International Journal of Research in Medical Sciences
Wadhawan M. Int J Res Med Sci. 2025 Feb;13(2):949-957
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250286

Review Article

Updates in chronic cholestatic liver diseases: Indian expert recommendations for diagnosing and managing complex cases

Manav Wadhawan*

Department of Gastroenterology, BLK Max Super Specialty Hospital, New Delhi, India

Received: 27 November 2024
Accepted: 02 January 2025

***Correspondence:**
Dr. Manav Wadhawan
E-mail: manavwadhawan @gmail.com

ABSTRACT

Cholestatic liver diseases (CCLDs) encompass hepatobiliary disorders leading to impaired bile secretion or reduced production, causing liver damage and fibrosis. Diagnosis relies on differentiation between hepatocellular and cholestatic diseases based on liver function tests (LFTs). Histological testing aids in detecting cholestasis-related alterations, crucial for identifying conditions like primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Non-invasive tests like FIB-4 and aspartate transaminase to platelet count ratio index (APRI), nonalcoholic fatty liver disease (NAFLD) fibrosis scoring, and elastography, offer alternatives to liver biopsy for fibrosis assessment. Evolving diagnostic procedures, such as endoscopic ultrasound-guided biopsies, complement traditional methods. Chronic cholestatic liver disease management includes treatment with ursodeoxycholic acid (UDCA). Alcoholic liver disease requires abstinence and nutrition therapy, while NAFLD management involves lifestyle changes and medications. Drug-induced liver injury necessitates prompt discontinuation and may involve UDCA, corticosteroids, and targeted therapies. Emerging treatments include farnesoid X receptor agonists, peroxisome proliferator-activated receptor agonists, fibroblast growth factor 19 agonists, and immunosuppressive agents for conditions like PSC and nonalcoholic steatohepatitis. Ongoing evaluations explore various drug classes with newer therapeutic targets for these liver conditions.

Key words: Cholestatic liver diseases, Primary biliary cholangitis, Primary sclerosing cholangitis, Non-invasive tests, Nonalcoholic fatty liver disease, Ursodeoxycholic acid

INTRODUCTION

Chronic cholestatic liver diseases (CCLDs) are diverse hepatobiliary disorders causing impaired bile secretion that leads to liver damage and fibrosis. CCLDs can manifest at any age with symptoms like weariness, pruritis, and jaundice. Presence of CCLDs elevates the risk of comorbidities such as metabolic bone disease, vitamin deficiency, dyslipidemia, and hepatocellular carcinoma or cholangiocarcinoma. The clinical course varies due to genetic and environmental factors. CCLDs contribute significantly to global morbidity and mortality. In India, CCLD prevalence in clinical settings ranges from 10% to 50% .[1] Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) both induce bile stagnation, with distinct pathophysiological processes. PBC primarily affects women, and involves intrahepatic bile duct inflammation leading to cirrhosis, often asymptomatic until biochemical cholestasis is discovered. Although its exact cause is unknown, autoimmune origins are suggested, particularly in genetically predisposed individuals.[2,3] Meetings with gastroenterologists from India were organized to enhance comprehension of the burden of CCLD in India, including its diagnostic criteria, pathophysiology, and management. This review aims to offer insights gleaned from relevant literature and discussions with Indian specialists regarding the diagnosis and management of complex cases of CCLD, with the objective of obtaining a comprehensive understanding of the disorder.

Diagnosis of cholangitis

The diagnosis of primary cholangitis primarily hinges on specific serum liver function tests (LFTs) that indicate cholestatic hepatitis, frequently complemented by the detection of circulating antimitochondrial antibodies.[4]

INTERPRETATION OF LFTS: SPECIAL CONSIDERATIONS IN THE CONTEXT OF CHRONIC LIVER DISEASES

LFTs represent pivotal laboratory parameters essential for the identification of liver injury and aiding in differential diagnosis. These encompass a spectrum of enzymes, including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin, prothrombin time (PT), international normalized ratio (INR), total protein, and albumin. Table 1 provides a comprehensive overview of these fundamental LFTs.[5]

In the context of chronic liver diseases, there are several important considerations. Chronic liver diseases encompass conditions such as alcoholic liver disease, autoimmune liver diseases like primary biliary cirrhosis, and various forms of sclerosing cholangitis. In alcoholic liver disease, an elevated AST to ALT ratio exceeding 2:1 indicates increased AST activity and potential liver damage.Diagnosing autoimmune liver diseases relies on detecting specific liver-related autoantibodies, including anti-nuclear antibody (ANA), smooth muscle antibody (SMA), anti- liver kidney microsome type 1 (LKM1), and anti-liver cytosol antibody Type 1 (anti-LC1).

