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Review Article

Recent advances in diagnosis and management of chronic cholestatic liver diseases: expert consensus

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ABSTRACT

Chronic cholestatic liver diseases (CCLD), primarily including primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), are characterized by impaired bile flow, leading to systemic complications such as pruritus, jaundice, fat soluble vitamin deficiencies and progressive liver damage. Recent advances in diagnostics, particularly the use of non-invasive tests like FIB-4, APRI and transient elastography, have significantly improved the early detection and assessment of liver fibrosis. Ursodeoxycholic acid (UDCA) remains the cornerstone treatment for PBC, effectively improving biochemical markers and delaying disease progression. In contrast, the treatment options for PSC remain limited. Emerging therapies targeting bile acid synthesis and gut microbiota modulation are under investigation, offering potential future solutions for PSC. In the Indian clinical setting, other causes of intrahepatic cholestasis, such as alcoholic liver disease (ALD) and drug-induced liver injury (DILI), are more prevalent. ALD with cholestasis is seen in 10-30% of patients, while DILI, often driven by tuberculosis medications and complementary and alternative medicines, accounts for a significant proportion of cases. Infectious causes like hepatitis A and fibrosing cholestatic hepatitis in hepatitis C patients post-liver transplantation also contribute to the disease burden. Experts recommend ongoing UDCA use in cholestatic conditions, regular non-invasive fibrosis assessments, and further research into new pharmacological agents for both PBC and PSC.

Keywords: Chronic cholestatic liver diseases, Obeticholic acid, Primary biliary cholangitis, Primary sclerosing cholangitis, Transient elastography, Ursodeoxycholic acid

INTRODUCTION

Chronic cholestatic liver diseases (CCLD) include various disorders that disrupt bile production, secretion or excretion, leading to bile accumulation in the liver and systemic complications. These diseases are classified as intrahepatic or extrahepatic, based on the site of bile flow disruption. Intrahepatic cholestasis stems from hepatocyte or cholangiocyte damage, often linked to immune dysfunction, infections, alcohol-related liver damage or drug-induced injury, without structural obstruction. In contrast, extrahepatic cholestasis arises from physical blockages, such as bile duct stones, tumors or strictures.[1] Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are major forms of chronic cholestatic liver disease. PBC, mainly affecting women, is an autoimmune disorder causing bile duct injury, leading to fibrosis, cirrhosis and liver failure if untreated. PSC involves inflammation and fibrosis of intrahepatic and extrahepatic bile ducts, with significant long-term risks, including cholangiocarcinoma.[2] CCLD often presents with symptoms like pruritus, jaundice, fatigue, metabolic bone disease and fat-soluble vitamin deficiencies. Disease progression can lead to cirrhosis, hepatocellular carcinoma and increased morbidity and mortality. While ursodeoxycholic acid (UDCA) is effective for PBC, treatment options for PSC are limited. However, recent advances in molecular mechanisms, including genetic factors and the gut-liver axis, offer new treatment possibilities.[3] This review provides an updated overview of

recent advancements in the diagnosis and management of CCLD, incorporating expert opinions to offer practical insights into evolving treatment strategies and patient care.

Epidemiology of CCLD, common causes and their prevalence

CCLD pose a substantial global health burden. Epidemiological data on CCLD in India is limited. However, an HCP survey by Ravindra BS et al, reports that CCLD affect 10-30% of liver disease patients in India. Common causes of intrahepatic cholestasis in India include viral hepatitis, alcoholic liver disease (ALD) and drug-induced liver injury (DILI), which, though less common than ALD, still contribute significantly to the overall disease burden. ALD associated with cholestasis is observed in 10-30% of patients as reported by 70.7% of physicians, while DILI associated with cholestasis affects less than 20% of cases.[3] The causes behind DILI in India are often unclear and under-recognized due to a heterogeneous population, varying disease burdens and prescription practices that include the widespread use of alternative medicine systems such as Ayurveda, Unani, Siddha and Homeopathy.[4]

In a nationwide Indian study on drug-induced liver injury (DILI), tuberculosis (TB) drugs, complementary and alternative medicines (CAM) and antiepileptic drugs accounted for 85% of cases, followed by antimicrobials, antimetabolites and antiretrovirals. The three-month mortality rate was 12%, with jaundice-linked mortality at 16%. Notably, paracetamol-induced DILI was rare, representing less than 1% of cases. CCLD is more common in males and those aged 41-60, as noted by 52.5% and 32.6% of physicians, respectively.[4]

