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Review Article

Expert consensus on the diagnosis and management of alcoholic liver disease

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ABSTRACT

Alcoholic liver disease (ALD) is a spectrum of liver injuries caused due to harmful use of alcohol. It is the primary cause of liver disease and is responsible for around 4% of mortality worldwide. ALD progresses from fatty liver to alcoholic hepatitis depending upon risk factors, such as continued alcohol consumption or comorbid liver diseases. Screening and diagnosis are suggested for patients with histological symptoms and in high-risk populations. Management of ALD includes strategies such as abstinence from alcohol consumption, nutrition therapy, pharmacological therapy, and liver transplantation, with alcohol abstinence being the most beneficial to reverse fatty liver conditions. Various novel treatment approaches having distinct mechanisms of action are also developed besides conventional corticosteroid therapy, which include microbiota-based precision medicine, monoclonal antibody therapy, hepatocyte regeneration therapy, epigenetic modulators, liver degeneration boosters, and targeting the gut-liver axis. Ursodeoxycholic acid (UDCA) has shown to benefit ALD patients with cholestasis by exerting biochemical improvements; hence, it can be considered as an adjunct therapy. National and regional advisory board meetings were conducted to discuss the current diagnostic and management techniques, including existing and novel pharmacological treatments available for ALD along with current clinical practices in India.

Keywords: ALD, Liver biopsy, Alcohol abstinence, Microbiota-based precision medicine, UDCA

INTRODUCTION

Alcoholic liver disease (ALD) is a core reason for liver diseases globally, and is a spectrum of liver injuries, ranging from hepatic steatosis to alcohol-associated cirrhosis, and is usually complicated by hepatocellular carcinoma (HCC). ALD contributes to the progression of chronic viral hepatitis, nonalcoholic fatty liver disease, and other severe liver diseases.[1] globally, ALD accounts for 4% of mortality and 5% of disability-adjusted life years (DALYS). In India, alcohol consumption is the most common cause of cirrhosis (34.3%), and approximately 20% of all liver disease patients are current alcohol consumers.[2]

Several regional and national advisory board meetings were conducted to discuss the current diagnostic and management practices for ALD in Indian clinical practice. According to the experts, ≥50% of patients with ald in the Indian setting belong to a low socioeconomic status and are from rural areas as, in general, there is better awareness in the urban population. They stated that ALD progression from fatty liver to alcoholic hepatitis (AH) and cirrhosis depends on several risk factors, such as continued heavy alcohol use, female sex, genetic susceptibility, diet, and comorbid liver disease.

DIAGNOSIS AND EVALUATION

Appropriate screening investigations are suggested for high risk-population such as patients identified from the alcohol rehabilitation clinics or heavy drinkers, or those patients presenting with extrahepatic manifestations of an

alcohol use disorder, such as pancreatitis or cardiomyopathy.[3]

Experts recommend using a questionnaire to track the patient's history of heavy alcohol consumption (>60 g/day for men and >40 g/day for women for >5 years); followed by a physical examination and testing for liver enzymes, such as gamma-glutamyl transpeptidase (GGT), serum alanine aminotransferase (ALT), and aspartate aminotransferase (AST).[3] Diagnostic techniques include imaging (ultrasonography [USG], computed tomography [CT] scan, or magnetic resonance imaging [MRI]), and liver biopsy, specifically the novel endoscopic ultrasound-guided liver biopsy.[3-5] After confirmation of ALD, it is necessary to differentiate between AH and cirrhosis based on the extent of liver fibrosis using transient elastography (TE).[3,5] Clinical diagnosis parameters include the onset of jaundice, which occurs within two months of continued consumption of >40 g alcohol/day for women or 60 g alcohol/day for men for >6 months. In early stages of the disease, physical examination is unremarkable; however, in severe cases of acute AH, USG of the abdomen may reveal an enlarged liver and signs of portal hypertension.

