Recent Developments and Novel Therapeutics in Alcohol-Associated Liver Disease

Avesh J. Thuluvath, MD, MS,[1] and Steven Flamm, MD[2]

[1]Division of Digestive and Liver Diseases, Columbia University Irving Medical Center, New York, New York

[2]Division of Digestive Diseases and Nutrition, Rush University Medical Center, Chicago, Illinois

Corresponding author:
Steven Flamm, MD
Rush University Medical Center
1725 W. Harrison Street, Suite 229
Chicago, IL 60612
Tel: (312) 942-2301
E-mail: steven_flamm@rush.edu

Abstract: The landscape of alcohol-associated liver disease (ALD) has changed dramatically in the past two decades. Gut dysbiosis has emerged as a critical driver of ALD pathophysiology, with growing evidence showing that the fungal mycobiome and intestinal virome amplify alcohol-induced hepatic inflammation. Readily available ethanol biomarkers have facilitated accurate monitoring of alcohol use in patients with ALD, providing objective markers to support periods of abstinence. Emerging data suggest that an interdisciplinary approach, including early initiation of pharmacotherapy for alcohol use disorder and treatment of psychiatric comorbidities, slows the progression of ALD. Most notably, the acceptance of early liver transplant (LT) in patients with severe alcohol-associated hepatitis has fundamentally changed clinical management of ALD. Numerous studies have shown that early LT (without the historical prerequisite of abstinence for 6 months) results in significant survival benefits in carefully selected patients with ALD. The long-term outcomes after early LT for ALD, however, remain unknown and will only be clear with time. This article highlights recent developments in the field of ALD, including new insights into ALD pathophysiology, biomarkers, and treatment modalities.

Keywords
Alcohol-associated liver disease, alcohol-associated hepatitis, early liver transplant, novel therapeutics, interdisciplinary care

Alcohol-associated liver disease (ALD) represents a spectrum of pathology ranging from steatotic liver disease (SLD) to alcohol-associated hepatitis (AH) and alcohol-associated cirrhosis.[1] ALD is now a leading cause of liver-related morbidity and mortality worldwide. As of 2017, an estimated 23.6 million individuals carried a diagnosis of ALD cirrhosis, with an increasing prevalence of disease in women and young adults.[2-5] This estimate likely underrepresents the current global disease burden, as ALD is often only diagnosed when patients develop advanced liver disease and related complications.[6] The COVID-19 pandemic significantly altered the ALD landscape with increased social isolation, anxiety, and depression, resulting in a higher incidence of alcohol use disorder (AUD) and AH-related hospitalizations, most notably in Hispanic patients in the United States.[7-9] Finally, the ALD treatment paradigm has shifted

dramatically over the past decade, with a wider acceptance of early liver transplant (LT) (ie, without the traditional 6 months of abstinence from alcohol) for severe AH and ALD cirrhosis, increased emphasis on pharmacotherapy for AUD, and an emphasis on interdisciplinary care. This article provides a focused review of recent developments in the field of ALD, including recent changes in AUD and ALD nomenclature and emerging insights into ALD pathophysiology, biomarkers, and treatment modalities.

Nomenclature

The nomenclature used to describe harmful patterns of alcohol use changed with the publication of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* in 2013. The terms *alcohol abuse* and *alcohol dependence* have been replaced by *alcohol use disorder,* with mild, moderate, and severe AUD classifications implemented to define the spectrum of symptoms and negative consequences attributed to alcohol use.[10] Binge drinking, a pattern of unhealthy drinking with significant impact on health outcomes, is defined as at least 4 or at least 5 drinks over a 2-hour period for adult women and men, respectively. Binge drinking is reported in up to 26% of adults and increases the risk of ALD.[11,12] In the field of hepatology, the term *alcoholic cirrhosis* has been replaced with *alcohol-associated liver disease*, reducing the stigma and negative connotations associated with the previous nomenclature. Steatohepatitis caused by alcohol intake is now referred to as *alcohol-associated steatohepatitis*. The term *alcoholic hepatitis* to describe severe liver inflammation caused by heavy alcohol use has largely persisted, although there has been a movement to use *alcohol-associated hepatitis* instead. It remains unclear whether this long-standing terminology will be replaced in the ALD literature given overall trends away from using the term *alcoholic*.[1]

