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Alcohol-Associated Liver Disease: Integrated Management With Alcohol Use Disorder

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Alcohol-associated liver disease (ALD) is the most common cause of cirrhosis and liver-related mortality in many regions worldwide. Around 75% of patients with cirrhosis are unaware of their disease until they are referred to the emergency department. An innovative, noninvasive screening approach is required for an earlier diagnosis of liver fibrosis. In patients with ALD the physician is inevitably dealing with 2 major disorders: the liver disease itself and the alcohol use disorder (AUD). Focus only on the liver disease will inevitably lead to failure because transient improvements in liver function are rapidly overturned if the patient returns to alcohol consumption. For this reason, integrated models of care provided by hepatologists and addiction specialists are an effective approach, which are, however, not widely available. There are multiple pharmacologic and non-pharmacologic therapies for AUD. Progress has recently been made in the management of patients with severe AH who have improved survival through better understanding of the concept of response to medical treatment, improved survival prediction, and the advent of early liver transplantation. The emerging concept is that listing for transplantation a patient with severe ALD could lead to adjusting the duration of abstinence according to the severity and evolution of liver dysfunction and the patient's addictive profile.

Keywords: Alcohol; Cirrhosis; Alcohol-Associated Hepatitis; Alcohol Use Disorder; Fatty Liver Disease.

Alcohol-associated liver disease (ALD) is the most common cause of cirrhosis, liver failure, and liver-related mortality in many regions of the world including Europe and North America. Excess alcohol consumption results in liver steatosis in virtually everyone because of reprogramming of lipid synthetic pathways and the excess number of calories consumed. Only a minority of heavy drinkers will develop alcohol-associated steatohepatitis, but this will lead to fibrosis, cirrhosis, and ultimately portal hypertension and decompensation. Along this trajectory 20%–30% of patients will experience an episode of alcohol-associated hepatitis (AH), which manifests as rapid onset jaundice with features of liver failure[1] (Figure 1). An episode of severe AH carries a mortality risk of 30% at 3 months, which is higher than the majority of acute medical emergency admissions.[2]

In patients with ALD the physician is inevitably dealing with 2 major disorders: the liver disease per se and the alcohol use disorder (AUD). Focus only on the liver disease will inevitably lead to failure because transient improvements in liver function are rapidly overturned if the patient returns to alcohol consumption. At all stages of liver disease, including decompensated cirrhosis, achieving and maintaining alcohol abstinence substantially improve the patient's prognosis. It behooves the hepatologist to address the AUD in the same way because there is an obligation to address other etiologies of liver disease such as viral infection or autoimmune disorders. AUD is challenging to treat, and the hepatologist needs to work with addiction services to provide psychosocial and pharmacologic treatment for addiction. An integrated service model has been adopted by a number of liver transplant units, resulting in high rates of complete abstinence.[3]

Despite the enormous burden of ALD there are no specific treatments, and there are substantially fewer commercially or academically sponsored clinical trials than currently observed in nonalcoholic fatty liver disease (NAFLD). Nevertheless, studies on the pathogenesis of ALD and AH have revealed several important biological pathways that are potential targets for therapeutic intervention.[4] In addition, improvements in best supportive care for patients with severe ALD have led to substantial improvements in survival.[2] A major advance

Abbreviations used in this paper: **AH, alcohol-associated hepatitis; AKI, acute kidney injury; ALD, alcohol-associated liver disease; AST, aspartate aminotransferase; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; CBT, cognitive-behavioral therapy; DAMP, damage-associated molecular pattern; GGT, gamma-glutamyl transferase; IL, interleukin; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MET, motivational enhancement therapy; NAFLD, nonalcoholic liver disease; RCT, randomized controlled trial; TLR, toll-like receptor.**

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in the management of AH has been the use of liver transplantation (LT) in an acute setting without the requirement for prolonged abstinence.[5] However, a key focus for the future management of patients with ALD must be for early diagnosis and intervention for AUD to prevent progress to end-stage liver disease and avoiding hospital admission.