These autoantibodies serve as crucial markers for identifying autoimmune liver diseases and guiding treatment selection. The carbohydrate-deficient transferrin test is a highly specific diagnostic tool for assessing liver damage due to excessive alcohol consumption. It provides valuable insights into the extent of liver injury caused by chronic alcohol abuse, facilitating early intervention and tailored management strategies. Elevated levels of alpha-fetoprotein (AFP) serve as a valuable marker for detecting and monitoring hepatocellular malignancies. AFP levels offer prognostic information, guiding treatment decisions and patient care.

According to guidelines from the American College of Gastroenterology (ACG), elevations in liver function tests (LFTs) exceeding 2 times the upper limit of normal (ULN) may indicate drug-induced liver injury (DILI).[6] Patients with DILI require close monitoring of liver function and may need to discontinue specific medications, such as statins and anti-tuberculosis treatment, to mitigate the risk of irreversible liver damage. ACG guidelines stress the importance of vigilant monitoring and timely intervention in cases of DILI, underscoring the critical role of healthcare providers in ensuring patient safety and optimal outcomes.[7]

Role of LFTs in pathophysiology of CCLDs

ALT and AST elevation indicate damage or inflammation. ALP elevation can signify liver or bone disease. Elevated GGT indicates liver or bile duct disease. Elevated bilirubin levels suggest liver disease or impaired bile flow. Altered PT and INR indicate prolonged liver dysfunction. Liver dysfunction or malnutrition can lead to a decrease in total protein and albumin levels, Abnormal patterns aid in distinguishing hepatocellular and cholestatic diseases. LFTs are crucial for diagnosing, monitoring, assessing severity, and evaluating treatment response in liver.[5]

Synthetic function tests, such as albumin measurement, reflect the liver's protein maintenance role. Albumin mirrors liver function and nutritional status because its synthesis is altered based on factors like osmotic pressure. Reduced serum albumin signals liver disease, while low albumin with intact liver function points to issues like malnutrition or protein loss.

PT, a critical synthetic function test, evaluates the liver's role in coagulation by measuring the conversion of prothrombin to thrombin. In the liver, most coagulation factors that are crucial for factors II, V, VII, and X are synthesized. Delayed PT, despite uncompromised liver function, may indicate warfarin use, consumptive coagulopathy, or vitamin K deficiency.[5]

Elevated AFP indicates hepatocellular malignancies and chronic viral hepatitis. Elevated carbohydrate-deficient transferrin levels indicate alcohol-induced liver injury. Carbohydrate antigen 19-9 (CA19-9) is crucial for monitoring PSC, which if untreated can manifest into bile duct tumors. Serum ferritin level is useful for diagnosing hemochromatosis, which is marked by excessive iron absorption. However, ferritin, a positive acute-phase reactant, can also rise in response to various diseases. In acute hepatic failure, damaged hepatocytes may release ferritin into the circulation.[5]

Expert opinion on LFTs

AST, ALT, and ALP are markers of liver injury, albumin and PT indicate liver function, and bilirubin is assessed to evaluate liver metabolism.

Patients with significant LFT abnormalities, liver disease symptoms, or signs of decompensation should undergo detailed evaluations. Including prothrombin time in LFT is recommended as it reflects portal hypertension. An altered AST/ALT ratio may signal fibrosis, and AST is valuable for monitoring treatment response due to its shorter half-life and quick reduction during recovery.

Non-invasive tests for fibrosis

Non-invasive tests (NITs) are essential for assessing liver health, risk identification, prognosis assessment, disease monitoring, and therapeutic response prediction. They

offer non-invasive alternatives to liver biopsy, which is traditionally considered the "gold standard" for fibrosis assessment.[8] NITs offer a reliable, accessible, and cost-effective solution for disease monitoring and assessing fibrosis levels. Sequential NIT use improves identification of advanced fibrosis, enhancing overall diagnosis rates.[9,10]

Current guidelines emphasize the vital role of NITs in liver health assessment. These tests offer significant prognostic utility, predicting mortality and liver-related complications in conditions like nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) and other chronic liver ailments.[8,11] Fibrosis is a key prognostic factor in NAFLD that strongly correlates with liver-related outcomes and mortality. The detection of advanced fibrosis requires comprehensive hepatological assessment including confirmatory biopsy and tailored intensive therapies. Thus, fibrosis assessment is important in the prognostication and management of NAFLD.[8]