Additionally, cholestatic hepatitis A accounts for between 0.8-5.2% of hepatitis A cases, with intrahepatic cholestasis occurring in approximately 0.4% to 0.8% of cases.[5,6] In symptomatic patients, 10-20% may experience an atypical disease course characterized by relapsing hepatitis, persistent cholestasis, the development of autoimmune hepatitis or fulminant liver failure.[7] A unique acute severe form of hepatitis C recurrence, known as fibrosing cholestatic hepatitis, occurs in 2-5% of patients transplanted for hepatitis C within 1 to 6 months post-transplant.[8]

Beyond these causes, autoimmune liver diseases such as PBC, autoimmune hepatitis and PSC are becoming increasingly common.[9] PBC, primarily affecting women around the age of 55, is marked by fatigue, pruritus, elevated serum alkaline phosphatase (ALP) levels and the presence of antimitochondrial antibodies (AMA). Infectious causes like hepatitis A, B and C and in some cases tuberculosis (TB) or cytomegalovirus (CMV) in immunocompromised individuals, also contribute to CCLD. Granulomatous cholestasis due to TB is particularly concerning, requiring a thorough diagnostic approach to identify the source of cholestasis.[10]

Table 1 provides the common causes of intrahepatic cholestasis. The epidemiology of CCLD in India shows diverse causes, with alcoholic liver disease (ALD) and autoimmune conditions being major contributors. Infectious causes and drug-induced liver injury (DILI) also play significant roles in certain populations. Continued research and better diagnostics are needed to address evolving CCLD patterns and improve patient outcomes.

SEROLOGY AND NON-INVASIVE TESTS (NIT'S) FOR ASSESSMENT OF FIBROSIS AND TRANSIENT ELASTOGRAPHY

Serological assessment of liver enzymes

PBC diagnosis relies on laboratory findings and serological markers, with elevated cholestatic markers such as serum alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bilirubin and IgM. The presence of anti-mitochondrial antibodies (AMA), targeting the PDC-E2 complex, is a highly specific marker for PBC, detectable in over 90% of patients. Elevated cholestatic markers combined with positive AMA testing offer an accurate diagnosis, often eliminating the need for a liver biopsy.[11]

Elevated alkaline phosphatase (ALP) and bilirubin levels indicate a cholestatic pattern. ALP can rise due to liver or bone disease and pregnancy, while gamma-glutamyl transferase (GGT) helps determine if ALP elevation is liver-related. ALP, produced in bile duct epithelial cells, commonly increases in cholestasis or biliary disorders. Anatomical and autoimmune conditions affecting the biliary system can cause this pattern and obstruction of the common bile duct (CBD) may also elevate aminotransferases.[12]

GGT elevation indicates biliary or hepatocyte disease but can also rise due to drugs, pulmonary or renal conditions. While sensitive to liver issues, GGT has low specificity. Bilirubin elevations are classified as direct (conjugated) or indirect (unconjugated), indirect hyperbilirubinemia often results from hemolysis or Gilbert's syndrome, whereas direct hyperbilirubinemia suggests liver conditions like cholestatic drug reactions, autoimmune diseases or biliary obstruction. Additional laboratory tests and imaging, including specific antibodies like anti-neutrophil cytoplasmic antibodies for primary sclerosing cholangitis and anti-mitochondrial antibodies for primary biliary cirrhosis, are essential for diagnosing autoimmune cholestatic liver diseases.[12] In a hepatocellular pattern, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels rise disproportionately compared to ALP and GGT, reflecting the release of aminotransferases from damaged hepatocytes. The R value is a useful tool for determining the pattern of liver injury, calculated as (ALT ÷ ULN ALT)/(ALP ÷ ULN ALP). An R value >5 suggests a hepatocellular pattern, 2–5 indicates a mixed pattern and <2 points to a cholestatic pattern.[12]

Diagnosis of liver fibrosis

Liver histology may show chronic nonsuppurative cholangitis, granuloma formation and progressive destruction of small intrahepatic bile ducts.[13] Accurate diagnosis of liver fibrosis and cirrhosis is essential for determining liver disease prognosis and facilitating timely interventions. In patients with PBC, cirrhosis or advanced liver fibrosis, such as bridging fibrosis, is associated with decreased long-term survival.[14] Although liver biopsy was previously the gold standard for diagnosing fibrosis, significant advancements in non-invasive methods now enable effective screening for clinically significant advanced liver disease and portal hypertension.[13]

