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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Overcoming Alcohol Addiction in Patients with Alcohol-Related Liver Disease

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Abstract

Purpose of Review This review provides a brief overview of key concepts in addiction medicine and provides tips and tricks as it pertains to treating patients with alcohol addiction in the setting of advanced alcohol-related liver disease (ALD).

Recent Findings Understanding the brain disease model of addiction by both providers and patients is a vital springboard for establishing a therapeutic relationship. Despite a paucity of high-quality evidence, psychosocial treatments have withstood the test of time and still form the foundation of alcohol use disorder (AUD) treatment in advanced ALD. Despite the inescapable link between AUD) and advanced ALD, there are no FDA-approved medications for use in this special population. In this urgent subgroup, only baclofen, used off-label, has been shown to be effective for AUD in randomized controlled trials.

Summary An integrated, multidisciplinary and longitudinal approach remains the best option for the management of AUD in advanced ALD.

Keywords Alcohol-use disorder · Alcohol-related liver disease · Baclofen · Alcoholism · Craving · Alcohol-related cirrhosis

Introduction

Overcoming addiction to alcohol in patients with alcohol-related cirrhosis (AC) is paramount to recovery but can be difficult to achieve. Alcohol use in patients with AC plays an outsized role in their medical management with regard to liver injury, complications, and eligibility for liver transplantation (LT). However, providers specializing in gastroenterology and hepatology are often under-trained to treat alcohol-use disorder (AUD). While progress is slowly being made in the fields of addiction and alcohol-related liver disease (ALD), they are occurring in parallel with inadequate cross-collaboration, despite significant overlap. This is particularly true in patients with advanced liver disease, in whom AUD treatment is steeped more in art than science. This review will focus on tips and tricks in the treatment of AUD in patients with ALD.

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Alcohol-Use Disorder

Publication of the 5th Edition Diagnostic and Statistical Manual marked a significant change in the terminology of alcohol-associated addiction [1]. The past categories of alcohol abuse and alcohol dependence has been replaced by the term alcohol-use disorder (AUD), characterized as mild, moderate, or severe based on the accumulation of negative consequences and symptoms (Table 1). New to this reorganization is the presence of "craving" symptoms as a criterion. Alcohol abuse is now encompassed by mild to moderate AUD and alcohol dependence as severe AUD [2•]. While the natural history of AUD can vary, including forms of intermittent alcoholism without progression, severe AUD is likely the end-stage of alcohol addiction [2, 3••]

Rising Prevalence of AUD and ALD.

The burden of alcohol on global health is well-characterized. Alcohol is estimated to be responsible for 5.9% of global mortality and is the third leading cause of preventable deaths in the USA [4, 5]. Of note, the alcohol-attributable fraction of mortality in patients with cirrhosis is a remarkable 50% worldwide [4]. Rates of AUD and high-risk drinking in the USA

Table 1 Alcohol-use disorder diagnostic criteria

In the past year, have you:	
1.	Alcohol is often taken in larger amounts or over a longer period than intended.
2.	There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3.	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4.	Craving, or a strong desire or urge to use alcohol.
5.	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6.	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7.	Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8.	Recurrent alcohol use in situations in which it is physically hazardous.
9.	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10.	Tolerance, defined as either of the following: A. Need for markedly increased amounts of alcohol to achieve intoxication or desired effect. B. Markedly diminished effect with continued use of the same amount of alcohol.
11.	Withdrawal, as manifested by either of the following: A. The characteristic alcohol withdrawal syndrome. B. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

The presence of at least 2 of these symptoms indicates an alcohol-use disorder (AUD):
- Mild: 2–3 symptoms
- Moderate: 4–5 symptoms
- Severe: 6 or more symptoms

have recently risen dramatically, with the prevalence of AUD in two nationally representative surveys of adults increasing by 50% between 2001 to 2013, with even greater increases among women, minorities, and those of lower socioeconomic status [6•]. Using the DSM-5 criteria, the 12-month prevalence of AUD was 13.9%, while the lifetime prevalence was almost one-third of the population (29.1%). AUD was significantly associated with disability, Axis I and II psychiatric diagnoses, yet only 19.8% of respondents with lifetime AUD were ever treated. So, it should not come as a surprise that ALD has ensued. Studies using different epidemiologic databases have recently reported the rising prevalence of, and, mortality from AC, particularly in younger patients aged 25–34 years [7–9]. The impact of alcohol on concomitant liver diseases like nonalcohol-related fatty liver disease (NAFLD) and chronic hepatitis C is difficult to study, but likely contributory.

