (9.6% vs. 21%) and development of cholangiocarcinoma (1.2% vs. 12%) were substantially lower for the small duct group (3). Nevertheless, about 20% of patients with small duct PSC progress to large duct PSC over a median period of 7.4 years.

The other condition in which a liver biopsy is helpful is overlap with autoimmune hepatitis. This occurs predominantly in children (up to 50% of all PSC), with the term "autoimmune sclerosing cholangitis" (AISC) coined to describe this population. In adults, overlap occurs in up to 20% of cases, and presentation may be simultaneous or sequential (4). Diagnostic criteria remain to be defined but use of the modified autoimmune hepatitis scoring system has been proposed. Alternatively, a combination of biopsy features, elevated IgG and presence of autoantibodies can be used although variable degrees of biliary interface hepatitis can be seen in PSC. A beneficial effect of steroids is suggested in this setting.

c. Why Should we Measure Serum Immunoglobulin (IgG) 4?

As recommended by AASLD and EASL guidelines, all patients with suspected PSC should undergo testing for serum IgG4 level. The reason is two-fold. First, PSC is a diagnosis of exclusion and all secondary causes of sclerosing cholangitis should be ruled out. That includes, although not limited to, IgG4-associated cholangitis (IAC). The biliary strictures of IAC represent the hepatobiliary manifestation of a systemic disorder named IgG4-associated systemic disease. IAC is diagnosed based on the HISORt criteria, mainly with a combination of histological, imaging and serological features(6). Characteristically, IAC responds well to steroids.

Second, 9% of patients with well established PSC, and who did not meet HISORt criteria for IAC, were found to have elevated serum levels of IgG4 (>140 mg/dL). These patients had worse biochemical markers, higher Mayo risk score and shorter time to transplantation, suggesting a more aggressive disease course. The significance of these findings is still unclear and additional work is needed to determine whether patients with PSC and elevated IgG4 would benefit from steroids.

II- Medical Management

a. What is the Role of Ursodeoxycholic Acid (UDCA)?

A major controversy in PSC is whether to use UDCA. Despite improvements in liver biochemistries noted in early studies with UDCA 13-15 mg/kg/day, a large randomized controlled 2-year study failed to demonstrate improvement in survival free of liver transplantation despite a biochemical effect. A subsequent Scandinavian study including 219 patients and using a daily dose of 17-23 mg/kg for 5 years found only a trend towards improved survival, although that trial was limited by insufficient power and poor compliance in the active treatment group. Finally, the US multicentre study involving 150 patients with PSC receiving UDCA 28-30 mg/kg/day was interrupted prematurely due to poorer outcomes in the
UDCA arm. The primary endpoints of the study were death, liver transplantation, reaching minimal listing criteria, development of esophageal/gastric varices, development of cirrhosis and cholangiocarcinoma. Patients on UDCA had a hazard ratio of 2.27 (1.24-4.16) for reaching a primary endpoint and 2.11 (1.04 – 4.28) for death, meeting minimal listing criteria or liver transplant compared to placebo (7). Indeed, a recent meta-analysis clearly demonstrated that UDCA is not associated with improved survival, histologic progression or development of cholangiocarcinoma. At this time, the AASLD recommends against the routine use of UDCA in PSC (8, 9).

The mechanism for worse clinical outcomes in patients receiving high dose UDCA has not been elucidated but it is thought to be related to increased production of hydrophobic, cytotoxic bile acids, especially lithocholic acid. Also controversial is whether UDCA can be used as a chemopreventive agent for colorectal malignancies. High dose UDCA should definitely not be used; in addition to the worse clinical outcomes discussed above, ad hoc analyses also demonstrated an increased risk of colorectal neoplasia (Hazard ratio 4.4 [1.3-20.1]). Two small retrospective studies and one small prospective study suggest the possibility that low dose UDCA can decrease the risk of colorectal neoplasia. Although AASLD guidelines recommend against using UDCA as a chemopreventive agent, EASL guidelines suggest that UDCA can be considered in high-risk groups such as those with strong family history of colorectal cancer, previous colorectal neoplasia or longstanding extensive colitis(8, 9).