The multisociety Delphi consensus statement published in 2023, which led to the new SLD nomenclature, replacing the term *nonalcoholic fatty liver disease* with *metabolic dysfunction-associated steatotic liver disease* (MASLD), notably also defined a new subset of patients with MetALD,[13] referring to patients with MASLD and increased alcohol intake. Men who consume more than 60 g of alcohol per day and women who consume more than 50 g of alcohol per day are classified as having ALD (regardless of MASLD risk factors), whereas men with MASLD who consume more than 30 g of alcohol per day and women who consume more than 20 g of alcohol per day now fall within the spectrum of MetALD disease. This new classification is critical to both clinical prognosis and research endeavors in SLD, as patients with MetALD demonstrate an accelerated progression of liver disease, owing to the synergistic effects of MASLD and alcohol.[13]

Pathophysiology

The inflammatory cascade triggered by alcohol metabolism and its impact on fatty acid synthesis and oxidation have been well described in the ALD literature.[1,14] Excessive alcohol consumption increases the production of acetaldehyde and reactive oxygen species while also leading to glutathione depletion and lipid peroxidation. This inflammatory cascade triggers hepatocyte damage and death, eventually stimulating progressive hepatic fibrosis.

In recent years, the pathogenesis of ALD has been further linked to gut microbiota changes, loss of intestinal epithelial integrity, and specific genetic variants. The gut-liver axis plays a crucial role in ALD pathobiology, particularly in ALD cirrhosis and AH. Data on the association between gut dysbiosis and early stages of ALD are less robust, with studies demonstrating mixed results, potentially because of difficulty differentiating changes in the gut microbiota owing to alcohol use alone vs underlying ALD.[15-17] Comorbid psychiatric disorders represent another potential confounder in early ALD, as depression and anxiety have been associated with AUD, gut microbiome changes, and intestinal permeability.[16,18]

The association between dysbiosis, ALD cirrhosis, and AH is more established. Patients with ALD cirrhosis have a relative predominance of specific bacteria taxa such as Enterobacteriaceae and decreased abundance of Lachnospiraceae and Ruminococcaceae. Decreased microbiome diversity is also evident in patients with AH, characterized by proliferation of *Escherichia coli* and *Enterococcus*.[17,19] *Enterococcus faecalis* is particularly abundant in patients with ALD; this bacterium secretes cytolysin, an exotoxin associated with greater severity of AH and higher risk of mortality.[19] The presence of increased pathogenic bacteria described in ALD leads to higher deleterious exotoxin production and other harmful microbial products such as lipopolysaccharides, which travel to the liver via the portal circulation and induce inflammation, hepatocyte death, and eventual fibrosis. Patients with ALD and cirrhosis who continue to consume alcohol also demonstrate increased secondary bile acid formation and enterohepatic circulation of bile acids, leading to cell membrane destabilization, intestinal barrier dysfunction, and increased hepatic vulnerability to alcohol-related injury.[20]

Although most studies have focused on the bacterial microbiome, recent data demonstrate that the fungal mycobiome and intestinal virome could also amplify the impact of alcohol use on hepatic inflammation, contributing to the development of ALD. Lang and colleagues found that *Candida albicans* were relatively predominant

Table 1. Direct Biomarkers of Ethanol Consumption

Biomarker	Specimen	Detection window	Threshold	Sensitivity	Specificity	PPV	NPV
PEth	Blood	3-4 weeks	20 ng/mL	73%-100%	66%-96%	85%	100%
EtG	Urine	3-7 days	500 ng/mL	70%-89%	93%-99%	81%-97%	85%-99%
EtG	Hair	3-6 months	30 pg/mg	58%-100%	66%-100%	68%-100%	86%-100%
EtS	Urine	3-7 days	75 ng/mL	73%-82%	86%-89%	70%	93%

EtG, ethyl glucuronide; EtS, ethyl sulfate; NPV, negative predictive value; PEth, phosphatidylethanol; PPV, positive predictive value.

in patients with ALD compared with controls without ALD or AUD.[21] Serum anti–*Saccharomyces cerevisiae* levels were also higher in patients with AH and associated with greater mortality in this population. Additionally, *Parvoviridae* and *Herpesviridae* were significantly higher in patients with AH, suggesting that the intestinal virome could play a role in the development and progression of ALD.[22]

Recently, individual genetic background has been recognized as a critical contributor to the pathophysiology of ALD, with specific genes increasing susceptibility to ALD or serving in protective roles. Most notably, patatin-like phospholipase domain-containing 3 (*PNPLA3*), hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*), and serpin family A member 1 (*SERPINA1*) have been identified as genes that increase an individual's susceptibility to ALD.[23,24] Specific loci associated with ALD include *rs58542926* in transmembrane 6 superfamily member 2 (*TM6SF2*) and *rs641738* in membrane-bound O-acyltransferase domain-containing 7 (*MBOAT7*) genes. Conversely, polymorphism in *HSD17B13* has been associated with a protective effect on ALD.[25]

Biomarkers of Alcohol Use

Biomarkers of alcohol consumption can be classified as direct or indirect measurements and have become increasingly crucial to the management of patients with ALD. The increased accessibility of accurate direct biomarkers of ethanol intake has significantly impacted the care of patients with ALD, allowing clinicians to monitor alcohol consumption without relying solely on patient report. This is particularly critical in patients being considered for LT and in LT recipients, in whom alcohol abstinence is of critical importance.