Informed Providers Can Affect Approach to Patient Care

Addiction medicine is scarcely taught in medical school, so it follows that medical providers often fail to diagnose and treat substance-use disorders [10]. A good starting point for provider education is the scientific evidence that addiction is an acquired brain disease [11•]. Moving away from the stigma of addiction as an irresponsible voluntary behavior allows for nonjudgmental diagnostic and treatment approaches. Even a rudimentary understanding of addiction neurobiology in which a drug induces dopamine dysregulation in the brain (midbrain, limbic, and prefrontal cortex) can refocus addiction into paradigms similar to hypertension or diabetes mellitus that are more familiar (and comfortable) to providers. Educating patients regarding the brain disease model of addiction can also be useful, particularly if they are adamant about "self-control" of drinking by declining pharmacologic or psychosocial interventions. The patient is asked if she/he would treat a new diagnosis of significant diabetes on their own or elect to receive care with insulin and diet counseling. Equating their "dopamine" problem with the "insulin" problem of diabetes may be enlightening and can foster candor, trust, and more willingness to "go to rehab."

Neurobiology of Addiction

The neurobiology of addiction posits progressive neuroadaptations in the brain via a positive feedback loop: alcohol intoxication activates the reward regions of the brain (globus pallidus); withdrawal affects the amygdala resulting in negative mood and sensitivity to stress; a depressed prefrontal cortex enhances craving and compulsion for alcohol and

reinitiates the cycle of addiction [11•]. What follows is the concept that the prior innumerable cycling through these addiction stages can be treated with psychosocial (also called behavioral) interventions to restore balance in brain circuitry. This can be accomplished by enhancing healthy rewards like social contact or exercise, coping strategies like early recognition and self-regulation by avoidance of vulnerable situations. The most effective strategy to achieve this rebalancing is the combination of psychosocial and pharmacological treatments [12].

Genetic Risks for Alcohol-Use Disorder and Alcohol-Related Liver Disease

There are complex genetic, sex, environmental, and societal risk factors for the development of both AUD and ALD. Recent genome-wide association studies have strengthened prior twin and familial studies demonstrating that polygenic influences exert a moderate to high etiological influence with a heritability of about 50% for AUD [13]. For example, polymorphisms in the alcohol metabolizing genes *ADH2* and *ALDH2* are strongly linked to risk of AUD [14]. Several single-nucleotide polymorphisms (SNPs) linked to lipid processing like *PNPLA3*, *TM6SF2*, *MBOAT7*, and *HSD17B13* are associated with the development of ALD (and NAFLD) [15••, 16].Remarkably, there is no overlap between known risk-conferring alleles in AUD and ALD, which helps explain, in part, why the majority (> 80%) of heavy drinkers never develop cirrhosis (Fig. 1). Understanding that these immutable (and less readily measurable) risk factors exist within each patient may foster therapeutic patient-provider relationships, in addition to the more frequently elicited amount, duration, and pattern of drinking.

Typology of Alcohol-Use Disorder

The natural history of alcohol-use disorder is complex, with numerous drinking, health, and social trajectories developing over time [3••]. In patients with advanced ALD, understanding the likelihood of achieving abstinence (or at least reduction in drinking) is especially important and often urgent when liver transplantation is being considered.

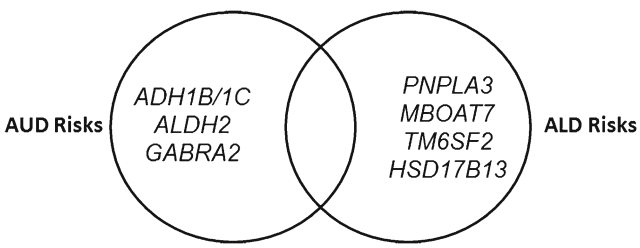

Fig. 1 Venn diagram of genetic risk loci in alcohol use disorder and alcohol-related liver disease