Non-invasive methods for diagnosing liver fibrosis assess biochemical properties and liver stiffness. Biochemical tests include the aspartate aminotransferase/platelet ratio index (APRI), FIB-4 score, Forns score, aspartate to alanine aminotransferase ratio (AAR), Enhanced Liver Fibrosis (ELF®) test, FibroTest®, FibroMeter®, hyaluronic acid and procollagen III propeptide. However, these markers are not widely recommended due to limited evidence supporting their accuracy in differentiating mild from severe fibrosis or distinguishing early from advanced histological stages (AUROC<0.80).[15]

While FIB-4 shows low to moderate accuracy in ALD and autoimmune hepatitis, it is useful for excluding fibrosis.[16] The FIB-4 score is primarily recognized for its utility in screening for liver fibrosis, particularly in high-risk populations. It demonstrates a high negative predictive value, indicating that a low FIB-4 score can effectively rule out advanced fibrosis.[17] However, its accuracy diminishes in longitudinal assessments post-intervention, as evidenced by studies showing inconsistent correlations with liver stiffness measurements and fibrosis stages.[18]

Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE)

Liver stiffness is commonly assessed using transient elastography (TE), the most widely used non-invasive fibrosis assessment method. Other modalities, including acoustic radiation force impulse (ARFI) elastography, shear wave elastography (SWE), real-time tissue elastography (RTE) and magnetic resonance elastography (MRE), yield comparable results to TE.[14]

VCTE has revolutionized non-invasive liver fibrosis assessment in chronic liver disease patients. Now widely used, it is the first-line tool for liver fibrosis evaluation in some countries. This quick, simple and reproducible method has well-established quality criteria. With a discriminative ability greater than 0.90. LSM by VCTE is the most reliable non-invasive method for detecting and excluding advanced fibrosis and cirrhosis across major chronic liver diseases.[19] The Baveno VI criteria suggest use of LSM of≤20 kPa by TE and PLT≥150×10^9/l as a validated, non-invasive tool for predicting low risk of clinically significant varices, eliminating the need for endoscopy. The Baveno VII consensus further extends this approach to diagnosing compensated advanced chronic liver disease (cACLD) and clinically significant portal hypertension (CSPH), aiding predictions for decompensated liver disease and variceal bleeding. An LSM≥10-11 kPa by VCTE reliably indicates severe fibrosis in PBC patients, with approximately 10 kPa optimally differentiating high and low risk for liver-related complications. The 2021 EASL guidelines strongly recommend LSM by VCTE at the 10 kPa threshold for diagnosing advanced PBC. A recent international study of over 3,000 patients has further validated the prognostic value of VCTE in PBC.[15]

Diagnosis of PSC

Liver ultrasound is typically used for the initial evaluation of patients with PSC. In advanced stages, it may show characteristic findings such as wall thickening of central intrahepatic or extrahepatic ducts, echogenic portal triads and segmental biliary duct dilation. However, in early PSC, ultrasound may appear normal, as these features develop later in the disease progression.[20]

EASL recommends diagnosing large duct PSC in adults with elevated cholestasis markers when typical sclerosing cholangitis findings are seen on high-quality MRCP, after excluding secondary causes. For patients with suspected PSC and a normal MRCP, a liver biopsy is advised to confirm or exclude small duct PSC Additionally, a liver biopsy should be considered for individuals with PSC exhibiting autoimmune hepatitis features, such as significantly elevated transaminases, high IgG levels and positive autoantibodies consistent with AIH.[19]

A diagnosis of small duct PSC should be considered in patients with elevated serum markers of cholestasis of unknown origin, normal high-quality cholangiography and compatible histological findings, particularly in those with concomitant inflammatory bowel disease (IBD) (LoE 3, strong recommendation, 88% consensus). Furthermore, autoantibodies should not be used to diagnose or risk-stratify individuals with PSC (LoE 4, strong recommendation, 100% consensus).[19]