b. What Other Therapies Are Under Investigation?
Antibiotics have occasionally been used for the treatment of PSC. Tetracycline, vancomycin, metronidazole, azithromycin and minocycline have been tested with or without concomitant use of UDCA in small pilot studies or case reports. Improvement in liver biochemistries is generally observed, but long term studies are lacking. More recently, a randomized trial divided 35 patients in 4 groups: low/high dose vancomycin (125 mg or 250 mg every 6 hours) and low/high dose metronidazole (250 mg or 500 mg every 8 hours)(10). The primary endpoint was improvement in alkaline phosphatase (ALP) at 12 weeks. Secondary endpoints were the Mayo risk score, serum bilirubin, pruritus and adverse events. Only the vancomycin groups reached primary endpoint, with a mean decrease in ALP of 43% for the low dose and 40% for the high dose. The Mayo risk score improved in the low dose metronidazole and low dose vancomycin groups. Pruritus only improved in the high dose metronidazole group, but at the expense of an increased rate of adverse events. Currently there are trials recruiting for use of rifaximin and vancomycin in PSC.

Supplementation with docosahexaenoic acid (DHA) has been evaluated in PSC with encouraging results. CFTR dysfunction, which has been demonstrated in patients with PSC, is associated with abnormalities of fatty acid metabolism. A decrease in DHA and increase in arachidonic acid (AA) have both been noticed in this setting. Furthermore, correction of such fatty acid abnormality in CFTR/- knockout mice led to reversal of bile duct injury usually seen in these mice. In an uncontrolled trial, 23 patients with PSC were treated with DHA 800 mg twice a day for 12 months(11). Serum levels of DHA and AA were corrected, and mean serum ALP decreased from 358± 37 IU/L to 297 ±38 IU/L, and five subjects (22%) had a reduction greater than 50% in serum ALP. There were no adverse events attributable to DHA.

Fibrates are peroxisome proliferator-activated receptor alpha (PPAR-alpha) agonists. When activated by various ligands this receptor will form heterodimers with retinoid X receptors and bind to the peroxisome proliferator response elements in the promoter region of their respective target genes. Among other actions, this nuclear receptor is involved in down-regulation of NF-kappaB activation and subsequent modulation of inflammatory response. Importantly, recent studies in patients with primary biliary cirrhosis have clarified that fibrates modulate expression of genes involved in bile acid synthesis, metabolism and transport, overall leading to choleresis. Two pilot studies evaluating use of fibrates in patients with PSC have been published in abstract form (12, 13). Together they included 21 patients treated for 6-12 months with fenofibrate 200 mg/day (n=13) or 160 mg/day (n=8), and both studies showed a significant decrease in serum ALP. Adverse events included myalgias (n=3; 1 discontinued study), nausea and worsening of psoriasis. Larger studies are warranted.

In addition to antibiotics, DHA and fibrates, ongoing trials are currently evaluating the use of nor-UDCA, retinoic acid and lysyl oxidase-like 2 (LOXL-2) antibodies in PSC.

c. How Do We Evaluate Response to Therapy?
Both Child-Pugh scoring system and the Mayo risk score for PSC can be used as prognostic tools in large patient cohorts. The Mayo risk score includes age, bilirubin, AST, albumin and history of variceal bleeding, and performs better earlier in the course of the disease (14). Specific cholangiographic features, especially the presence or absence of dominant strictures, also appear to have prognostic importance (15). However, no single prognostic model currently available can accurately predict outcomes for the individual patient.
Three recent studies consistently indicate that a reduction or normalization of serum ALP levels is associated with better overall prognosis in PSC (16-18). Stanich et al studied 87 patients with a new diagnosis of PSC and followed for a median period of 7.3 years, and found that 40% (n=35) of these patients normalized serum ALP after a median period of 1.03 years (16). Interestingly, patients with normalization of ALP reached an endpoint less frequently than patients with persistent ALP abnormalities. The proportion of patients receiving UDCA was similar in both groups (with and without normalization of ALP), and there was no difference in survival between patients who normalized their ALP spontaneously compared to those who normalized while on UDCA.