Indirect Biomarkers

Indirect biomarkers represent biologic changes that capture end-organ manifestations of ethanol ingestion. Notable indirect biomarkers of ethanol consumption include aminotransferase elevations (with aspartate aminotransferase [AST] typically greater than 2 times that of alanine aminotransferase [ALT]), elevation in gamma-glutamyl transpeptidase (GGT), increased mean corpuscular volume (MCV), and increased carbohydrate-deficient transferrin (CDT). Elevations in AST, ALT, and GGT are not specific to ethanol consumption and can be attributable to both generalized hepatic and nonhepatic organ dysfunction, limiting their utility. Both ALT and AST are found in many tissues. Although ALT is most highly concentrated in the liver, AST is highly enriched in hepatic, cardiac, and muscle tissues. Elevations in ALT and AST represent nonspecific hepatocyte injury, which can occur with numerous hepatic insults and not ethanol alone. GGT is a microsomal glycol enzyme that is present predominantly in the liver and can be increased in heavy ethanol use. However, GGT has a specificity of 40% to 90% for detecting heavy ethanol use, as it can also be elevated owing to biliary obstruction, hepatotoxic drugs, and both heart and kidney disease.[26]

Elevations in MCV (ie, macrocytosis) can occur with chronic ethanol consumption, which leads to decreased production of hematologic precursors and abnormal morphology of mature red blood cells (RBCs). Given that the average lifespan of an RBC is 3 months, elevated MCV can capture periods of prolonged and heavy ethanol consumption, persisting for up to 3 months after alcohol cessation. Nevertheless, a wide variety of hematologic disorders can also lead to elevations in MCV, decreasing its sensitivity in detecting chronic ethanol ingestion.

Finally, CDT is an isoform of transferrin, an iron transport glycoprotein predominantly found in the liver. CDT is upregulated with sustained ethanol ingestion, which alters the transferrin glycosylation process. Using CDT as a marker of ethanol use, however, has limitations similar to those of other indirect biomarkers. Most notably, standardized assays for CDT and universally accepted CDT thresholds are lacking. Furthermore, CDT can be impacted by underlying liver disease unrelated to alcohol use, such as autoimmune hepatitis and primary biliary cholangitis, further limiting its value as a biomarker of ethanol consumption.[26-28]

Direct Biomarkers

Direct biomarkers of ethanol are directly derived from products of ethanol metabolism and are more specific to ethanol consumption. Approximately 95% of ingested ethanol enters systemic circulation, with the remainder excreted via urine, sweat, or breath. The majority of circulating ethanol undergoes oxidative metabolism by hepatic alcohol dehydrogenase, resulting in the generation of acetaldehyde, a highly reactive and toxic metabolite that leads to hepatocyte injury with accumulation. Acetaldehyde is subsequently metabolized into acetate, a nontoxic metabolite that can enter the Krebs cycle. A small portion of ingested ethanol undergoes nonoxidative metabolism, which produces the majority of currently available direct ethanol metabolites, such as ethyl sulfate (EtS), ethyl glucuronide (EtG), and phosphatidylethanol (PEth) (Table 1).[1,27]

PEth, an alcohol-derived phospholipid largely found in RBC membranes, has recently emerged as the direct biomarker of choice among hepatologists, with a cutoff of 80 ng/mL resulting in a sensitivity of 91% and a specificity of 77% for detecting heavy drinking (≥4 drinks/day) in the past 4 weeks. The specificity of PEth for identifying any ethanol consumption in the past 4 weeks increases to 95% when the PEth threshold is lowered to 20 ng/mL.[29] EtG, produced by ethanol glucuronidation by uridine-5' diphospho-glucuronosyltransferase, and EtS, produced by ethanol sulfonation by sulfotransferases, can both be detected in the urine for 3 to 7 days after alcohol consumption. Although both urine biomarkers have similar kinetics and can detect small amounts of ethanol consumption (<10 g), clinical utility is limited by their short half-lives. Conversely, EtG in the hair can be utilized to detect ethanol consumption in the past 3 to 6 months, but is not readily available to most clinicians.[28,30]