The diagnosis of PSC should be made only after excluding causes of secondary sclerosing cholangitis. For suspected small duct PSC, histological features consistent with the disease, such as periductal fibrosis (in fewer than half of samples), fibro-obliterative cholangitis (in 5-10% of samples), ductular reaction, periductal inflammation, ductopenia and varying portal inflammation, must be present to confirm the diagnosis.[21] A liver biopsy is not required for diagnosing PSC when cholangiographic findings are indicative of the disease. In small duct PSC, cholangiography may show normal bile ducts, but MRI can reveal abnormal findings that raise clinical suspicion. Additionally, measuring serum IgG4 levels in all adult patients with large duct sclerosing cholangitis is

recommended to distinguish IgG4-related disease from PSC at diagnosis.[20]

Experts' consensus on diagnosis

CCLD is diagnosed using elevated alkaline phosphatase (ALP), antimitochondrial antibody (AMA) or histological evidence of cholangitis. ALP elevation correlates with ductopenia severity, while increased aminotransferase and IgG levels reflect necrosis and inflammation; hyperbilirubinemia indicates advanced ductopenia. Non-invasive PBC evaluation uses LSM, with a threshold of 9.6 kPa to identify high-risk patients; LSM>25 kPa indicates clinically significant portal hypertension (CSPH), warranting beta-blocker therapy without endoscopy. Sclerosing cholangitis requires yearly MRCP, with additional imaging if jaundice worsens. Endoscopic retrograde cholangiopancreatography (ERCP) or biopsy is recommended for suspected lesions. FIB-4 and APRI scores help screen for advanced fibrosis, with a FIB-4 cut-off of 1.3 guiding further elastography assessment.

LSM≥10 kPa suggests advanced fibrosis in PBC and LSM≤15 kPa with platelets>150,000/µl rules out high-risk varices, reducing the need for endoscopy. ALP is key for PBC prognosis, with overlap syndromes involving autoimmune hepatitis and sclerosing cholangitis commonly seen in India. Liver biopsy is reserved for cases with discordant non-invasive test results, aiding in determining disease etiology.

MANAGEMENT OF CHRONIC CHOLESTATIC LIVER DISEASE AND NEWER MOLECULES IN THE PIPELINE

Management of cholestatic liver disease focuses on addressing the underlying cause and providing symptomatic relief. Obstructive cholestasis often requires surgical or endoscopic intervention, while cessation of drugs or alcohol is recommended for drug-induced cases. Antiviral therapy is indicated for viral hepatitis and ursodeoxycholic acid (UDCA) is effective for immune-related cholestasis.[1] Pharmacological treatments, including UDCA, obeticholic acid (OCA), budesonide, fibrates, S-adenosyl-L-methionine (SAM-e) and cholestyramine, aim to reduce hepatocyte and cholangiocyte damage and regulate bile acid metabolism.[1] This review focuses on the treatment of PBC and PSC.

Treatment of PBC

UDCA is the first-line treatment for PBC, enhancing biochemical markers, slowing disease progression and improving transplant-free survival. At 13–15 mg/kg/day, UDCA comprises 40% of bile acids in patients, with higher doses (28–32 mg/kg/day) showing no additional benefits. It is generally well tolerated, with only minor adverse effects.[1] UDCA inhibits the synthesis and reabsorption of toxic hydrophobic bile acids, promotes the production of less harmful bile acids, enhances bicarbonate secretion by bile ducts and reduces cholangiocyte apoptosis. These mechanisms protect the liver and improve outcomes in PBC, with lifelong use recommended for patients who tolerate and respond well to treatment.[1] A multicenter meta-analysis of 4,119 PBC patients treated with UDCA established the GLOBE score, which predicts transplant-free survival based on clinical and biochemical variables after one year of treatment. UDCA significantly improved transplant-free survival rates at 5 years, 90% of treated patients remained transplant-free versus 79% of untreated patients; at 10 years, the rates were 78% for UDCA-treated and 59% for untreated and at 15 years, 66% of UDCA-treated patients survived without transplantation compared to 32% untreated.[22]

The AASLD 2018 and EASL 2017 guidelines recommend UDCA at 13-15 mg/kg/day as the first-line treatment for PBC, irrespective of histologic stage. A biochemical response should be evaluated after 12 months to assess the need for second-line therapy. If bile acid sequestrants are needed, UDCA should be taken either 1 hour before or 4 hours after. EASL advises lifelong UDCA use, including post-liver transplant for recurrent PBC, which may improve liver biochemistry.[23,24] Around 40% of PBC patients do not achieve adequate biochemical improvement with UDCA, often indicated by an ALP level exceeding 1.67×ULN after one year. For these patients, second-line therapies include OCA, budesonide and fibrates, with only OCA officially approved by EASL and AASLD; budesonide and fibrates are used off-label.[1]