Given the myriad of contributions to the neurobiology of addiction, it is not surprising that there is no single criterion that can accurately predict future abstinence or the return to harmful drinking [17]. One strategy of assessment that is long-established in the addiction community, but underutilized by hepatologists, is the classification of patients using the rubric of AUD typology [18•]. The typology of AUD assumes that there are common propensities of AUD patient subgroups leading to meaningful stereotypes that can inform research and management. Fortunately, the most commonly used AUD typology is relative simple: type A or type B. The characteristics of these AUD subtypes are outlined in Table 2. For example, a young patient presenting with alcohol-related hepatitis or advanced ALD often elicits an emotional response from providers with conjectures about heavy genetic/environmental risks. Assessing for type B characteristics provides a framework to more objectively classify the patient and the general expectation of future relapse (more likely with type B). A more recent characterization of AUD using a nationally representative database classified AUD into five different subtypes, with clusters 4 and 5 closely resembling type B. Linkage to AUD typology during LT evaluations would also recognize the relapsing-remitting course of alcohol addiction, particularly of younger patients, and allow LT centers to personalize treatment and support for those more likely to relapse [19].

Treatment of AUD

Abstinence

The essential requirement for treating AUD in patients with ALD is achieving and maintaining abstinence from alcohol [2•]. While harm reduction can be a suitable goal for some patients, only abstinence will reduce the risk of disease progression [21]. Ongoing alcohol use is associated with a 4-year survival of 70% and 49% in patients with alcoholic fatty liver and AC, respectively [22]. In AC with hepatic decompensation, abstinence improves 5-year survival by half (60% vs 30% with continued drinking) [23]. Even in less advanced forms of ALD, evidence is lacking for a safe threshold for continued alcohol use, with "controlled" drinking often progressing to harmful patterns over time [24].

Psychosocial Treatments

There are several effective psychosocial treatments for AUD, although very few have been studied in patients with ALD (Table 3). Given the urgency in a patient with established ALD, multidisciplinary management with an addiction specialist and referral for treatment of AUD is

Table 2 Alcohol-use disorder typologies [19, 20]

Characteristic	Type A	Type B
Age of onset	Older	Younger
Family history of AUD	Weaker (first-degree relatives)	Stronger
Childhood	Fewer early risk factors	Deprivation/abuse and conduct disorder
Personality	Lower impulsivity and novelty seeking	High impulsivity and novelty seeking
Alcohol dependence	Less severe	More severe
Substance use	Primary alcohol, more episodic	Polysubstance, more chronic
Psychiatric disorders	Lower severity	Adult personality disorders like antisocial
Natural remission	30% per year	10% per year

essential. Overall, categories of psychosocial treatment include inpatient alcohol rehabilitation, one-on-one therapies, family/couples counseling, and peer-support groups like Alcoholics Anonymous (AA). Recently, the NIAAA has launched a user-friendly alcohol treatment navigator, found at https://AlcoholTreatment.niaaa.nih.gov, to provide education and a step-by-step guide to find highly-qualified treatment professionals.

Counseling-type interventions are widely available and commonly known. Twelve-step facilitation is an abstinence-based program grounded in acceptance, spirituality, and moral inventories and involves participation in AA group meetings [19]. AA is supported by longitudinal studies and has the advantage of wide recognition allowing for reduced stigmatization, but many patients dislike its group environment, particularly if other attendees are not considered "peers" by the patient [3••, 19]. Many AUD patients with ALD are not treatment-seeking and are only doing so in the context of liver disease [25•]. In addition, AA typically does not include random testing of alcohol biomarkers to assess for adherence to abstinence, which limits its utility for assessing suitability for liver transplantation.

One-on-one treatments include motivational interviewing (MI), motivational enhancement therapy (MET), and cognitive behavior therapy (CBT). Motivational interviewing is a patient-centered method to enhance motivation to change by exploring and resolving ambivalence through open-ended questions and reflective listening [2•]. MI has been shown to help patients change behaviors, including alcohol use [20]. Motivational enhancement therapy is a similar but more structured form of MI that frames the decision to stop drinking in terms of a dilemma [27]. The patient works through the dilemma by "rolling with the resistance" to change. Cognitive behavior therapy is a structured, goal-directed form of psychotherapy that focuses on identifying triggers and maladaptive behaviors that cause relapse [28]. CBT develops new