Interdisciplinary Care

The evaluation and management of AUD in the context of ALD is multifaceted and longitudinal, necessitating an interdisciplinary approach to deliver high-quality and evidence-based care. Interdisciplinary care models are well established in other fields of medicine, most notably at the intersection between psychiatry and primary care. Similarly, an interdisciplinary care model is standard of care in LT evaluation, when patients with ALD have already developed end-stage liver disease or severe alcoholic hepatitis. In fact, LT evaluation epitomizes the core principles of interdisciplinary care, in which experts from various health care domains (ie, psychiatry, social work, nutrition, physical therapy, medicine, and surgery) must work together to integrate a preponderance of data (objective and subjective) and make high-stakes decisions regarding a patient's LT candidacy.[31]

Patients with ALD benefit from an interdisciplinary care model early in the course of ALD, when downstream complications of ALD (ie, ALD cirrhosis or AH) and the potential need for LT can be avoided or delayed. Comorbid psychiatric comorbidities and substance use disorder are common in patients with ALD and cannot be adequately treated by a primary care provider or hepatologist without specialized addiction training.[32] Early involvement of specialists across the domains of psychiatry, psychology, addiction medicine, and social work is critical to addressing the breadth of ALD pathophysiology. Psychiatric comorbidities, including mood, anxiety, and personality disorders, can contribute to maladaptive behaviors such as heavy alcohol and polysubstance use and are most effectively treated with a combination of cognitive behavioral therapy and pharmacotherapy.

In addition to facilitating cognitive behavioral therapy, the psychiatry team is particularly relevant in patients with ALD, as many psychiatric medications have the potential to exacerbate hepatic complications or potentially lead to inaccurate diagnoses. For example, insomnia is common in both patients with ALD and those with mood disorders, resulting in a higher likelihood that these patients are prescribed benzodiazepines. Along with other sedating medications such as opioids, benzodiazepines can increase the risk of hepatic encephalopathy or potentially lead to misdiagnosis of this decompensating complication. Serotonin reuptake inhibitors are commonly prescribed to treat mood disorders and may increase the risk of gastrointestinal bleeding from portal hypertension owing to their impact on platelet function. Carefully selected medications, on the other hand, have the potential benefit of treating psychiatric comorbidities, AUD, and other complications of ALD simultaneously. For example, gabapentin can be used off-label to treat AUD while also treating insomnia and peripheral neuropathy, both of which are prevalent in patients with ALD.[31,33]

Alcohol Use Disorder–Directed Treatment in Alcohol-Associated Liver Disease

Initiation of pharmacotherapy to treat AUD is effective and has been shown to reduce the risk of decompensation in patients with compensated cirrhosis. Historically, AUD medications have been underutilized in patients with ALD, likely driven by variable hepatologist prescribing comfort and patient misconceptions regarding treatment. In a mixed-methods study investigating barriers to AUD treatment in ALD, Mellinger and colleagues found that many patients with ALD thought that AUD treatment was unnecessary and ineffective once ALD develops.[34] In

Table 2. AUD Pharmacotherapy in ALD

Medication	Dose	Class	FDA-approved for AUD	Clinical considerations
Naltrexone (pill)	50 mg daily	Opioid receptor antagonist	Yes	• Can be used in patients with early ALD and with caution in patients with compensated ALD cirrhosis • Contraindicated in patients with severe acute AH and decompensated ALD cirrhosis • Contraindicated in patients with ongoing or recent opioid use
Naltrexone (injection)	380 mg every 4 weeks	Opioid receptor antagonist	Yes	
Acamprosate	666 mg three times per day	NMDA receptor antagonist	Yes	• Does not undergo hepatic metabolism and, therefore, is not contraindicated in patients with cirrhosis • Must be dose adjusted in patients with chronic kidney disease and is contraindicated in patients with CrCl <30 mL/min
Disulfiram	Loading: 250-500 mg daily for 1-2 weeks Maintenance: 250 mg daily	Aldehyde dehydrogenase inhibitor	Yes	• Contraindicated in ALD owing to hepatotoxicity from hepatic metabolism and association with idiosyncratic liver injury in patients with chronic liver disease
Gabapentin	Starting dose: 300 mg daily Maximum dose: 900 mg daily	Anticonvulsant/ analgesic	Off-label	• Limited data in ALD, but not contraindicated
Baclofen	5-15 mg three times per day	$GABA_B$ receptor agonist	Off-label	• Most-studied medication in ALD • Decreases alcohol use and abstinence rates in patients with AH and ALD cirrhosis
Topiramate	Starting dose: 25-50 mg daily Maximum dose: 100 mg twice per day	Anticonvulsant	Off-label	• Limited data in ALD, but not contraindicated