Noninvasive liver fibrosis assessments initially involved the use of class II biomarkers, which lacked direct representation of fibrosis-related changes. Subsequently, class I biomarkers were developed with the aim of precise identification. Imaging tools were initially used in the diagnosis of chronic hepatitis C, but they are now widely applied in the diagnosis of diverse liver diseases and in the monitoring of progression and prediction of clinical outcomes.[12] Current noninvasive methods show high accuracy in detecting advanced fibrosis. Integrating genetic, proteomic, and metabolomic assessments into these methods will allow early fibrosis identification and pave the way for future research and clinical applications.[13]

COMMONLY USED NONINVASIVE TESTS (NIT) IN CLINICAL PRACTICE

Simple scores for assessing liver fibrosis

Simple scores for liver fibrosis assessment use standard liver tests and patient data. These scores combine factors like liver enzymes, platelet count, and patient demographics to estimate fibrosis severity. The fibrosis-4 (FIB-4) index considers factors such as age, platelet count, and liver enzyme levels to predict fibrosis/cirrhosis. The aspartate AST-to-platelet ratio index (APRI) utilizes AST and platelet count for fibrosis assessment. These scores have been validated in large patient cohorts.[13]

The APRI is a noninvasive tool for liver fibrosis assessment in chronic liver diseases, including hepatitis C. It can accurately diagnose fibrosis and cirrhosis, thus potentially reducing the need for biopsies, especially in alcoholic liver disease. further validation is needed before routine clinical use. APRI is derived from AST and platelet count; therefore, it is suitable for rapid bedside or outpatient clinical evaluation.[13] In a retrospective study by Angulo et al, APRI was identified as a predictor of long-term outcomes such as liver-related complications, transplantation need, and overall mortality in patients with NAFLD. High APRI scores were associated with advanced fibrosis and elevated risk of liver-related events or transplantation. High-risk individuals had significantly higher adjusted hazard ratios (20.9 for liver-related events and 9.8 for death or transplantation) than the low-risk group. Thus, APRI was found to be clinically useful in identifying high-risk NAFLD patients.[14]

In a recent meta-analysis involving a cohort of 8855 patients with chronic hepatitis B virus (HBV) infection, varying threshold values for APRI, including both low (0.5) and high (1.5) cutoffs, were employed to gauge its ability to detect significant fibrosis (meta-analysis of histological data in viral hepatitis (METAVIR) $\geq$ F2). Previous studies indicated that APRI only has moderate level of sensitivity and accuracy in detection of HBV-related fibrosis.[15]

The NAFLD fibrosis score (NFS) is a noninvasive tool for assessing fibrosis in patients with NAFLD. The score is based on readily available clinical parameters such as age, hyperglycemia, body mass index (BMI), platelet count, albumin level, and AST/ALT ratio. Clinicians can easily use this scoring system during routine office visits or using online calculators.[16,17]

In the retrospective study by Angulo et al, NAFLD-FS was found to be a good predictor of long-term outcomes, including death or the need for liver transplantation.[15]

Proprietary serum tests biomarkers associated with fibrosis stage

Proprietary serum tests assess biomarkers related to the liver fibrosis stage. Examples include FibroTest, Fibrometer, and Hepascore, which have shown high diagnostic accuracy for advanced fibrosis and cirrhosis in alcoholic liver disease. These tests combine serum markers like PT, GGT, apolipoprotein A1, and α2-macroglobulin for fibrosis assessment. FibroTest and Fibrometer are linked to survival in alcoholic liver disease patients. Enhanced liver fibrosis (ELF) assay is validated for predicting significant fibrosis, cirrhosis, and clinical outcomes in patients with PBC.

Imaging techniques for liver stiffness

Imaging techniques are essential for assessing liver stiffness, a key indicator of liver fibrosis. Transient elastography (TE), or FibroScan, is a widely adopted method that employs ultrasound waves to measure liver stiffness. TE exhibits good diagnostic accuracy in detecting significant fibrosis and cirrhosis in various liver diseases. Other imaging methods like magnetic resonance elastography (MRE) and acoustic radiation force impulse (ARFI) imaging are also used to assess liver stiffness and fibrosis. MRE relies on magnetic resonance imaging, while ARFI imaging utilizes ultrasound waves to evaluate liver stiffness.[13]

Transient elastography

TE is an imaging tool used to detect both liver fibrosis and steatosis It allows measurement of stiffness (kPa) for fibrosis and attenuation parameter (dB/m) for steatosis and is recommended by the American Association for the Study of Liver Diseases (AASLD) for advanced fibrosis in NAFLD. It evaluates liver stiffness over a significantly larger area. In patients with high BMI (>30 kg/m²), there are challenges with acquiring accurate readings, but use of custom probes can help mitigate this limitation. In conditions like hepatitis or cholestasis, careful interpretation of results is required as there is scope for potential overestimation.[18,19] Longitudinal studies have shown that TE has good prognostic value for fibrosis in individuals with NAFLD. These assessments predict overall mortality and specific risks related to both liver complications and extra-hepatic causes.[20]