Alcohol-Associated Liver Disease

Epidemiology and Burden of the Disease

Currently, 43% of the global population consumes alcohol. The alcohol annual per capita consumption in 2016 was 6.4 L of alcohol per person aged 15 years or older worldwide.[6] Furthermore, the global prevalence of AUD is 5.1%, with the highest prevalence in the European and the Americas regions. One-third of patients with AUD will develop various forms of ALD.[7] Of note, AUD tends to be more prevalent in men and high-income countries.[8] Heavy alcohol drinking is a major risk factor for morbidity and mortality.[6,9] Indeed, 5.3% of worldwide mortality is related to alcohol consumption per year.[6,8] This associated mortality is not only dependent on liver disease. Alcohol increases the risk of liver disease mortality 260-fold, cardiovascular mortality by 3.2-fold, and cancer mortality by 5.1-fold.[10] Heavy alcohol consumption accounts for more than 50% of the attributable fraction of cirrhosis worldwide.[7] Alarmingly, the mortality attributable to ALD has been increasing in developed countries in the last decade[11]; furthermore, heavy alcohol consumption and ALD-related burden have increased during the coronavirus disease 2019 pandemic, and it is expected that alcohol consequences will persist.[12] Alcohol remains as the most common cause for LT waitlisting in men and the second after NAFLD for women in the United States.[13]

The incidence of AH, the severe inflammatory form of the disease, with up to 50% mortality at 3 months has been also increasing, especially in youth and women.[14] Indeed, more than 70% of the disease burden comes from the population aged 15–44 years.[6,14] This correlates with the fact that alcohol consumption in late adolescence is associated with an increased risk of severe liver disease later in life.[15] In addition, ALD often coexists with other causes of liver disease, including viral hepatitis and NAFLD. These associations have become even more relevant these days because of the growing prevalence of obesity and type 2 diabetes mellitus worldwide.[16] Furthermore, obesity, diabetes mellitus, and metabolic syndrome may also potentiate the severity of all stages of ALD in a synergistic fashion.[17] Indeed, even moderate alcohol consumption has been shown to increase the rates of hepatic steatosis, fibrosis, and hepatocellular carcinoma among patients with obesity or NAFLD.[17] These data should prompt the development of a whole-society approach and implementing specific public health policies.[18]

Alcohol-Associated Hepatitis

Diagnosis and Prognosis Assessment

The diagnosis of ALD is usually made clinically, on the basis of clinical history, physical examination, and laboratory findings, in patients with reported chronic heavy alcohol consumption (>20–30 g/d for women and 40–50 g/d for men), elevated liver biochemistries, and/or an abnormal imaging study. Laboratory blood tests such as mean corpuscular volume, gamma-glutamyl transpeptidase (GGT), and aspartate amino transferase (AST) can indicate alcohol-related disease. ALD is often only diagnosed when the patient develops complications of cirrhosis. Advanced ALD is suspected if there is concomitant increase of the international normalized ratio, elevated serum bilirubin, or decreased serum albumin or platelet count. For the clinical diagnosis of AH, a National Institute on Alcohol Abuse and Alcoholism consortia defined the criteria listed in Table 1.[19] Imaging should exclude biliary obstruction, and an extensive workup for other causes such as viral hepatitis, autoimmune liver disease, and Wilson disease should be performed. When the diagnosis is not clear and/or there are confounding factors, a transjugular liver biopsy is recommended.[19] Histologically, AH is characterized by features of alcohol-associated steatohepatitis (ie, ballooned hepatocytes, Mallory-Denk bodies, neutrophil infiltration), ductular reaction, bilirubinostasis, and pericellular and sinusoidal fibrosis ("chicken wire" appearance). However, many of these features are similar to those described in nonalcoholic steatohepatitis,[20] making it difficult to differentiate both diagnoses when the history of alcohol consumption is not clear.