OCA, a semisynthetic bile acid analog and FXR agonist, inhibits bile acid synthesis and alleviates cholestasis. Phase 3 trials showed that OCA significantly improved biochemical responses in PBC patients unresponsive to UDCA. However, it increased pruritus in 56–68 of treated patients versus 38% in the placebo group, with more serious adverse events in the OCA group. Despite these side effects, OCA received FDA approval for PBC patients with poor UDCA response, necessitating close monitoring due to the risk of pruritus and fatigue.[1] Fibrates like bezafibrate and fenofibrate, used with UDCA, have shown promising results as PPAR agonists that reduce bile acid synthesis by downregulating CYP7A1 expression. Studies indicate significant reductions in ALP and improved survival rates in PBC patients. The BEZURSO trial reported a 67% ALP normalization rate with bezafibrate versus 2% in the placebo group.[1] Budesonide has also shown potential in PBC treatment, though larger trials are needed. In one study, a combination of UDCA and budesonide over 36 months significantly improved ALP levels but did not halt histological progression. Budesonide (6–9 mg/day) is recommended by the APASL for non-cirrhotic PBC patients with a poor UDCA response, though more evidence is required to confirm its long-term benefits.[1] The United States- Food and Drug Administration (US-FDA) has granted an accelerated approval to Seladelpar, a PPAR delta agonist, was evaluated in a 12-month phase 3, double-blind, placebo-

controlled trial for PBC patients with inadequate response to or intolerance of UDCA. Administered at 10 mg, seladelpar significantly improved biochemical response (61.7% vs. 20.0%) and ALP normalization (25.0% vs. 0%), while also reducing pruritus in those with moderate-to-severe symptoms. Adverse events were similar between seladelpar (86.7%) and placebo (84.6%), with serious adverse events reported in 7.0% and 6.2% of patients, respectively.[25] Another agent, oral dual PPAR-α/δ agonist, Elafibranor, has received accelerated US-FDA approval for PBC. It was assessed in a phase 3, double-blind, placebo-controlled trial for patients with PBC who had an inadequate response to or intolerance of UDCA. Patients received 80 mg of elafibranor or placebo once daily. A biochemical response, the primary endpoint, was achieved in 51% of elafibranor-treated patients compared to 4% in the placebo group. ALP normalization occurred in 15% of elafibranor patients and none in the placebo group. While pruritus improvements did not significantly differ between the groups, adverse events like abdominal pain, diarrhea and nausea were more frequent with elafibranor. Elafibranor showed greater improvements in biochemical markers of cholestasis than placebo.[26] There are various drugs in phase 2 and 3 for PBC. The detailed list is provided in Table 3.

Table 1: Common causes of intrahepatic cholestasis.[11,12]

Immune mediated	Primary biliary cholangitis (PBC)
	Primary sclerosing cholangitis (psc)
	Autoimmune cholangitis
	Igg4 cholangiopathy
Infectious	Granulomatous cholestasis
	Viral hepatitis
	AIDS cholangitis
Others	Drug induced (DILI)
	Alcohol associated liver diseases.
	Malignancy
	Familial disorders like PFIC/ BRIC/ Alagille Syndrome
	Intrahepatic cholestasis of Pregnancy
	Idiopathic Amyloidosis
	Sarcoidosis
	Benign recurrent intrahepatic cholestasis

Table 2: R ratio and interpretation.[12]

R value	Interpretation
>5	Hepatocellular pattern
>2 but <5	Mixed pattern
<2	Cholestatic pattern

Table 3: Drugs in pipeline for PBC/PSC.[27]

Treatment	Target	Clinical trial phase
Linerixibat	IBAT inhibitor	Phase 2b
Saroglitazar	PPAR α/γ	Phase 2
Setanaxib	NADP oxidase 1/4 inhibitor	Phase 2
A4250	IBAT inhibitor	Phase 2
Benafibrate	PPAR	Phase 2
HTD1801 (BUDCA)	Hypolipidemic agent	Phase 2
TQA3526	FXR	Phase 2
ASC 42	FXR	Phase 2
EP547	MRGRP family member X4	Phase 2
Probiotics	Micro V probiotics	Phase 2
OP-724	CREB binding protein/β-catenin inhibitor	Phase 1
CNP-104	Immunomodulating agent	Phase 1/ 2

IBAT: Ileal bile acid transporter inhibitor. NADP: Nicotinamide adenine dinucleotide phosphate, PPAR: Peroxisome proliferation activated receptors. FXR: Farnesoid-X receptor. MRGRPS: Mas-related G protein-coupled receptors. CREB: cAMP-response element binding protein.