AH, alcohol-associated hepatitis; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; CrCl, creatinine clearance; FDA, US Food and Drug Administration; $GABA_B$, gamma-aminobutyric acid, type B; NMDA, N-methyl-D-aspartate.

this study, patients misperceived their current lack of alcohol cravings as a permanent resolution of their addiction, not grasping the chronic nature of AUD. These cognitive barriers to AUD medication initiation and longitudinal adherence are most effectively addressed in an interdisciplinary care model, in which hepatologists, psychiatrists, and psychologists can educate patients on the complexities of ALD, AUD, and addiction simultaneously.

The US Food and Drug Administration has approved 3 medications for AUD (naltrexone, acamprosate, and disulfiram) but use in ALD has qualifications.[35] Disulfiram is contraindicated in patients with ALD, as it is metabolized in the liver and has been associated with idiosyncratic drug reactions in chronic liver disease.[36] Acamprosate is effective in patients with compensated and decompensated ALD cirrhosis but must be used with caution in patients with chronic kidney disease. Acamprosate must be dose-adjusted in chronic kidney disease and avoided in patients with a creatinine clearance below 30 mL/min.[37,38] Naltrexone is another effective treatment option for AUD in patients with ALD, but should not be prescribed in patients with decompensated cirrhosis and patients taking opioids.[39] Numerous other medications have been studied off-label in patients with ALD, such as baclofen, gabapentin, and topiramate, with growing evidence to support their use. In fact, baclofen is perhaps the most-studied drug in patients with ALD and can be utilized across the spectrum of ALD (including those with decompensated cirrhosis) (Table 2).[40,41]

Early initiation of AUD medication is of utmost importance. Although outpatient follow-up care after an AH-triggered admission often focuses on management of corticosteroid therapy, it is critical that AUD treatment is prioritized in this critical window when there is a high rate of alcohol relapse and alcohol-associated mortality. Outpatient follow-up in intensive outpatient programs

and cognitive behavioral therapy, as well as adherence to pharmacotherapy during this period, can also serve as valuable markers of insight into the patient's AUD diagnosis and willingness to engage in AUD treatment—two important factors that inform LT candidacy.

Liver-Directed Treatment in Alcohol-Associated Liver Disease

Management of Alcohol-Associated Hepatitis

For decades, the fundamental approach to AH management remained unchanged: (1) abstinence from alcohol; (2) nutritional support, including ensuring adequate caloric intake (goal of 35-40 kcal/kg/day) and appropriate vitamin repletion (vitamin B complex, vitamin D, and vitamin K); (3) early detection and treatment of infections, which carry significant morbidity and mortality in alcoholic hepatitis; (4) treatment of liver-related complications of AH (renal dysfunction, hepatic encephalopathy, volume overload, and gastrointestinal bleeding); and (5) corticosteroid therapy in carefully selected patients.[1,27,40] The landmark STOPAH trial demonstrated that corticosteroids (prednisolone) result in a modest numerical 30-day survival benefit (not reaching statistical significance) in select patients with AH, but not a long-term (90-day) survival benefit. Additionally, STOPAH demonstrated that pentoxifylline therapy does not result in significant survival benefit, whether administered alone or in combination with prednisolone.[42]

Corticosteroids have historically been initiated in cases of severe AH, defined by a Maddrey discriminant function of at least 32 or Model for End-Stage Liver Disease (MELD) score of at least 20, when patients do not have any contraindications such as active infections, gastrointestinal bleeding, or acute kidney injury.[43] In a retrospective multicenter cohort study, Arab and colleagues found that the maximum beneficial effects of corticosteroid treatment were observed in patients with a MELD score ranging from 20 to 39, with corticosteroids resulting in a 21% to 30% survival benefit. Those patients with a MELD score over 51, on the other hand, did not demonstrate any survival benefits.[44]

After STOPAH, other studies have shown that the combination of prednisolone and N-acetylcysteine further improves short-term outcomes in patients with severe AH compared with prednisolone alone, including reducing the incidence of infections, deaths related to hepatorenal syndrome, and 30-day all-cause mortality.[45] The combination of prednisolone and empiric antibiotics, on the other hand, has not been shown to improve outcomes despite the significant risk of infections in AH.[46] It is critical to note that neither prednisolone alone nor the combination of prednisolone and N-acetylcysteine has resulted in improvement in longer-term outcomes such as 60-day survival, further underscoring the need to develop novel and effective interventions to treat severe cases of AH.