Al Mamari and colleagues compared outcomes between patients with and without sustained improvement of serum ALP to < 1.5 X ULN (17). Of 139 patients, 40% achieved ALP < 1.5 X ULN within a median time of 2 years, and these patients had lower rates of clinical deterioration (variceal bleeding, liver transplantation and liver-related deaths) as well as absence of development of cholangiocarcinoma and improved overall survival. Of note, improvement of ALP to < 1.5 X ULN was comparable to normalization of ALP with respect to prognosis.

Finally, Lindstrom et al re-evaluated the 219 patients previously enrolled in the Scandinavian PSC UDCA trial (1996-2001) and who were followed until 2010 (18). Patients were considered biochemical responders if serum ALP dropped by ≥40% or normalized after 1 year in the trial, regardless of receiving UDCA or placebo. Once again, patients with biochemical response had improved survival independent of treatment assignment. Taken together, these studies suggest that serum ALP may be used as a biochemical marker of response. In addition, it is possible that patients with PSC treated with standard doses of UDCA and who achieve such biochemical response within the first 1—2 years may indeed have a survival benefit. Further studies are needed to answer this question (19).

## III- Cancer Surveillance

### a. What is the Risk and How Do We Survey for Malignancies in PSC?

The incidence of both intra- and extra-hepatic malignancies is increased in patients with PSC. In a Swedish study from 2002 including 604 patients with PSC the incidence of hepatobiliary cancers (cholangiocarcinoma [CCA], hepatocellular carcinoma [HCC] and gallbladder carcinoma) was 13.3% (standardized incidence ratio [SIR] 161; 95%CI 120.3-210.1)), with 37% of these diagnosed within 1 year of the diagnosis of PSC. The cumulative incidence of colorectal carcinoma/dysplasia was 7.4%, and it only occurred in patients with concomitant IBD (SIR 10; 95% CI 5.3-18.1)). The risk of pancreatic cancer was also increased, with SIR 14; 95% CI 4.7-33.4 (20). A recent study also from Sweden including 199 patients with PSC confirmed an exceedingly high SIR for hepatobiliary malignancies (177; 95% CI 110-271), especially CCA (SIR 868; 95% CI 505-1390), but failed to confirm an increased risk for colorectal cancer (SIR 4.31; 95% CI 0.88-12.6) (21). This was an unexpected finding, perhaps justified by substantial changes in the modern management and surveillance of patients with IBD.

Despite the increased risk of cancer and the high mortality attributed to these cancers, surveillance guidelines are not uniform. The following recommendations are supported by European (EASL) and American (AASLD) guidelines (8, 9):

- **Annual ultrasound should be obtained to evaluate for gallbladder mass/polyps and cholecystectomy considered if lesion of any size is found. Polyps ≥ 8mm have higher likelihood of harboring malignancy (22).** Importantly, liver-related complications occur in >10% of patients undergoing cholecystectomy, especially if Child Pugh score is >7. Given rapid growth of these polyps, some experts recommend surveillance every 6 months as opposed to yearly.

- **Many clinicians rely on annual cross-sectional imaging with MRI or ultrasound in combination with serum CA 19-9 to screen for CCA, although this strategy is not evidence-based. ERCP with brush cytology ± biopsies are indicated if there is clinical suspicion of CCA: dominant strictures, clinical deterioration, worsening biochemical parameters, elevated CA 19-9 or MRI changes consistent or suspicious for CCA. If available, fluorescent in situ hybridization (FISH) technique should be employed to increase the sensitivity of conventional cytology. In the setting of clinical suspicion for CCA, finding of CA 19-9 > 130 or FISH polysomy should lead to initiation of management of CCA. If suspicion is high and MRI is negative, tests should be repeated over time. Over 70% of patients with serial polysomy on FISH have or will develop CCA (23).**

- **Per EASL guidelines, patients with PSC and cirrhosis should undergo surveillance for HCC as recommended for other causes of cirrhosis whereas the AASLD guidelines do not make a statement. The incidence of HCC has not been well studied in PSC and may be below the 1.5%/year threshold necessary to require**
surveillance (24). However, the cross-sectional imaging
tests used to survey for gallbladder carcinoma and CCA
would assist in detecting HCC as well.
- All patients with a new diagnosis of PSC without known
  IBD should undergo colonoscopy with random
  biopsies. Patients with PSC and IBD should undergo
  surveillance colonoscopies every 1-2 years to exclude
colorectal neoplasia.

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