PBC complications and its treatment

Pruritus and fatigue are common complications in PBC, affecting around 80% of patients. Pruritus can occur at any stage but often improves as liver disease progresses. The first-line treatment is cholestyramine, a bile acid sequestrant taken 4–6 hours apart from UDCA to avoid absorption interference. Rifampicin serves as a second-line option for those intolerants to cholestyramine but requires caution due to its effects on coagulation and vitamin K absorption. Naltrexone, a third-line treatment, may cause side effects like nausea and should be used cautiously in patients with decompensated liver disease.[1]

Fatigue, affecting over 50% of PBC patients, is a major contributor to impaired quality of life. It is generally unrelated to disease severity and considered a normal response in PBC. No specific licensed treatments exist, but exercise may help manage fatigue.[1]

Management of PSC

UDCA is the most widely used treatment for PSC, improving serum biliary enzyme levels, though its long-term impact on prognosis is uncertain. High doses (>28 mg/kg/day) have been linked to worsened outcomes and increased adverse events. While guidelines differ on its use, there is no evidence that standard doses (13–15 mg/kg/day) harm prognosis. As no alternative therapy exists, UDCA remains the recommended first-line treatment in clinical practice.[28]

The potential efficacy of statins in PSC has been explored in a limited capacity, with evidence stemming primarily from a single retrospective cohort study involving Swedish PSC patients, sourced from national databases. The study found that statin use was associated with a significant reduction in all-cause mortality, the combined outcome of death or liver transplantation and adverse liver events.[29]

When limited to patients with at least two statin prescriptions, only the association with death or liver transplantation remained significant. Key limitations included the lack of data on statin types, exclusion of PSC patients without IBD and unaccounted confounding factors like advanced liver disease that could have influenced statin use.[28]

Clinical trials for PSC face challenges due to the lack of standardized inclusion criteria and clear clinical endpoints. Similar to trials for PBC, PSC trials often focus on agents such as FXR agonists and PPAR agonists. Currently, there are no approved drug treatments for PSC and liver transplantation remains the primary treatment option.[1]

PSC is believed to be linked to gastrointestinal dysfunction, as many patients present with concurrent conditions like IBD. Recent clinical trials have explored targeting the gut microbiota, with promising results from antibiotic interventions (e.g., vancomycin, metronidazole) and fecal microbiota transplantation, which have shown improvement in biochemical markers. However, larger studies are needed to confirm these therapeutic approaches' effectiveness.[1]

EXPERTS' CONSENSUS ON THE MANAGEMENT OF CCLD

UDCA is the first-line treatment for PBC. It improves biochemical indices, delays fibrosis progression, reduces varices risk and enhances survival without transplant. Lifelong use is recommended.

Around 20% of PBC patients may show an incomplete response to UDCA, but continuing therapy reduces the risk of liver transplant or death by 1.8-fold compared to untreated patients.

OCA is a second-line option in PBC for patients with incomplete response to UDCA but should be avoided in decompensated cirrhosis due to side effects like pruritus and elevated LDL levels.

Cholestyramine, Rifampicin or Naltrexone can be used for managing pruritus in PBC; severe cases unresponsive to medical treatment may require liver transplantation. Fibrates, when added to UDCA, show promise in difficult-to-treat cases, although they may cause side effects like myalgias and reversible creatinine elevation.

Triple therapy with UDCA, OCA and fibrates has demonstrated better ALP reduction in challenging PBC cases. PSC is more common than PBC in India. UDCA remains the most used drug in this condition, but promising results from clinical trials with OCA, fibrates and Seladelpar require further data.

Antibiotics like vancomycin and altering the gut microbiota with probiotics or fecal microbiota transplantation (FMT) are potential future therapies for PSC. Emerging therapies for chronic cholestatic liver diseases under investigation include Cilofexor, norUDCA and Setanaxib. Fatigue and pruritus are the most common symptoms of PBC, with hyperlipidemia, metabolic bone disease and Sjogren's syndrome also frequently observed.