An episode of severe AH can be associated with mortality up to 30%–40% at 90 days.[21] The current models used to predict short-term mortality include the Maddrey's modified discriminant function,[22] the Model for End-Stage Liver Disease (MELD),[23] the Glasgow AH score,[24] and the age-bilirubin-INR-creatinine score.[25] At baseline, the MELD score has proven to be the best static scoring system in a multinational multiethnic cohort, and it is recommended for patient risk stratification and decision over initiation of treatment with corticosteroids. The Lille score is a dynamic score (including data at baseline and after the initiation of corticosteroids) useful to assess prognosis, and to define corticosteroids nonresponders, it is calculated at day 7, but it may be alternatively calculated at day 4.[26,27] In addition, the presence of systemic inflammatory response syndrome and acute kidney injury (AKI) predict multiorgan failure and acute-on-chronic liver failure.[28] It must be highlighted that the main factor influencing long-term

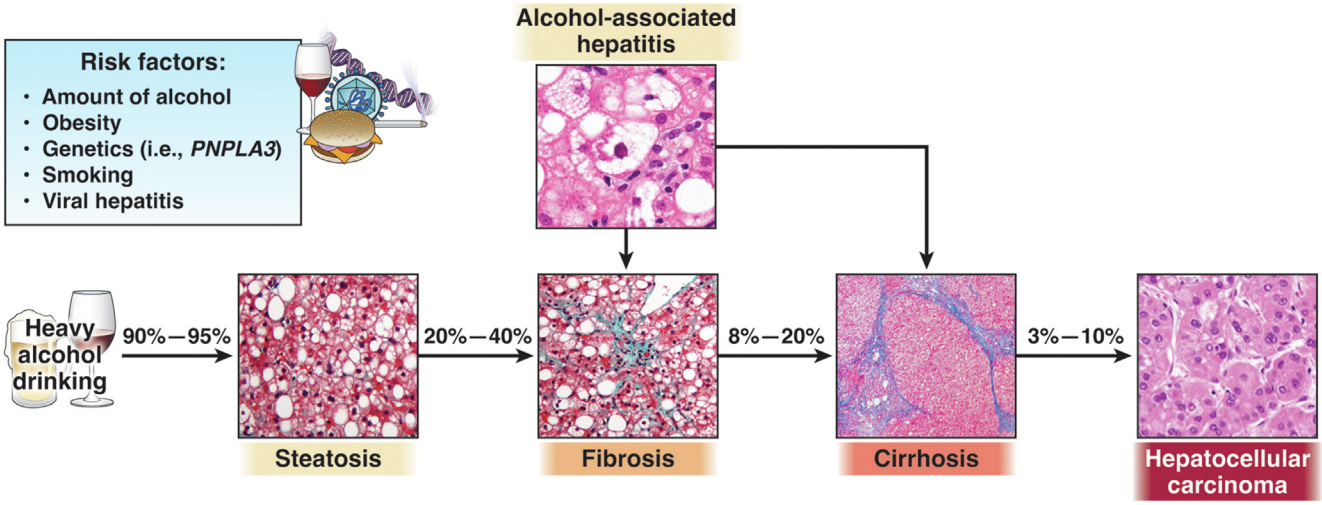

Figure 1. Disease spectrum of alcohol-associated liver disease. Alcohol-associated liver disease (ALD) represents a spectrum of liver injury resulting from alcohol consumption, ranging from hepatic steatosis to more advanced forms including different degrees of liver fibrosis and alcohol-associated cirrhosis. At any point of the disease, with or without cirrhosis, patients can develop the inflammatory form of the disease as an acute alcohol-associated hepatitis.

prognosis after an episode of AH is prolonged alcohol abstinence.[29]