Shear wave elastography (2D SWE)

SWE is an ultrasound-based technique that provides real-time tissue stiffness measurements via induced shear waves. With a clinically relevant threshold of 13.1 kPa, SWE discriminates effectively between cases and controls based on liver stiffness. Additionally, in patients with cirrhosis, it can predict gastroesophageal varices at a diagnostic threshold of 26.5 kPa with a sensitivity of 88% and specificity of 85%.[21]

Liver biopsy and interventional radiology

Cholestasis histology assesses impaired bile flow disorders and reveals features like bile plugs. In PBC and PSC, abnormal histological findings include inflammation, fibrosis, and bile duct damage. In DILI, bile duct injury, hepatocellular damage, and inflammatory changes are evident on histology. Liver biopsy is crucial for diagnosing and managing cholestatic liver disorders by examining histological alterations.[5]

Liver biopsy is crucial for evaluating and diagnosing liver diseases. It enables functional and prognostic assessments. Interventional radiology has witnessed continuous growth, expanding the scope and variety of liver-related procedures, including biopsy, drainage, and ablation.[22] Percutaneous biopsy and drainage techniques are well established and reliable diagnostic tools with low complication rates.[23] Percutaneous biopsy of the liver (PBL) plays a crucial role in diagnosing parenchymal liver disease and assessing focal hepatic lesions. PBL is performed to gather critical information for diagnosis, prognosis, or treatment decisions. Despite advancements in imaging and serologic testing, PBL remains invaluable in uncertain diagnostic situations.[24]

Image guidance

For focal liver lesion biopsies, essential image guidance, including real-time ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), ensures accurate needle placement and facilitates the precise collection of tissue samples. Fusion imaging techniques, combining real-time ultrasound with other modalities, have demonstrated success in precise collection of biopsy samples of focal lesions.[25]

Guidelines of the British society of gastroenterology, the Royal College of Radiologists, and the Royal College of Pathology advocate use of image assistance to minimize complications in liver biopsy. Blind biopsies are discouraged, especially without prior liver imaging, and should only be considered when clinically or logistically justified.[25]

Bleeding is a common risk in liver biopsies, with rates reaching up to 10.9%. Major bleeding occurs in 0.1% to 4.6% of patients, and minor bleeding in up to 10.9% of patients. Risk factors for bleeding are patient age, inpatient status, comorbidities, and coagulation status. Procedure-related risks include needle size and the presence of a patent track on post-biopsy ultrasound.[26]

Computed tomography-guided biopsies

CT-guided percutaneous biopsies are crucial in diagnosing liver lesions. Evaluating radiation exposure is vital for radiation protection during these interventions. Deeper liver lesions require significantly increased radiation doses compared to superficial lesions. Procedures using additional biopsy-guiding CT spirals may result in higher radiation doses.[27]

Novel liver biopsy techniques

Innovative liver biopsy techniques broaden diagnostic possibilities. Endoscopic ultrasound-guided biopsy minimizes complications and targets fine-needle aspiration, showing promise in assessing focal lesions. Percutaneous ultrasound-guided cholecystocholangiography with microbubbles, combined with liver biopsy, is effective in diagnosing conditions like biliary atresia.[24]

Chinese guidelines for cholestatic liver diseases advocate diagnostic criteria using laboratory markers, CT, magnetic resonance cholangiopancreatography (MRCP), and ultrasound for cholestasis differentiation. Liver biopsy is recommended when the cause is uncertain, especially in unexplained intrahepatic cholestasis or suspected hereditary cases. Hemolytic disease is a pertinent consideration in jaundiced patients.[28]

Liver biopsy is essential for evaluating and diagnosing liver diseases and provides critical insights into liver health, prognosis, and treatment decisions. Advances in image-guided techniques and strict guidelines enhance safety and accuracy. Novel approaches, such as endoscopic ultrasound-guided biopsies and percutaneous ultrasound-guided cholecystocholangiography, hold

promise for improved diagnostics. In cholestatic liver diseases, comprehensive strategies involving laboratory markers, imaging, and genetic testing are recommended.

Expert opinion on CCLD diagnosis

GGT is a liver-specific marker. In alcohol-induced liver injury, elevated AST reflects hepatocyte damage, while GGT rise indicates enzyme induction. In cholestasis of pregnancy, elevated transaminases and bile acid levels are significant markers, often diagnosed via clinical examination and blood tests without the need for biopsy. Autoimmune tests can have false positive rates in the rage of 5%-10%, and MRCP can aid PBC diagnosis alongside elevated antimitochondrial antibody (AMA) levels. Liver biopsy remains the gold standard for PBC diagnosis.