MANAGEMENT OF OTHER CONDITIONS CAUSING INTRAHEPATIC CHOLESTASIS

DILI with associated cholestasis

DILI is a challenging condition, often difficult to diagnose due to the absence of specific markers. Diagnosis primarily relies on excluding other causes, assessing clinical features and understanding the hepatotoxic potential of the implicated agent. Over 1200 agents, including prescription medications, herbal products and supplements, have been linked to liver injury, making management complex.[30] The primary approach to managing DILI is the immediate discontinuation of the

offending drug, along with avoiding future re-exposure to prevent further liver damage. Patients with jaundice require close monitoring with regular liver function tests and those with significant coagulopathy often require hospitalization.[31]

N-acetylcysteine (NAC), with its strong antioxidant properties, is beneficial in acute liver failure (ALF) due to idiosyncratic DILI, particularly in the early stages. In non-paracetamol-induced ALF, NAC has shown improved transplant-free survival rates. Given its favorable safety profile, NAC may be a reasonable option in patients with coagulopathy before the development of overt hepatic encephalopathy.[30]

Corticosteroids, although effective in autoimmune hepatitis, have uncertain benefits in ALF, as studies have shown mixed results. However, DILI patients with severe hepatocellular injury have demonstrated symptom resolution and faster recovery with corticosteroid therapy. Side effects such as infection, GI bleeding and diabetes must be considered carefully before use.[32]

UDCA, known for its hepatoprotective effects in cholestatic diseases, may also be useful in hepatocellular and mixed DILI. It has been shown to reduce bilirubin and transaminase levels, but more randomized controlled trials are needed to fully establish its therapeutic efficacy.[33]

Alcoholic liver disease associated cholestasis

ALD can be associated with cholestasis, particularly in severe alcoholic steatohepatitis (ASH), whether in the pre-cirrhotic or cirrhotic stages. In ALD, hepatocellular injury and fibrosis are often more pronounced compared to other liver conditions. Cholestasis is rarely observed in patients with NAFLD. In patients with alcoholic hepatitis (AH), cholestasis is an independent predictor of short-term outcomes.[34]

The medical management of alcohol use disorder (AUD) in patients with ALD includes the use of naltrexone, nalmefene, disulfiram and acamprosate, all of which are approved for treating AUD. However, disulfiram should be avoided in patients with severe ALD. Naltrexone, disulfiram and acamprosate are approved for promoting and maintaining abstinence in these patients.[33]

In an early placebo-controlled cross-over trial study conducted by Plevris et al, in 11 patients with alcoholic cirrhosis. After 4 weeks of UDCA treatment (15 mg/kg), significant reductions in bilirubin, GGT and ALT levels were observed compared to placebo. These findings suggest that UDCA may help reduce hepatic damage in ALD, even with continued alcohol consumption, warranting further trials.

In a study by Nikolovska et al, (2019), long-term therapy with UDCA (15 mg/kg/day for 36 months) improved clinical symptoms in 51 of 53 patients and biochemical markers of cholestasis and hepatocellular damage (ALP/GGT, transaminases and bilirubin) in 46 of 53 patients. Additionally, liver histology showed improvement in 12 of 29 patients with alcoholic steatosis and hepatitis.[36] A retrospective study in India found that UDCA significantly reduced elevated liver enzymes (AST, ALT, GGT) compared to Herbal Preparation 1 ($p<0.05$). The decrease in conjugated bilirubin was greater in the UDCA group (45.2%) versus Herbal Preparation 1 (33.5%, $p<0.001$). No serious adverse events were reported. UDCA is commonly used as an initial therapy for ALD patients with altered liver enzymes.[37]

Viral hepatitis with associated cholestasis

Atypical presentation of persistent cholestasis especially in acute viral hepatitis A infection, where impaired bile flow causes bile accumulation in the liver due to liver cell damage and inflammation. This condition is marked by elevated serum bile acids and bilirubin, with symptoms like jaundice and pruritus. Treatment with UDCA may stabilize cell membranes, but its effect on the overall progression of acute viral hepatitis is limited.[38] In a multicentre, double-blind trial of UDCA in chronic hepatitis C patients, UDCA significantly reduced ALT, AST and GGT levels, with the 600 mg/day dose being optimal for decreasing ALT and AST. The 900 mg/day dose further decreased GGT levels, particularly in patients with higher baseline GGT, but no effect on HCV-RNA was observed.[39]

Intrahepatic cholestasis of pregnancy (IHCP)