Table 3 Psychosocial treatments for AUD

Treatment	Description
Motivational interviewing	A directive, client-centered counseling style of eliciting behavior change by helping patients explore and resolve ambivalence. The examination and resolution of ambivalence are the central purpose, and the provider is intentionally focused on pursuing this goal.
Motivational enhancement therapy (MET)	A time-limited, 4-session therapy that uses motivational psychology to evoke rapid and internally motivated change. Provider feedback to the initial assessment stimulates discussion about alcohol use and eliciting self-motivational statements. Subsequently, the provider monitors change, reviews cessation strategies being used and continues to encourage commitment to change or sustained abstinence.
Cognitive behavioral therapy (CBT)	A time-limited, 12-session therapy that identifies "high-risk" situations that increase the risk of AUD. CBT trains and prepares patients to adopt active behavioral and cognitive methods, rather than alcohol, as coping mechanisms during "high-risk" situations.
Counseling-type interventions	A widely available outpatient group therapy like Alcoholics Anonymous (AA) that capitalizes on the social reinforcement offered by peer discussion (a form of positive incentive) and to help promote drug-free lifestyles. Group therapy can be heterogeneous with non-alcohol substance users and can be steeped in spirituality which may discourage some patients.

coping mechanisms to allow replacement of alcohol-laden with alcohol-free circumstances. Smartphone applications designed to support abstinence are now available that may serve as an adjunct to treatment [29].

While these different psychosocial treatments should be tailored to the individual patient, evidence from large randomized trials demonstrate that they are all similarly effective [30, 31]. There is little data showing a particular intervention that is consistently superior to another across all categories of populations [32]. One confounding factor is that patients with moderate to severe ALD may not be physically able to participate meaningfully in "talking treatment" programs due to frequent hospitalizations, fatigue, frailty, and hepatic encephalopathy.

Pharmacological Treatments

Treatment for alcohol withdrawal is similar in patients with or without ALD and has been discussed extensively in several reviews and will not be discussed here [2•]. Remarkably, there are no FDA-approved medications for AUD indicated in patients with advanced liver disease, the subgroup at greatest risk for mortality with continued drinking. Cirrhosis has been an exclusion criterion in nearly all clinical trials of pharmacological treatments for AUD, largely due to hepatotoxicity concerns. Given the focus of this review on treating AUD in patients with advanced ALD, emphasis will be given to preferred medications for this special population. The best evidence starts with baclofen, which is ironically not currently FDA-approved for this indication.

Non-FDA Approved Medications for AUD (Off-Label)

Baclofen is the only medication to have been formally tested in a randomized controlled trial (RCT) in AUD patients with advanced liver disease. It is a selective ɣ-aminobutyric acid (GABA) receptor agonist FDA-approved to control spasticity, but also inhibits dopamine-mediated alcohol-reinforced behaviors. The effectiveness of baclofen in AUD (without ALD) has been demonstrated in numerous case series and 2 RCTs using high doses (60–180 mg/day) to reduce alcohol use and increase abstinence rates [2•]. These data, along with its safety profile and wide use, led to a landmark RCT testing baclofen in AUD patients with cirrhosis at a single-center in Italy [33••]. Patients were randomized to receive baclofen 10 mg three times per day or placebo for 12 weeks. Out of 42 patients receiving baclofen, 30 (71%) achieved and maintained abstinence compared with 12 (29%) of 42 receiving placebo (OR 6.3 [95% CI 2.4–16.1]; $p = 0.0001$). The cumulative abstinence duration was about twofold higher in the baclofen arm (62.8 vs 30.8 days; $p = 0.001$). Baclofen was well-tolerated with no difference in side effects compared to placebo (including liver-related). Significant improvements in liver enzymes were also noted. Notably, patients with HE were excluded from this trial since baclofen may cloud mentation, a side effect which may be exacerbated in more advanced liver disease. The optimal dosing of baclofen requires further study and should be tailored to each patient.