Fibroscan is valuable for assessing steatosis and fibrosis in patients with NAFLD, especially when combined with noninvasive blood tests and imaging techniques. Presence of varices correlates with high liver fibrosis scores and portal hypertension, with platelet count being crucial for assessment. MRI-proton density fat fraction is a useful method for steatosis assessment in fatty liver.

More accurate tests are needed for patients with mid-range values on NITs to enable early intervention. Liver biopsy is often performed in patients with CCLD to diagnose and rule out overlap syndromes, as data on NIT use in CCLD is limited. Fibroscan can aid in assessing fibrosis in alcoholic cirrhosis and obese patients with NASH and may motivate lifestyle changes. Autoimmune antibodies like ANA, ASMA, anti-LKM-1, and IgG, along with specific titers, are preferred for diagnosis. AMA is a key predictor of CCLD risk.

Reduction in albumin levels indicates liver disease lasting over 3 weeks, while prolonged PT indicates severe hepatic dysfunction within 24 hours. Liver stiffness measurement (LSM) via TE is recommended in Baveno guidelines to assess high-risk varices. Endoscopy remains the primary method for diagnosing and managing esophageal varices.

Compensated advanced chronic liver disease (cACLD) is defined by LSM scores >15 kPa on TE. Ultrasound alone cannot quantify liver fat content, but indices like the fatty liver index, FibroScan-AST (FAST) score, and controlled attenuation parameter (CAP), based on CAP and AST levels, are useful for steatosis assessment. MELD-Na is commonly used to assess the prognosis of CLD.

Management approaches for CCLD

Cholestasis treatment focuses on the underlying cause and symptom management. Etiological interventions, removal of obstructions, and surgery are effective. UDCA is considered for PBC and PSC, while cessation is crucial for drug- or alcohol-induced liver diseases. Antiviral treatment is recommended for hepatitis B or C, and autoimmune hepatitis may require glucocorticoids and/or immunosuppressants. Lifestyle changes, including diet and exercise, are encouraged for metabolic-related fatty liver diseases.[29]

Management of PBC

The guidelines from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) advocate for the continuous use of UDCA as the primary treatment for PBC. Administered at a dose of 13-15 mg/kg/day, UDCA demonstrates efficacy in enhancing bile flow, protecting liver cells, reducing inflammation, and modulating the immune response, thereby improving LFTs. Moreover, UDCA treatment has been linked to improvements in biochemical markers, attenuation of histological progression, and enhanced survival rates, potentially negating the necessity for liver transplantation.

As a second-line therapy option, obeticholic acid (OCA) has garnered FDA approval for specific scenarios. It can be used adjunctively with UDCA for patients who have shown inadequate response to at least one year of UDCA therapy or as a standalone treatment for those unable to tolerate UDCA. Initial dosing of OCA for individuals with well-preserved liver function and compensated PBC typically begins at 5 mg daily, with the option to escalate to 10 mg daily after three months if tolerated and if LFTs persist abnormal. Ongoing investigations are underway to evaluate the efficacy of OCA in PBC patients, with particular focus on its benefits in those with decompensated liver disease. Notably, pruritus (itching) emerges as the most prevalent adverse effect associated with OCA, occasionally necessitating management with antihistamines or bile acid-binding resins.[28,29]

Management of PSC

Clinical trials in patients with PSC have not shown improvement in long-term outcomes with existing therapies. According to the International PSC Study Group, there is limited data on biomarkers of clinical effectiveness in patients with PSC. While UDCA may improve enzyme levels, a favorable prognosis is observed in patients with reduced ALP levels one year after starting UDCA treatment.[30]

Management of overlap syndrome with autoimmune hepatitis

Autoimmune hepatitis (AIH) coexisting with PBC and PSC is rare. AIH is usually managed with corticosteroids and immunosuppressive agents. In PBC with AIH overlap syndrome, combining corticosteroids and UDCA is common. A meta-analysis comparing treatment strategies found that corticosteroid and UDCA combination led to improvement in biochemical markers and higher transplant-free survival rates.[31]

Management of ALD & associated cholestasis

Alcohol abstinence stands as the cornerstone of alcoholic liver disease (ALD) treatment, often yielding significant improvements within a mere two weeks of cessation. Nutritional therapy assumes a pivotal role in managing ALD, while pharmacological interventions, such as pentoxifylline or prednisolone, are reserved for cases of alcoholic hepatitis. UDCA may be employed as a hepatoprotective agent, particularly in ALD patients with cholestasis, and in severe cases, liver transplantation emerges as a viable treatment option.[32]