FibroScan

TE (FibroScan) is a new, noninvasive, rapid, and reproducible method that measures liver stiffness (LS). LS is an excellent surrogate marker of advanced fibrosis (stage F3) and cirrhosis (stage F4), outperforming all previous noninvasive approaches to detect cirrhosis (Figure 1). According to the experts, FibroScan is an efficient technique to estimate the severity of fibrosis, as well as some amount of steatosis.[6]

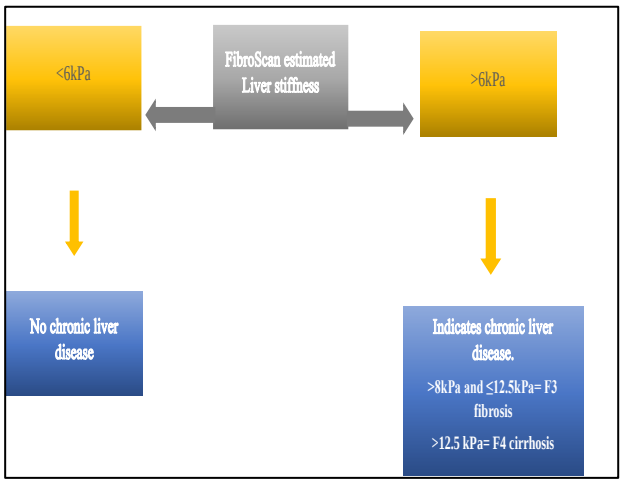

Figure 1: Measurement and interpretation of liver stiffness by FibroScan.

Liver biopsy

Liver biopsy is the gold standard for diagnosis as it is the direct measurement of liver fibrosis and a significant predictor of disease progression. However, only 2% to 3% of suspected alcoholics undergo biopsy in clinical practice. Liver biopsy is beneficial for ALD patients without a precise diagnosis and in patients in whom the clinician suspects more than one type of underlying liver disease. It is also favorable in establishing the stage and severity of the liver disease. Liver biopsy can facilitate the differentiation between simple steatosis and steatohepatitis based on distinct histological features. Limitations include treatment of biopsy bleeds, which may require hepatic artery angiography to diagnose bleeding sites and interventions and processing of liver biopsies.[5]

TREATMENT OF ALD

ALD treatment strategies include lifestyle changes such as abstinence from alcohol consumption and controlling obesity, nutrition therapy, pharmacological therapy, and liver transplantation (Figure 2).[7]

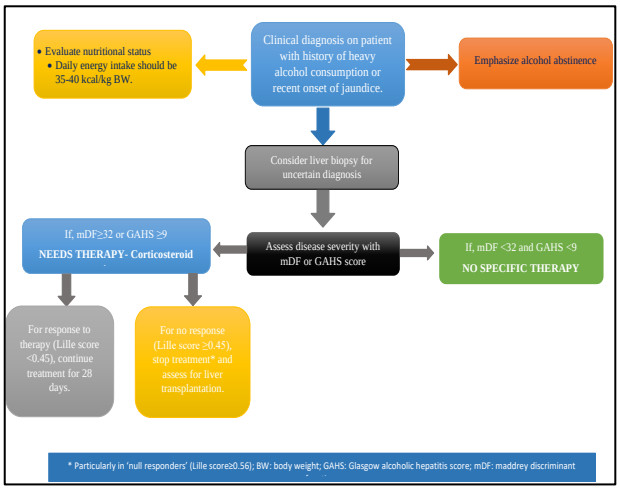

Figure 2: Proposed therapeutic algorithm for suspected ALD patients.

Abstinence-A therapy with proven benefit

According to the experts, patients with severe ALD should practice abstinence from alcohol consumption.[7] ALD patients with continuing alcohol consumption have an increased rate of variceal bleeding, risk of developing HCC, and death.[7] Fatty liver is reversible with abstinence in more than 90% of patients at four to six weeks.[7]

Baclofen, a gamma-aminobutyric acid (GABA-B) receptor agonist, increases the abstinence rate and alleviates relapse in alcohol-dependent patients. It is the only alcohol pharmacotherapy tested in patients with significant liver disease.[3]

Nutritional therapy-a therapy with likely benefit

The experts reinstated that since patients with chronic alcohol abuse have a deficiency of macro and

micronutrients, nutritional supplements can be useful in improving prognosis. It was found that patients with a daily calorie intake below 21.5 kcal/kg of body weight (BW) had a significantly higher risk of mortality and infections.[3] The energy intake is suggested to be 35-40 kilocalories/kg BW, and protein intake to be 1.5-2 g/kg BW. Other measures include increasing the frequency of meals, incorporating night-time snacks rich in proteins and preparing an individualized diet plan.[8] β-carotene, vitamins A, C, and E, zinc, and selenium supplementation that potentially counter the oxidative stress associated with ALD are of crucial importance.[1]

Abstinence and nutritional assessment or intervention are proven treatment modalities at any stage of the disease.