Recent data have also shaped the manner in which treatment response is monitored. A recent multinational retrospective study of 260 patients with severe AH demonstrated that a day 4 Lille score had a similar accuracy as the traditional day 7 Lille score in predicting response to corticosteroids.[47] This finding theoretically allows clinicians to decrease the length of hospital stays and minimize unnecessary exposure to corticosteroids, thereby decreasing the risk of infections that contribute to significant morbidity and mortality in this population.

Early Liver Transplant for Alcohol-Associated Liver Disease

ALD is now the leading indication for LT in the United States.[48] Although this change in the LT landscape can be partially attributed to a decline in hepatitis C virus infection and rising prevalence of ALD, a dramatic shift in the transplant community's attitude toward pre-LT alcohol abstinence has also played a pivotal role. LT centers historically required at least 6 months of abstinence prior to LT. This requirement was not based on empiric data but, rather, was guided by expert opinion that posited that 6 months of abstinence prior to LT identified individuals most likely to maintain abstinence after LT. This requirement, though well intentioned, led to high rates of mortality in patients with severe AH, with 6-month mortality reaching as high as 70%. In 2011, the landmark study by Mathurin and colleagues provided the first evidence that early LT (without requiring 6 months of abstinence) significantly improved 6-month survival in 26 selected patients with severe AH unresponsive to corticosteroids, with survival benefits lasting up to 2 years after LT. Notably, only 3 LT recipients returned to alcohol consumption after transplant.[49]

Two multicenter studies in the United States and Europe by Lee and colleagues and Louvet and colleagues have since confirmed the significant survival benefit of early LT in selected patients with severe AH.[50,51] Lee and colleagues found 1- and 3-year survival in early LT to be comparable to standard LT for ALD cirrhosis and superior to other indications for LT, including hepatocellular carcinoma. Louvet and colleagues found that 2-year survival was not significantly different between early and standard LT for patients with ALD. The risk of alcohol relapse, however, was slightly higher in early LT recipients, with Lee and colleagues noting a 34% risk of alcohol relapse in this group at 2 and 3 years compared with 25% at 2 years in the standard LT group in the study by Louvet and colleagues. Although any alcohol use post-LT was associated

Table 3. Alcohol Relapse Risk Prediction Tools

Tool	Components (points)	Score interpretation
High-Risk Alcohol Relapse score	1. Years of heavy drinking: ≤11 (+0), 12-24 (+1), ≥25 (+2) 2. Usual number of daily drinks: <9 (+0), 9-17 (+1), ≥18 (+2) 3. Number of prior alcohol rehabilitation attempts: 0 (+0), 1 (+1), >1 (+2)	Score ≥4: Associated with harmful drinking (>40 g of ethanol consumption per day, with associated physical or mental manifestations of AUD)
Sustained Alcohol Use Post–Liver Transplant score	1. Greater than 10 drinks/day at initial hospitalization (+4) 2. Multiple prior alcohol rehabilitation attempts (+4) 3. Prior legal issues related to alcohol (+2) 4. Prior illicit substance abuse (+1)	Score <5: 95% NPV for sustained alcohol use Score ≥5: 25% PPV for sustained alcohol use
Stanford Integrated Psychosocial Assessment for Transplantation score	1. Patient readiness level (+0-24) 2. Social support system (+0-20) 3. Psychological suitability and psychopathology (+0-35) 4. Lifestyle and effect of substance use (+0-29) Note: Higher scores in each domain represent worse evaluation of this domain.	Score 0-6: Excellent candidate Score 7-20: Good candidate Score 21-39: Minimally acceptable candidate Score: 40-69: Poor candidate Score ≥70: High-risk candidate Note: Score ≥21 is associated with alcohol relapse after transplant.

AUD, alcohol use disorder; NPV, negative predictive value; PPV, positive predictive value.

with a higher risk of mortality, sustained alcohol use (continued alcohol consumption over a period of ≥100 days) was the strongest predictor of death (hazard ratio, 4.59; *P*=.01). In fact, Lee and colleagues found that sustained alcohol consumption only occurred in 11% of patients during the follow-up period, resulting in a cumulative incidence of 10% at 1 year and 17% at 3 years post-LT.