Management of NAFLD & associated cholestasis

NAFLD being a lifestyle disease, lifestyle modifications have important role in its management. For management of NAFLD, a 45-minute exercise routine for at least 5 days a week and heart rate target between 60% and 70% of maximum are recommended. Activities like brisk walking, jogging, or rhythmic aerobic exercises should also be included in the workout regimen.[33]

For patients with NAFLD, weight reduction equivalent to 10% of the total body weight within a period of 6 to 8 months is recommended as part of the management plan.[34] Pilot studies suggest insulin sensitizers like thiazolidinediones and antioxidants such as vitamin E improve clinical and histological aspects of NASH. In a phase 3 trial by Sanyal et al, both vitamin E and pioglitazone notably reduced AST and ALT levels within 24 weeks, and these reductions were sustained throughout treatment, while bilirubin levels remained stable.[35] In a meta-analysis by Zhang et al on effectiveness of UDCA in NAFLD treatment, randomized controlled trials published before September 1, 2019, were comprehensively reviewed. The analysis revealed a significant reduction in ALT levels with UDCA treatment.[36]

Management of DILI

Effective management of DILI hinges on swift cessation of the suspected drug and the judicious use of therapeutic interventions. UDCA stands as a cornerstone therapy, complemented by corticosteroids in cases of hypersensitivity-driven hepatotoxicity. Adjunctive measures such as cholestyramine, carnitine, and N-acetylcysteine offer additional avenues for mitigating liver damage and promoting recovery.[37]

Expert opinions on management of CCLD

In Indian clinical settings, CCLDs such as PBC and PSC are not common, and treatment modalities have not significantly evolved. PSC is a challenging condition to treat. Steroids are effective in isolated autoimmune hepatitis cases, except for PSC-autoimmune overlap. For treating PBC, high-dose monotherapy with UDCA up to 20 mg/kg/day is typically used, with OCA sometimes used in combination with UDCA. OCA is dosed at 10 mg/day, but it can be hepatotoxic. Fenofibrate is generally considered a third-line drug.

In cases of DILI, anabolic steroids, and herbal drugs like Giloy are important, especially when cholestasis is present. Some patients may progress to cirrhosis and require liver transplantation. In ICP (intrahepatic cholestasis of pregnancy), UDCA is a commonly used drug, with second-line options including S-adenosyl-L-methionine (SAMe), cholestyramine, rifampicin, and anti-histaminic drugs. The standard UDCA dose for ICP is 15 mg/kg/day. In the Indian context, only few cases of NASH may exhibit cholestasis especially in cases of cirrhosis, regardless of the causality.

NEW THERAPEUTIC TARGETS AND DRUGS UNDER DEVELOPMENT FOR CCLD

Farnesoid X receptor (FXR) agonists

OCA, Tropifexor, Cilofexor, and EDP-305, are under investigation for PBC. A phase II trial revealed that EDP-305 significantly improved liver biochemical indicators in PBC compared to a placebo. Tropifexor and Cilofexor are also in phase II.[37]

Peroxisome proliferator-activated receptor (PPAR) agonists

PPARs are nuclear receptor proteins acting as transcription factors, with three isotypes: PPARα, PPARβ, and PPARγ. Fenofibrate, a PPARα agonist, and bezafibrate, a pan-PPAR agonist targeting all three isotypes, have shown efficacy in PBC, validated by the BEZURSO trial. Seladelpar, a selective PPARδ agonist, and Elafibranor, a dual PPARαδ agonist, exhibit reduction in ALP and total bilirubin levels, presenting promising options for cholestatic liver disease treatment in addition to UDCA. Both drugs now approved by USFDA for management of PBC.

Fibroblast growth factor 19 agonists

FGF19, induced by FXR activation in the intestine, serves as a potential therapeutic target for cholestatic liver diseases, particularly PBC. NGM282, a synthetic FGF19 analog, demonstrated significant reductions in ALP and transaminase levels in randomized trials involving patients with PBC, indicating its promise in mitigating liver damage and enhancing liver function.[37]

Immunosuppressive agents

Therapies targeting the "upstream" immune response in PBC include rituximab, which targets CD20 on B cells, showing potential in improving ALP levels. Ustekinumab, an anti-interleukin 12/23 antibody, demonstrated promise in enhancing ALP levels over 28 weeks, with some limitations in its effectiveness.[37]

Table 1: Normal ranges for liver function tests.[5]

Test	Normal range
Alanine transaminase (ALT)	0-45 IU/l
Aspartate transaminase (AST)	0-35 IU/l
Alkaline phosphatase (ALP)	30-120 IU/l
Gamma-glutamyl transferase (GGT)	0-30 IU/l
Bilirubin	2-17 mmoles/l
Prothrombin time (PT)	10.9-12.5 sec
Albumin	40-60 g/l
Total proteins	3-8.0 g/dl

Table 2: New therapeutic agents and targets for the treatment of PSC.[38]

Drug	Target	Development status
NorUDCA	Bile acid	Phase 3
OCA	FXR	Phase 2
Budesonide	Glucocorticoid receptor	Pilot study
Methotrexate	Folic acid	Pilot study
Etanercept and Infliximab	TNFα	Pilot study
Vancomycin		Pilot study
Probiotics		Pilot study

Table 3: New therapeutic agents and targets for NAFLD or NASH.