Pharmacological treatment

Various pharmacological therapies currently available.

Corticosteroids: Beneficial pharmacotherapy for ALD

Evidence suggests that prednisolone (40 mg/day) or methylprednisolone (32 mg/day) can be prescribed for 28 days.[8] Steroid therapy improves short-term survival at one month but has no further mortality benefit, and around 30%-40% of patients are non-responsive to the treatment. Experts stated that corticosteroids, because they increase viral replication, should not be prescribed to patients with active viral infections, including hepatitis C. They recommended to perform pan cultures, blood and urine cultures, and chest X-rays to identify any sepsis and initiate antibiotic prophylaxis.[8] Corticosteroid therapy exhibits an increased risk of sepsis and GI bleeding and has numerous contraindications. Corticosteroids should be stopped in patients with no response, particularly "null responders" (defined by Lille score ≥0.56). Patients with active bacterial infections should avoid steroids; fever and leukocytosis may deter physicians from prescribing corticosteroids due to a concern that the patient may be suffering from an infection.[9] Steroids should be avoided in patients with massive ascites, but are advisable for patients having jaundice and coagulopathy without any ascites or renal dysfunction.[8] Steroids should be stopped on no improvement after 1 week of treatment, to reduce risk of infection because of immunosuppression.[8]

N-acetyl cysteine: A potential useful pharmacotherapy

N-acetyl cysteine exerts antioxidant properties, and when combined with corticosteroids, reduces the risk of renal failure and mortality. Further, N-acetyl cysteine has a better safety profile than corticosteroids and exhibits no immunosuppressive side effects.[1,3,8]

Fecal microbiota transplantation (FMT): An alternative therapy

It is a promising alternative for patients ineligible or non-responsive to steroid treatment and those with persistent liver failure despite the completion of steroids. The experts state that FMT is complicated as preparing the fecal microbiota is complex, and identifying a suitable donor is challenging.[11]

Pentoxifylline

It is a competitive, non-selective phosphodiesterase inhibitor that inhibits tumor necrosis factor (TNF) and leukotriene synthesis to reduce liver inflammation and disease progression. Pentoxifylline has a better safety profile than steroids and is effective in patients with contraindications to corticosteroids. Evidence for a survival benefit of pentoxifylline therapy in patients with severe AH is very weak, and the drug is no longer recommended.[3]

S-adenosylmethionine therapy (SAMe)

SAMe effectively increases hepatic glutathione levels, the natural defense mechanism against oxidative stress, and traps excess free radicals in patients with ALD. SAMe therapy was reported to reduce mortality or liver transplant incidence in ALD patients.[12] SAMe is particularly important in opposing the toxicity of free oxygen radicals generated by various pathogens, including alcohol, which causes oxidative stress primarily by the induction of cytochrome P4502E1 (CYP2E1) and its metabolite acetaldehyde.[13]

Other therapeutic agents

Metadoxine is an antioxidant that aids in the synthesis of glutathione and inhibits hepatic steatosis.

Colchicine, an anti-fibrotic agent, has failed to improve short-term survival in AH; hence, it is not recommended.[7]

Phosphatidyl choline attenuates ethanol-induced fibrosis. It has a half-life of 10-14 days which can be longer with more chronic, repeated heavy alcohol consumption.[1]

Combination of vitamin E and antioxidants showed no benefit, but it can be used as it does not cause any side effects.[8,14]

Extracorporeal liver support procedures are potentially useful for patients with severe AH as they can eliminate some potentially damaging circulating molecules.

However, these extracorporeal liver support devices have demonstrated no clear benefit.[3]

Cholestasis and ALD: role of UDCA

Patients with ALD frequently manifest clinical or histologic evidence of cholestasis, presenting elevated serum concentrations of bile acids and cholic acid.[15] UDCA targets different pathogenetic processes of cholestatic liver disease, it protects injured

cholangiocytes against toxic effects of bile acids, stimulates impaired biliary secretion, inhibits hepatocyte apoptosis, or demonstrates cytoprotective action towards cholangiocytes. The mechanism of action depends on the specific cholestatic liver disease and the stage of the disease.[16] According to the experts, UDCA is beneficial in ALD patients with cholestasis and exhibits biochemical improvement far better than histological improvement. UDCA has several beneficial properties, such as anti-apoptotic, anti-inflammatory, antioxidant, immunomodulatory, and it increases the hydrophilic bile acid pool, thereby providing a cytoprotective effect.[15]