Medical Management

The cornerstones for medical management are alcohol abstinence, nutrition, early identification/treatment of infections, prevention/treatment of AKI, treatment of the complications of portal hypertension, and the use of corticosteroids in selected patients. Malnutrition is very common in patients with AH, but it has a significant impact on morbidity and mortality. Thus, it is important to ensure adequate enteral nutrition for caloric and protein intake (35–40 kcal/kg/day, with protein 1.5 g/kg/day).[30] Infections are also common (especially in those patients non-responding to corticosteroids) and should be actively ruled out and treated because the early identification and appropriate treatment have been associated with a decrease in the related mortality.[31] In this sense, identifying and treating an infection are not a contraindication for corticosteroid use if it is under control. In the STOPAH trial, 12.5% of patients had baseline infection, 23% developed infections during corticosteroids treatment, and 8.2% did it after treatment discontinuation. Bacterial infections are the most frequent, but fungal infections can be seen in up to 16% of patients with AH and carry a significant mortality.[32] The main risk factors for fungal infections are younger age, higher MELD score, and corticosteroid therapy.[33] AKI can be present in up to one-third of the patients with severe AH and is associated with a 9-fold increase in 90-day mortality.[34] The use of albumin, vasoconstrictors, and renal replacement therapy may be indicated in a case-by-case basis until more consistent data are available.

Regarding specific treatment, corticosteroids have a short-term beneficial effect in patients with severe AH.[35] The STOPAH trial showed a trend to improve 1-month survival but increased infections.[36] Subsequently, a meta-analysis showed improved 30-day (but not 60- or 90-day) survival.[37] More recently, a study from a large multinational multiethnic cohort of 3380 patients identified the optimal MELD therapeutic window for the use of corticosteroids. The maximum benefit (defined as at least 20% survival benefit) was achieved with MELD scores between 25 and 39.[21] These studies also provided evidence on the futility of the use of pentoxifylline for AH.[36,37] There are some promising data for adding N-acetylcysteine to prednisolone. However, further studies are needed before recommending its use.[38]

Emerging Therapies

A consequence of the lack of durable benefit from corticosteroids, the only currently recommended intervention for AH, is a significant unmet need that has recently attracted the attention of biotech and pharmaceutical companies.[37] As our understanding of the disease improves, the number of therapeutic targets increases, and these can be categorized into 3 groups: microbiome, inflammation, and regeneration.

The intestinal microbiome of patients with ALD and particularly those with AH is significantly different from healthy individuals.[39] Several studies have documented changes in the prevalence of bacteria, fungi, and viruses in the stool of ALD patients. However, this is not merely an association of dysbiosis with the disease, because it has been shown that transfer of the microbiome from patients with AH into mouse models of ALD results in more severe inflammation and liver damage than a healthy human microbiome.[40] There may be a large number of microbial structures (eg, lipopolysaccharide), toxins, and metabolites that mediate liver damage after

Table 1. NIAAA Criteria for the Diagnosis of Alcohol-Associated Hepatitis

1. Onset of jaundice within the prior 8 weeks
2. Ongoing consumption of more than 3 drinks (~40 g) per day for women and 4 drinks (~50–60 g) per day for men for 6 months or more
3. Less than 60 days of abstinence before the onset of jaundice
4. Total serum bilirubin >3 mg/dL (>50 μmol/L)
5. Aspartate aminotransferase (AST) >50 IU/mL, AST to alanine aminotransferase (ALT) ratio of >1.5, and both values <400 IU/L
6. Ruling out other liver diseases such as drug-induced liver injury (DILI), autoimmune and ischemic hepatitis

translocating through the intestinal epithelium. Thus, one approach to treatment is replacement of the unhealthy microbiome with a microbiome taken from a healthy individual using fecal microbial transplantation.[41] Although fecal microbial transplantation can be considered as a rather crude intervention, early trials suggest a significant improvement in survival among patients who are not eligible for corticosteroid treatment. Further randomized trials are currently in progress.

An alternative strategy is to gain a deeper understanding of the microbial factors that are responsible for exacerbating AH. This is well-illustrated in a recent study demonstrating a marked increase in the prevalence of *Enterococcus faecalis* in patients with AH.[42] Furthermore, AH was associated with an *E faecalis* strain producing a cytolysin toxin that causes hepatotoxicity. In animal studies this strain can be targeted with highly specific phages, resulting in clearance of the toxin and amelioration of the hepatotoxicity. Although this strain of *E faecalis* is not found in all patients with AH, its presence is associated with much higher mortality levels, making this an ideal target for therapeutic intervention. Phage therapy has previously been used to eliminate antibiotic resistant bacteria in other diseases and may be applicable in this scenario. Alternatively, strain specific antibodies engineered for oral delivery could be used to target the cytolysin-producing *E faecalis*.