Drug	Target	Development status
Resmetirom	Thyroid hormone receptor beta (THR-β) agonist	USFDA approved
Lanifibranor	Pan-PPAR agonist	Phase 3
Efruxifermin	FGF-21	Phase 3
Semaglutide	GLP-1 RA	Phase 3
NorUDCA	Bile acid	Phase 3
Aramchol	Hepatic stearoyl CoA desaturase (SCD1)	Phase 2
Pegbelfirmin, and BFK8588A	FGF-21	Phase 2
MET 409	FXR	Phase 2
VK2809	THR- β	Phase 2

Antifibrotic drugs

Setanaxib, an anti-fibrotic agent targeting downstream processes, showed effectiveness in a PBC phase II study. It notably reduced serum ALP and γ GTP levels within six weeks without significant reported side effects.[38]

Expert opinions on novel therapies for CCLD management

Ongoing evaluations for PSC include nor-UDCA, SAMe, cholestyramine, OCA, fibrates, UV irradiation, and albumin dialysis. Clinical trials for NASH are ongoing for Lanifibranor, Efruxifermin and Semaglutide.

CONCLUSION

CCLDs encompass diverse hepatobiliary disorders characterized by impaired bile secretion or reduced bile formation, leading to liver damage. Conditions like PBC and PSC, primarily affect women and often progress asymptomatically. LFTs are crucial for differentiation between hepatocellular and cholestatic diseases. NITs like APRI, FIB-4 and transient elastography offer alternatives to liver biopsy. Image-guided techniques and interventions, including endoscopic ultrasound, are vital in liver disease assessment. Management involves treating underlying causes and symptoms. Promising treatments under clinical development are FXR agonists, PPAR agonists, FGF19 agonists, and immunosuppressive agents for various conditions like PBC, PSC, and NASH.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Ravindra BS, Lahoti D, Das K. Epidemiology and treatment practices of chronic cholestatic liver disease in India: a physician survey-based study. Int J Sci Rep. 2023;9:17-27.
2. Hasegawa S, Yoneda M, Kurita Y, Nogami A, Honda Y, Hosono K, et al. Cholestatic liver disease: Current treatment strategies and new therapeutic agents. Drugs. 2021;81:1181-92.
3. Parés A. Primary biliary cholangitis. Med Clin (Barc). 2018;151:242-9.
4. European Association for the Study of the Liver. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67:145-72.
5. Lala V, Zubair M, Minter DA. Liver function tests. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. Available at: https://www.ncbi.nlm.nih.gov. Accessed on 12 August 2024.
6. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol. 2017;112:18-35.
7. Ashraf J, Ali Khan M, Minhaj S, Khatti S, Aarij KM, Shehzad M, et al. Statins and abnormal liver function tests: Is there a correlation. Cureus. 2020;12(8):10145.
8. Sberna AL, Bouillet B, Rouland A, Brindisi MC, Nguyen A, Mouillot T, et al. European association for