Differentiating sustained alcohol use from alcohol slips (ie, brief lapses in alcohol use after which abstinence is quickly reestablished) represents a fundamental change in attitudes toward alcohol consumption post-LT. Although brief lapses in alcohol use are observed in up to 20% of LT recipients with a history of ALD, the effect of these brief lapses on post-LT outcomes is significantly less deleterious than sustained alcohol use, which can lead to rapid graft fibrosis and loss.[50,52] The pre-LT evaluation paradigm in ALD has thus pivoted from identifying patients who may consume any alcohol after LT to identifying patients at lowest risk of sustained alcohol use after LT.

Multiple tools have been used to identify this low-risk subset of patients, most notably the Sustained Alcohol Use Post–Liver Transplant (SALT), Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT), and High-Risk Alcohol Relapse (HRAR) scores (Table 3).[53-56] Although the SALT and SIPAT scores demonstrate excellent negative predictive value (90%-95%), both scores show poor positive predictive value (PPV). In a recent comparative study of alcohol-relapse tools, SIPAT demonstrated the highest C-statistic (0.67), followed by SALT (0.62) and HRAR (0.59).[57] Although all of the available tools produce a limited PPV, it is likely that the SIPAT's slightly higher PPV is because of its integration of psychosocial factors into alcohol relapse prediction, which are not included in the SALT or HRAR scores. However, it is important to note that this comparative study evaluated each tool's ability to predict any alcohol use after LT, rather than sustained alcohol use, which has the highest association with post-LT graft dysfunction and mortality. Additionally, Black patients, those with Medicaid, and those without college degrees tend to score worse on SIPAT, even after adjusting for other sociodemographic variables, suggesting that it could be contributing to early LT access disparities.[58] Further studies are necessary to investigate the performance of SIPAT across various ethnic, racial, and socioeconomic strata. Most importantly, these scores should never be used in isolation to decide LT candidacy, but rather interpreted as one data point in a complex clinical and psychosocial picture.

A similar shift in perspectives has occurred in the post-LT setting, where clinicians now benefit from reliable biomarkers to identify alcohol slips early in the relapse course. Current transplant practice has evolved from viewing any post-LT alcohol consumption as failure in LT candidate selection to embracing early intervention strategies, including both pharmacotherapy and cognitive behavioral therapy, to prevent progression from brief relapses to sustained alcohol use. This approach is best implemented when interdisciplinary ALD care extends from the pre- to post-LT setting, increasing the likelihood of adherence to AUD medications after LT and facilitating longitudinal care of psychiatric comorbidities that can often trigger return to alcohol use.

Emerging Therapies and Future Directions

Emerging Therapies in Alcohol-Associated Liver Disease

Although early LT has dramatically improved survival rates for a select subset of ALD patients, novel therapeutics are urgently needed for those who do not meet the criteria for early transplant listing. This is particularly relevant in patients with severe AH who do not respond to corticosteroids, given exceptionally high 6-month mortality rates. There are currently various medications under investigation to treat AH, including interventions targeting hepatic regeneration, hepatic inflammation, and the liver-gut axis.

Granulocyte colony-stimulating factor (GCSF), which could have hepatic regenerative effects, was initially shown to improve 3-month survival in patients with severe AH who were either nonresponsive to or ineligible for corticosteroids.[59,60] Further studies, however, have not replicated the original findings from studies conducted in Asia, with European and US studies showing that both GCSF alone and the combination of GCSF and prednisolone result in similar 90-day survival outcomes as prednisolone alone.[61-63] Additional multicenter studies are needed to investigate the potential benefits of GCSF in ALD.

F-652, a recombinant fusion protein of human interleukin (IL)-22 and immunoglobulin G2 fragment crystallizable (IgG2 Fc), could have hepatic regenerative and antioxidant effects. Preclinical murine models have shown that recombinant IL-22 reduces serum AST and ALT levels.[64,65] In a phase 2 study, Arab and colleagues demonstrated that F-652 was associated with an improvement in day 7 Lille and MELD scores, along with temporally reducing markers of inflammation and increasing markers of hepatic regeneration.[66] Given these promising results, future randomized controlled trials (RCTs) are necessary to study the efficacy of F-652.

Larsucosterol, an endogenous cholesterol derivative, 25-hydroxycholesterol 3-sulfate (25HC3S or DUR-928), inhibits DNA methyltransferase-1, which is associated with aberrant DNA methylation and transcriptomic reprogramming linked to hepatic dysfunction in AH. In a phase 2a study, larsucosterol resulted in a day 7 Lille score of more than 0.45 in 89% of patients, with a significantly lower Lille score compared with the standard-of-care arm.[67] In AHFIRM, a subsequent phase 2b RCT, patients randomized into the 30- and 90-mg larsucosterol groups showed lower 90-day mortality rates (14.7% and 16.7%, respectively), compared with the placebo group (24.3%).[68] Although this difference did not reach statistical significance, a phase 3 trial is planned to further investigate the potential efficacy of this medication.