Gabapentin is FDA-approved for the treatment of seizures and neuropathic pain and structurally similar to GABA. A recent RCT trial ($N = 150$) compared placebo, 900 or 1800 mg per day plus counseling over 12 weeks in California [34]. Gabapentin, particularly the high dose, demonstrated significantly improved rates of abstinence and no heavy drinking (17% and 44.7% vs 4.1% and 22.5% in placebo group). Relapse-related symptoms of insomnia, dysphoria, and craving were also improved, without differences in adverse events or study dropout. A subsequent large, multicenter RCT of an extended-release form of gabapentin did not confirm the results of the previous study, with no differences in heavy drinking days or craving [35]. Although gabapentin is well-tolerated in patients with cirrhosis anecdotally, these studies excluded patients with advanced liver disease with mixed results, making the utility of gabapentin for AUD unclear.

Varenicline is a nicotinic acetylcholine receptor partial agonist that is FDA-approved for smoking cessation. A few studies have also suggested efficacy in AUD, with one RCT showing a reduction in heavy drinking and craving in smokers and nonsmokers with dose escalation to 2 mg per day compared to placebo [36]. Varenicline has minimal hepatic metabolism and is generally well-tolerated (some headache, nausea, insomnia), making it a promising medication for treatment of AUD in advanced ALD that warrants future study [2•].

Several additional medications have been studied for off-label treatment of AUD like topiramate, ondansetron, and sodium oxybate, which are described in Table 4. Anecdotally, topiramate is not well-tolerated in advanced liver disease, particularly with hepatic encephalopathy, and ondansetron is expensive with many insurances declining long-term coverage for this off-label use. Sodium oxybate is FDA-approved for narcolepsy, but has the potential for misuse as gamma-hydroxybutyrate (GHB), a known street drug [2•]. A recent review of anticipated medications under study for AUD has also been published [37•].

FDA-Approved Medications for AUD

Acamprosate is a N-metil-D-aspartate (NMDA) glutamate receptor antagonist which is effective in reducing alcohol intake and maintaining abstinence. It was FDA-approved for treatment of AUD in 2004 and recommended for use immediately following recovery from alcohol withdrawal and the start of abstinence, continuing even with relapse. It is limited by significant diarrhea (10–17%) and thrice daily

Table 4 Pharmacological treatments for AUD

Medication	Dosage	Mechanism	Hepatic metabolism	Evidence in advanced ALD
Not FDA-approved				
Baclofen	10–20 mg TID	$GABA_B$ receptor agonist	Minimal	Yes
Gabapentin	900–1800 mg TID	GABA transmission modulator	Minimal	No
Varenicline	2 mg daily	Nicotinic acetylcholine receptor partial agonist	Minimal	No
Topiramate	300 mg daily	Increases GABA transmission, decreases glutamatergic activity	Yes	No
Ondansetron	1–16 mcg/kg BID	$5HT_3$ antagonist	Yes	No
Sodium oxybate	50 mg/kg/day	$GABA_B$ receptor agonist	Yes	No
FD-approved				
Acamprosate	666 mg TID	NDMA receptor antagonist	Minimal	Limited
Naltrexone	Oral: 50 mg daily IM: 380 mg monthly	mu- and kappa-opiate receptor antagonist	Yes	No
Disulfiram	250–500 mg daily	Acetaldehyde dehydrogenase inhibitor	Yes	No

dosing. A recent meta-analysis has demonstrated that the efficacy of acamprosate and naltrexone is similar in AUD [38]. While there are no clinical trials of acamprosate in advanced ALD, its lack of hepatic metabolism, absence of reports of hepatotoxicity, and positive anecdotal evidence suggest that it can be used in this subgroup of ALD [39].

Naltrexone is a mu- and kappa-opiate receptor antagonist which reduces alcohol-related dopamine release in the nucleus accumbens [2•]. It was FDA-approved for treatment of AUD in 1994 and now comes in pill form and extended-release injections. This leads to a reduction of reward sensation and a decline in motivation to drink alcohol. Its use is limited by common side effects of headaches, nausea, dyspepsia, anorexia, anxiety, and sedation. In advanced ALD, naltrexone should be used with caution as it can cause hepatocellular liver injury (mostly elevated alt, usually mild and self-limiting) [39]. However, off-label usage of the oral formulation in liver disease-related pruritus is anecdotally effective and safe.

Disulfiram was the first drug approved by the FDA for the treatment of AUD in 1949. It is an inhibitor of acetaldehyde dehydrogenase, leading to the deterring "acetaldehyde syndrome" of nausea, vomiting, flushing, hypotension, headache, and diarrhea [2•]. While its efficacy is controversial, its role in advanced ALD is virtually zero given its FDA "black box" warning for hepatotoxicity and liver failure.