In AH, inflammation is driven by both intrinsic and extrinsic processes. Metabolism of excess alcohol through the cytochrome P450 system results in the generation of reactive oxygen species causing intracellular damage. Mitochondrial damage and endoplasmic reticulum stress result in hepatocyte necrosis and apoptosis releasing damage-associated molecular pattern (DAMP) molecules, which stimulate inflammation. In addition, bacterial cell wall and other structural components that translocate into the portal venous system encounter resident macrophages (Kupffer cells) in the hepatic sinusoids. Kupffer cells recognize bacterial products through toll-like receptors (TLRs), in particular TLR-4. TLR engagement results in the release of proinflammatory cytokines and chemokines including interleukin (IL) 1β. Inhibition of IL-1β, either through receptor blockade with Anakinra or with the monoclonal antibody Canakinumab, might prove to be therapeutic, but current trials have not confirmed a survival benefit.[43] An alternative strategy would be targeting of TLR-4, which mediates inflammatory responses from lipopolysaccharide as well as DAMPs. A recent study in a mouse model of acute-on-chronic liver failure suggests that this may be feasible, but human trials are lacking.[44]

AH is characterized by profound loss of liver function that persists for weeks after cessation of alcohol consumption. The regenerative response that would normally restore the functioning liver cell mass is impaired because of a high prevalence of senescent cells and epigenetic changes, which result in loss of the HNF4a mediated hepatocyte differentiation pathway.[4] Potential therapeutic options include the cytokine IL-22 and hepatocyte growth factor, which stimulate hepatocyte regeneration. An early phase trial of IL-22 has recently been published with promising results for clinical outcomes compared with historical controls.[45] Finally, larsucosterol, an epigenetic modulator, has been evaluated in patients with AH in a phase 2a study.[46] Compared with matched historical controls, patients treated with larsucosterol had significantly improved Lille responses and good clinical outcomes, paving the way for a large phase 2b study that is currently recruiting.

Early Liver Transplantation

Development of prognostic dynamic models such as the Lille model[47] or the combination MELD and Lille models[48] makes it possible to quantify the risk of short-term mortality after 1 week of evolution under treatment. Nowadays, clinicians can propose early on new strategies in patients with severe AH not responding to medical therapy who disclose a 6-month mortality rate around 70%–80%. Therapeutic management has changed since the advent of early LT.[49] However, few patients undergo transplantation after a very selective process including meetings to obtain the team consensus listing only patients with supportive family members and without significant comorbidities or psychiatric illnesses, history of serious alcohol-related events, and no awareness of a diagnosis of underlying cirrhosis. Recent studies have observed 2-year survival around 80%–90%, with a cumulative incidence of any alcohol use of 20%–30%.[50,51] A young age was predictive of alcohol relapse after LT. The first controlled study observed that alcohol relapse and the time spent drinking alcohol were not significantly different in patients early transplanted for AH (34%) than their controls listed after at least 6 months of abstinence.[51] However, AH patients who relapsed had higher alcohol consumption with more

prolonged periods of alcohol consumption than their controls listed after at least 6 months of abstinence.[51] To propose new strategies with a rational approach, new outcomes need to be investigated such as duration of abstinence or time spent with excessive alcohol consumption, key prognostic factors in graft survival and long-term liver-related deaths.[52] Early LT for AH continues to expand across the world including the United States, with 50% of American centers performing this procedure in 2018, whereas none had performed it in 2005. The listing procedure remains very stringent, with less than 20% patients evaluated, only 4% transplanted, and around 3%–5% and 2% of grafts used for this indication in France and United States, respectively.[53]