A study demonstrated that UDCA improves biochemical tests of cholestasis in primary biliary cirrhosis and primary sclerosing cholangitis. In a placebo-controlled cross-over trial in 11 patients with alcoholic cirrhosis, four weeks of treatment with UDCA (15 mg/kg) caused a significant decrease in bilirubin and GGT levels compared with placebo. UDCA therapy also caused a significant reduction in ALT levels suggesting an effective treatment of hepatic damage in ALD despite continued alcohol abuse.[17]

Novel treatment strategies

In novel treatment strategies target actions and treatment options are shown as follows in the Table 1.

Table 1: Novel treatment strategies.

Target action	Treatment options
Agents targeting hepatic inflammation[18]	Anakinra- a recombinant IL-1Ra
	Canakinumab-a recombinant human monoclonal antibody against IL-1β.
	Emricasan-a pan-caspase inhibitor that appears to decrease amino transferase activity, decreases apoptosis and inflammation.
Epigenetic modulators[18]	Sulfated oxysterol (DUR-928)- an endogenous molecule that modulates nuclear receptors regulates lipid homeostasis, inflammation, cell survival and tissue regeneration.
Boosting liver degenration[18]	G-CSF facilitates the mobilization of immune cells from bone marrow that may aid liver regeneration
	IL-22 is a pluripotent cytokine and member of the IL-10 family affecting parenchymal cells
	OCA is a selective FXR agonist that is 100-fold more potent than the endogenous ligands of the receptor.
Targets the gut-liver axis[18]	Antibiotics- rifaximin or vancomycin, gentamicin, and meropenem combination.
	Bovine colostrum- rich in immunoglobulin G antibodies, reduces translocation of bacterial products and subsequent inflammatory responses.
	Zinc supplementation regulates tight junctions between intestinal epithelial cells and controls bacterial translocation.
	Probiotics administration

*IL, interleukin; G-CSF, granulocyte-colony stimulating growth factor, OCA, obeticholic acid; FXR, farnesoid X receptor.

Microbiota-based precision medicine in ALD

The expert panel mentioned that dysbiotic gut bacteria engage in the development and progression of severe alcoholic hepatitis (AH). Specific gut microbiota, their interactions, and metabolites are associated with complications of SAH and treatment outcomes. Microbiota-based precision medicine as adjuvant treatment may be a new therapeutic area. Specific microbiota and their interactions show promising results as an adjuvant treatment but not as individual therapy.[19]

Hepatocyte regeneration therapies

Granulocyte-colony-stimulating factor (G-CSF) improves the functioning of normal and dysfunctional granulocyte which in turn stimulates liver regeneration, and it also mobilizes hematopoietic stem cells which can protect against liver injury, and improve survival rates in ALD patient.[20]

Interleukin (IL)-22 is a hepatoprotective cytokine that protects against AH via multiple targets. It displays anti-apoptotic, anti-oxidative, anti-lipogenic, and proliferative effects on hepatocytes and promotes the production of antimicrobial proteins.[18,20]

Monoclonal antibody therapies

Monoclonal antibody therapies targeting inflammatory cytokines, including TNFα and IL1β, are novel treatment strategies for ALD. Promising agents such as anakinra, and canakinumab, IL-1 β receptor antagonists, can prevent or suppress hepatic inflammation. They are being tested in combination with zinc and pentoxifylline in trials, and the results are awaited.[18]

CONCLUSION

ALD is the primary cause of liver disease and accounts for approximately 4% of mortality worldwide and is more likely to occur in those consuming large quantities of alcohol daily for several years. ALD can be clinically diagnosed based on the appropriate alcohol intake history, fever, jaundice, ascites, and testing of liver enzymes. Imaging techniques such as USG, CT, MRI,