Other therapies targeting anti-inflammatory pathways have shown promise but require additional investigation. For example, IL-1 receptor blockers have resulted in attenuation of hepatic inflammation and promotion of hepatic regeneration in murine models, but have yet to be replicated in human RCTs. In a recent double-blind, placebo-controlled trial, canakinumab, a monoclonal antibody targeting IL-1β, did not result in significant biochemical or clinical improvement compared with placebo in patients with biopsy-confirmed AH.[69]

Microbiome modulation with probiotics or fecal microbiota transplant (FMT) has demonstrated encouraging early results and requires further large-scale clinical trials. Murine models and small clinical trials focused on mild-to-moderate AH show that probiotics could reduce inflammatory markers and potentially improve hepatic function in patients with ALD.[70-74] FMT in AH has generated significant enthusiasm, with a recent RCT (n=195) showing that FMT was associated with a higher 1-year survival compared with prednisolone (88% vs 33%; P=.02).[75] Larger multicenter clinical trials assessing the impact of FMT in ALD, however, are necessary prior to clinical implementation and are ongoing.

Emerging Therapies in MetALD

The new MetALD nomenclature has raised several important clinical and research questions. Namely, should MetALD patients be treated differently than those with MASLD or ALD? If so, should these patients simply receive a combination of therapies catered to both MASLD and ALD, or should they be approached with unique pharmacotherapy? There are more than 500 active or completed drug trials for MASLD and approximately 90 trials for ALD. However, there are currently no active trials investigating pharmacotherapy for MetALD.[76]

Although launching new clinical trials with MetALD-specific endpoints is critically important, behavioral changes such as regular aerobic exercise and alcohol cessation are likely to remain important components of MetALD management. It is well known that alcohol consumption significantly increases the risk of fibrosis progression in MASLD.[13] Therefore, although MetALD patients do not reach the alcohol consumption thresholds necessary for a diagnosis of ALD, the combination of behavioral therapy, treatment of psychiatric comorbidities, and AUD medication must be implemented to ensure complete alcohol cessation.

There are also several promising drugs that could target MetALD and must be investigated further. Patients with excessive alcohol consumption were excluded from previous glucagon-like peptide-1 (GLP-1) receptor agonist trials; however, liraglutide and semaglutide (Ozempic and Wegovy, Novo Nordisk) have been shown to decrease alcohol cravings and total alcohol consumption in limited

human trials.[77] Thus, GLP-1 receptor agonists could have a favorable therapeutic profile, treating both metabolic syndrome comorbidities and decreasing alcohol intake in patients with MetALD.[76] Farnesoid X receptor agonists have been shown to improve liver enzymes in patients with metabolic dysfunction-associated steatohepatitis and also reduce hepatic injury in murine ALD models. These preclinical findings in ALD models suggest that farnesoid X receptor agonists could target multiple mechanisms of MetALD pathophysiology and should be the focus of future clinical trials.[78] Other therapies, including sodium-glucose cotransporter 2 inhibitors, fibroblast growth factor 21 analogs, and thyroid hormone receptor–beta agonists, have limited or conflicting data in ALD, making them less promising targets for initial clinical trials in MetALD.[76]

Conclusion

The care of patients with ALD has evolved significantly over the past two decades and will continue to do so as long-term posttransplant data from early LT for ALD become available. Growing data on the efficacy of AUD pharmacotherapy should prompt early implementation of these medications in patients with ALD to prevent progression of underlying fibrosis and eventual decompensation. As early LT for ALD gains acceptance as standard of care in clinical practice, emerging medical therapies must be integrated into an ALD interdisciplinary care model to deliver high-quality, evidence-based, and patient-centered care. AUD pharmacotherapy must remain an integral aspect of post-LT care, just as it is before LT. Serial monitoring with direct biomarkers of ethanol ingestion is imperative in post-LT practice. Detection of alcohol slips should not be viewed as a failure of LT recipient selection, but as an anticipated clinical reality and a pivotal intervention point when multifaceted care can prevent sustained alcohol use and graft dysfunction. Future studies must investigate how novel therapeutics impact early LT candidate selection and post-LT outcomes. It is also imperative to identify current barriers to early LT, including LT referral patterns for ALD and specific psychosocial factors that influence early LT candidacy, to ensure appropriate access for all patients with ALD.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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