the study of the liver (EASL), European association for the study of diabetes (EASD) and European association for the study of obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes. Diabetic Medicine. 2018;35(3):368-75.
9. Tapper EB, Sengupta N, Hunink MG, Afdhal NH, Lai M. Cost-effective evaluation of nonalcoholic fatty liver disease with NAFLD fibrosis score and vibration controlled transient elastography. Am J Gastroenterol. 2015;110:1298-304.
10. Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol. 2019;71:371-8.
11. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice guidance from the American association for the study of liver diseases. Hepatolo. 2018;67:328-57.
12. Martínez SM, Crespo G, Navasa M, Forns X. Noninvasive assessment of liver fibrosis. Hepatol. 2011;53:325-35.
13. Kruger FC, Daniels CR, Kidd M, Swart G, Brundyn K, van Rensburg C, et al. APRI: a simple bedside marker for advanced fibrosis that can avoid liver biopsy in patients with NAFLD/NASH. S Afr Med J. 2011;101:477-80.
14. Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Barrera F, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterol. 2013;145:782-9.
15. Zeng DW, Dong J, Liu YR, Jiang JJ, Zhu YY. Noninvasive models for assessment of liver fibrosis in patients with chronic hepatitis B virus infection. World J Gastroenterol. 2016;22:6663-72.
16. NAFLD fibrosis score. Available at: https://www.mdcalc.com. Accessed on 20th September 2023.
17. Alkhouri N, McCullough AJ. Non-invasive diagnosis of NASH and liver fibrosis within the spectrum of NAFLD. Gastroenterol Hepatol (NY). 2012;8:661-88.
18. Grandison GA, Angulo P. Can NASH be diagnosed, graded, and staged noninvasively? Clin Liver Dis. 2012;16:567-85.
19. Kemp W, Roberts S. FibroScan® and transient elastography. Aust Fam Physician. 2013;42:468-71.
20. Boursier J, Vergniol J, Guillet A, Hiriart JB, Lannes A, Le Bail B, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol. 2016;65:570-8.
21. Zaki, M, Hazem, M, Elsamman M. Shear wave elastography in assessment of liver stiffness and prediction of gastro-esophageal varices in patients with liver cirrhosis. Egypt J Radiol Nucl Med. 2019;50:1-9.
22. Ravindran S, Hancox SH, Howlett DC. Liver biopsy: past, present and future. Br J Hosp Med (Lond). 2016;77:90-5.
23. Shankar S, van Sonnenberg E, Silverman SG, Tuncali K. Interventional radiology procedures in the liver. Biopsy, drainage, and ablation. Clin Liver Dis. 2002;6:91-118.
24. Miraglia R, Maruzzelli L, Caruso S, Milazzo M, Marrone G, Mamone G, et al. Interventional radiology procedures in adult patients who underwent liver transplantation. World J Gastroenterol, 2009;15:684-93.
25. Neuberger J, Patel J, Caldwell H, Davies S, Hebditch V, Hollywood C, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. Gut. 2020;69:1382-403.
26. Midia M, Odedra D, Shuster A, Midia R, Muir J. Predictors of bleeding complications following percutaneous image-guided liver biopsy: a scoping review. Diagn Interv Radiol. 2019;25:71-80.
27. Zensen S, Opitz MK, Grueneisen JS, Li Y, Haubold J, Steinberg HL, et al. Radiation exposure, organ and effective dose of CT-guided liver biopsy as a function of lesion depth and size. J Radiol Prot. 2022;42(3):80.
28. Lu L, Chinese Society of Hepatology and Chinese Medical Association. Guidelines for the management of cholestatic liver diseases. J Clin Transl Hepatol. 2022;10:757-69.
29. de Vries EM, Wang J, Leeflang MM, Boonstra K, Weersma RK, Beuers UH, et al. Alkaline phosphatase at diagnosis of primary sclerosing cholangitis and 1 year later: evaluation of prognostic value. Liver Int. 2016;36:1867-75.
30. Freedman BL, Danford CJ, Patwardhan V, Bonder A. Treatment of overlap syndromes in autoimmune liver disease: a systematic review and meta-analysis. J Clin Med. 2020;9(5):1449.
31. Galán AI, Muñoz ME, Palomero J, Moreno C, Jiménez R. Role of S-adenosylmethionine on the hepatobiliary homeostasis of glutathione during cyclosporine A treatment. J Physiol Biochem. 2000;56(3):189-200.
32. Duseja A, Singh SP, Saraswat VA, Acharya SK, Chawla YK, Chowdhury S, et al. Non-alcoholic fatty liver disease and metabolic syndrome-Position Paper of the Indian National Association for the Study of the Liver, Endocrine Society of India, Indian College of Cardiology and Indian Society of Gastroenterology. J Clin Exp Hepatol. 2015;5:51-68.
33. Farrell GC, Wong VW, Chitturi S. NAFLD in Asia--as common and important as in the West. Nat Rev Gastroenterol Hepatol. 2013;10:307-18.
34. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010;362:1675-85.

35. Zhang W, Tang Y, Huang J, Hu H. Efficacy of ursodeoxycholic acid in non-alcoholic fatty liver disease: An updated meta-analysis of randomized controlled trials. Asia Pac J Clin Nutr. 2020;29:696-705.
36. Giordano C, Rivas J, Zervos X. An update on treatment of drug-induced liver injury. J Clin Transl Hepatol. 2014;2:74-9.
37. Hasegawa S, Yoneda M, Kurita Y, Nogami A, Honda Y, Hosono K, et al. Cholestatic liver disease: Current treatment strategies and new therapeutic agents. Drugs. 2021;81(10):1181-92.

Cite this article as: Wadhawan M. Updates in chronic cholestatic liver diseases: Indian expert recommendations for diagnosing and managing complex cases. Int J Res Med Sci 2025;13:949-57.