Precision Medicine for Alcohol-Use Disorder

There is growing evidence for genetic variation accounting for the divergent effectiveness of pharmacotherapy for AUD among patients. Identification of alleles related to a medication's mechanism of action opens the possibility of assessing the likelihood of pre-treatment response and the enrichment of future clinical trials with these "responders." One example is the *OPRM1 A118G* (rs1799971) polymorphism encoding the mu-opioid receptor gene, the target of naltrexone [40]. This allele is associated with the binding affinity of β-endorphin to the receptor, and > 20 studies have demonstrated that *OPRM1 A118G* is significantly associated with response to naltrexone (craving, relapse, abstinence). A similar association has been found with *GABRA6 1519C* (a $GABA_A$ receptor subunit gene) and acamprosate response [41]. Future advances in addiction pharmacogenetics may contribute to the dawn of precision medicine in AUD.

Optimal Treatment Is Combination Treatment

Given the limited pharmacologic options for patients with AUD and advanced ALD, psychosocial treatments are the foundation for treating AUD in this population. Notably however, a recent systematic review of AUD treatment trials (13 studies, $n = 1945$) in ALD found no evidence for any form of psychosocial intervention alone in maintaining abstinence [42••]. However, when integrating CBT, MET, and comprehensive medical care over 2 years, there was a significant increase in abstinence (74% vs 48% in control group, $p = .02$). Based on these findings, an integrated, multidisciplinary, and longitudinal approach (addiction specialist and hepatologist) remains the best option for the management of AUD in advanced ALD. The additional support of social workers, psychologists, nutritionists, and surgeons would maximize the potential to properly manage all aspects of AUD [fer Addolo]. While such an approach is common to transplant programs, it may not be practical in other health care settings.

Other Tips and Tricks

Patients with AUD and advanced ALD experience their condition in different ways. For instance, abstinence can unmask nutritional deficiencies and pain syndromes, especially alcohol-related polyneuropathy. Overtly linking alcohol-specific symptoms to AUD can provide patient education and insight that may affect motivation towards abstinence. Treating neuropathy with high-dose thiamine (500 mg daily) and gabapentin (potential dual effect on AUD too) and treating pain with acetaminophen (< 2 g daily) and low-dose opioids like tramadol can be highly effective and promote a therapeutic relationship [43].

In some patients with milder forms of ALD, performing serial transient elastography (Fibroscan) can be more useful to assess liver health than liver enzymes which can be normal even with significant drinking. Demonstrating and discussing fluctuating stiffness values with the patient during abstinence or after relapse can also serve as a motivating tool, particularly in patients attuned to objective numeric values over time.

Alcohol biomarkers refer to tests of urine, blood, or hair which identify metabolites or surrogates of alcohol use and provide an estimated timeframe of recent drinking. Alcohol biomarkers should be used to aid diagnosis, to support recovery, and as catalysts for discussion with the patient, rather than as punitive tools to "catch" them in the act [44]. Providers should discuss biomarker use with patients *prior to* testing in order to maintain a therapeutic alliance and improve candor about alcohol. Since available alcohol biomarkers have significant limitations (particularly false positives), they should not be used solely to confirm or refute alcohol use but be combined with interviews, physical exam, and other lab testing (including other alcohol biomarkers). Several recent reviews highlight the emergence and utility of biomarkers like urine ethyl glucuronide and (serum) phosphatidylethanol (which are currently preferred in advanced ALD) [45•, 46].

Conclusions

Overcoming addiction to alcohol in patients with advanced ALD is crucial to recovery, since persistent drinking results in a higher risk of liver-related complications and ineligibility for liver transplantation (LT). Improved patient and provider education about the neurobiologic basis of addiction can reduce stigma and judgment. Given the paucity of medications currently available for AUD in advanced ALD, the best approach is with an integrated, multidisciplinary, and longitudinal effort ideally anchored by psychosocial treatment with an addiction specialist plus medical care from a hepatologist. Since successful management of these patients are often based on more art than science, tips and tricks may be utilized to optimize treatment in these complex patients.

Compliance with Ethical Standards

Conflicts of Interest Gene Im declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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