IHCP is a liver disorder occurring in the late second or third trimester, marked by itching, elevated bile acids and increased liver enzymes. It commonly affects older, multiparous women and those with a history of IHCP or contraceptive-induced cholestasis. Genetic mutations, particularly in the ABCB4 variant, contribute to its pathogenesis. High bile acid levels in IHCP can lead to fetal complications like arrhythmia, fetal distress, preterm delivery and fetal death, with risks increasing when bile acids exceed 40 µmol/l.[40]

UDCA is the preferred treatment for IHCP, reducing bile acids, improving liver function and relieving maternal symptoms. It normalizes liver enzymes in nearly 100% of cases and may lower fetal distress and future metabolic risks, though its effect on preterm birth is unclear. Meta-analysis studies report that UDCA significantly improves maternal outcomes in ICP, notably by reducing pruritus and improving liver function tests, including reductions in ALT and bile acid levels.[41-44] In terms of fetal and neonatal outcomes, meta-analyses indicate that UDCA treatment is associated with lower rates of preterm birth and reduced need for neonatal intensive care unit (NICU) admissions.[41,42] There is also a trend toward improved Apgar scores and reduced fetal distress.[41] These studies' finding suggest that UDCA is generally well tolerated, with mild gastrointestinal symptoms being the most

commonly reported adverse effects.[41-44] These findings emphasize UDCA's role in managing ICP, enhancing maternal and neonatal outcomes while maintaining a favourable safety profile. In severe IHCP, additional treatments like rifampicin and early delivery (at 37 weeks or earlier) are recommended. Breastfeeding is safe.[40]

EXPERTS' CONSENSUS ON THE OTHER CONDITIONS

DILI is commonly triggered by antibiotics like amoxycillin-clavulanic acid, hormonal medications such as contraceptive pills and anabolic steroids and alternative medicines like Giloy and excessive green tea consumption. Concomitant medication history is crucial for diagnosis, with history and R value helping differentiate between hepatocellular and cholestatic injury.

In cases of DILI with a hepatocellular pattern, N-acetylcysteine is preferred, while UDCA is recommended for cholestatic DILI. Steroids may help in conditions like DRESS syndrome, autoimmune hepatitis and immune checkpoint inhibitor-induced DILI. Chronic DILI, especially in older patients or those with cholestatic injury, can last over a year and may be associated with dyslipidemia and prolonged drug exposure. Secondary sclerosing cholangitis due to drugs like Floxuridine, Ketamine, Ceftriaxone or immune checkpoint inhibitors has a poor response to corticosteroids. Additionally, Vanishing Bile Duct Syndrome (observed in 7% of DILI patients) has poor outcomes, while autoimmune hepatitis (DIAIH), seen with drugs like Nitrofurantoin or Minocycline, is often treated with corticosteroids and doesn't relapse post-treatment.

UDCA plays a significant role in cholestatic DILI, especially in cases related to antibiotics or hormonal medications. For alcoholic hepatitis, corticosteroids and UDCA help reduce inflammation and jaundice, while plasma exchange may be beneficial in patients with high bilirubin who are not candidates for liver transplantation. Intrahepatic cholestasis of pregnancy (ICP), typically observed in the third trimester, is managed with UDCA as the first-line therapy. If symptoms persist, cholestyramine or Ademetionine can be added. Fetal monitoring is critical, with early delivery at 37 weeks recommended in severe cases.

CONCLUSION

CCLD are liver disorders marked by impaired bile flow, which leads to liver damage and systemic complications. In India, while PBC and PSC contribute to CCLD, other prevalent causes of intrahepatic cholestasis include viral hepatitis, DILI and ALD. Recent advances, such as non-invasive tools like transient elastography, have improved the diagnosis and monitoring of liver fibrosis in CCLD. Treatment options have expanded with the approval of Elafibranor and Seladelpar for PBC, offering promising new approaches. However, these therapies remain unavailable in India, where UDCA is the primary treatment for cholestatic liver disease, with OCA as a secondary option. For PSC, treatments remain limited, with UDCA showing some benefit, while emerging therapies like antibiotics and fecal microbiota transplantation show potential for future management.

India faces a significant CCLD burden, requiring greater awareness and early diagnosis. Expanding research into novel treatments and improving strategies to manage complications, such as cirrhosis and hepatocellular carcinoma, are critical. Addressing these needs will enhance outcomes for CCLD patients and help reduce the disease's broader impact on public health.

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