and liver biopsy are essential too. Liver biopsy aids in the confirmation of ALD. FibroScan is an efficient, non-invasive, and reproducible technique to estimate the severity of fibrosis by measuring liver stiffness. Alcohol abstinence is a standard approach for managing ALD. Since most of the ALD patients are malnourished, nutritional supplementation consisting of vitamins and minerals (including zinc), protein (1.5-2 g/kg BW), and calories is essential. Corticosteroid treatment is recommended for treating ALD but should be avoided in patients with active viral infections and stopped in patients with no response, particularly "null responders." Other treatments, such as antioxidants, anti-TNF-alpha inhibitors, and SAMe therapy, are effective pharmacological treatments for ALD. Currently, multiple novel treatment approaches are introduced with various therapeutic targets that may benefit in managing ALD effectively. New approaches to treatment that reduce the inflammatory component and increase liver regeneration while maintaining differentiated liver functions are needed. The complexity of the pathogenesis of ALD will likely require combination therapy to improve recovery significantly. The rapid expansion of knowledge and understanding of this problem should facilitate the development of new treatments.

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REFERENCES

1. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-related liver diseases: 2019 practice guidance from the American association for the study of liver diseases. Hepatology. 2020;71:306-33.
2. Mitra S, De A, Chowdhury A. Epidemiology of non-alcoholic and alcoholic fatty liver diseases. Trans Gastro Hepato. 2020;5:1-17.
3. EASL clinical practical guidelines: Management of alcoholic liver disease. J Hepatol. 2012;57:399-420.
4. Johnson KD, Yee EU, Laoveeravat P, Perisetti A, Thandassery RB, Tharian B. Endoscopic ultrasound guided liver biopsy: Recent evidence. World J Gastrointest Endosc 2020;12:83-97.
5. Torruellas C, French S, Medici V. Diagnosis of alcoholic liver disease. World J Gastroenterol. 2014;20:11684-99.
6. Mueller S, Sandrin L. Liver stiffness: A novel parameter for the diagnosis of liver disease. Hepat Med 2010;2:49-67.
7. Marsano LS, Mendez C, Hill D, Barve S, McClain CJ. Diagnosis and treatment of alcoholic liver disease and its complications. Alcohol Res Health. 2003;27:247-56.
8. Maher JJ. Alcoholic steatohepatitis: Management and prognosis. Curr Gastroenterol Rep. 2007;9:39-46.
9. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatol. 2010;51:307-28.
10. Tijera FH, Servin-Caamano AI, Cruz-Herrera J, Serralde- Zuniga AE, Perez-Torres E, Abdo-Francis JM et al. Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis. World J Gastroenterol. 2015;21:4975-85.
11. Shasthry SM. Fecal microbiota transplantation in alcohol related liver diseases. Clin Mol Hepatol. 2020;26(3):294-301.
12. Medici V, Virata MC, Peerson JM, Stabler SP, French SW, Albanese A et al. S-Adenosylmethionine treatment of alcoholic liver disease: A double-blind, randomized, placebo-controlled trial. Alcohol Clin Exp Res. 2011;35:1960-5.
13. Lieber CS. S-Adenosyl-L-methionine: Its role in the treatment of liver disorders. Amer J Clini Nutr. 2002;76:1183S-7S.
14. Nanji AA, Yang EK, Fogt F, Sadrzadeh SM, Dannenberg AJ. Medium chain triglycerides and vitamin E reduce the severity of established experimental alcoholic liver disease. J Pharmacol Exp Ther. 1996;277:1694-700.
15. Tung B Y, Carithers Jr R L. Cholestasis and alcoholic liver disease. Clin Liv Dis. 1999;3:585-601.
16. Paumgartner G, Beuers U. Mechanisms of action and therapeutic efficacy of ursodeoxycholic acid in cholestatic liver disease. Clin Liv Dis. 2004;8:67-81.
17. Pelvris JN, Hayes PC, Bouchier IAD, Pelvris J. Ursodeoxycholic acid in the treatment of alcoholic liver-disease. Eur J Gastroenterol Hepatol. 1991;3:653-6.
18. David T, Gynogyi S. Emerging medical therapies for severe alcoholic hepatitis. Clin Mol Hepatol. 2020;26:686-96.
19. Philips CA, Augustine P, Ganesan K, Ranade S, Chopra V, Patil K et al. The role of gut microbiota in clinical complications, disease severity, and treatment response in severe alcoholic hepatitis. Indian J Gastroenterol. 2022;41:37-51.
20. Wang H, Mehal W, Nagy LE, Rotman Y. Immunological mechanisms and therapeutic targets of fatty liver diseases. Cell Mol Immun. 2020;18:73-91.

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