Alcohol Use Disorder

Screening by the Gastroenterologist/ Hepatologist

Excessive alcohol consumption should be assessed in all patients with liver disease. Structured, standardized questionnaires have been developed to aid the identification of individuals with underlying AUD. The Alcohol Use Disorders Identification Test (AUDIT) comprises 10 questions with a specific scoring system.[54] A score greater than 8 is considered a positive screening test result and indicates a high likelihood of AUD. AUDIT scores of 15 for men and 13 for women have 100% specificity but low sensitivity (20% and 18%, respectively) detecting alcohol dependence prompting brief intervention and monitoring. In addition, a score >20 implies the presence of alcohol dependence and should be referred to addiction specialists.[55] The AUDIT-C is an abridged questionnaire designed to facilitate widespread implementation and reduce the time requirements associated with administering the full test. It consists of only 3 questions, each with a specific grading system giving a total score between 0 and 12. It is considered positive screening with a result ≥3 for women and ≥4 for men.[56]

Alcohol use is often underreported because of its associated stigma and consequences on care. In this sense, the use of biomarkers may overcome this barrier. On the one hand, indirect markers of alcohol consumption, such as GGT, mean corpuscular volume, AST, and carbohydrate-deficient transferrin, have a very low specificity.[57] On the other hand, biomarkers of alcohol metabolism, such as ethyl glucuronide, ethyl sulfate, and phosphatidylethanol, may be useful to screen for alcohol use because they have the benefit of higher specificity (Table 2). Ethyl glucuronide and ethyl sulfate are nonvolatile, water-soluble metabolites formed during the elimination of ethanol. They can be detected in urine up to 90 hours after alcohol ingestion; their performance is not influenced by the presence of liver disease. Metabolites are detectable in urine for 4–5 days after alcohol consumption, with a reported sensitivity of 62%–89% and specificity of 93%–99%. Phosphatidylethanol is a phospholipid formed only in the presence of alcohol and can be identified from a whole blood sample. The test can be used to detect alcohol consumption in the last 28 days, with a reported sensitivity of 90%–99% and specificity of 100%.[58]

Pharmacologic and Non-pharmacologic Management of AUD in ALD

Total alcohol abstinence and alcohol relapse prevention are the goals of therapy in patients with AUD and ALD. The most effective strategy for achieving these objectives is the combination of pharmacologic therapy, medical management, and psychosocial interventions.[59] Disulfiram, acamprosate, naltrexone, nalmefene, sodium oxybate, and baclofen have been approved in different countries as medications for the treatment of AUD (Table 3). Topiramate, ondansetron, gabapentin, and varenicline are also used off-label.[60] However, available data on these medications in AUD patients with ALD are limited because they are usually excluded from pharmacologic trials because of the concerns about liver safety.[58]

Disulfiram increases acetaldehyde blood levels if alcohol is consumed during disulfiram treatment, leading to life-threatening adverse effects, so patients are discouraged to drink alcohol. Hepatotoxicity (including liver failure) due to the accumulation of toxic metabolites is a possible side effect of disulfiram, particularly in patients with liver disease.[61] Although disulfiram has not been tested in AUD patients with advanced liver disease, its characteristics would make the drug unmanageable in these patients. Currently, it is contraindicated to use disulfiram in patients with cirrhosis.

Acamprosate is indicated to reduce alcohol intake, to improve a long-term alcohol abstinence, and to prevent alcohol relapse. Its poor hepatic metabolism would make acamprosate a medication with a very manageable pharmacologic liver profile and potentially useful for AUD patients with ALD. Currently, there is no evidence of hepatotoxicity related to acamprosate administration. Compared with placebo, acamprosate has never been associated with elevations in serum liver biochemistries, and no acute liver injury related to this drug has been reported. Nevertheless, acamprosate has never been formally tested in randomized controlled trials (RCTs) in patients with ALD. Acamprosate can be used with caution in early phase of ALD, and adjustment may be required when renal dysfunction is also present.[58]

Naltrexone reduces the alcohol reward, decreasing alcohol craving and consumption and promoting alcohol abstinence. Although limited evidence suggests a possible relationship between standard dose naltrexone administration (50–100 mg per day) and liver toxicity, naltrexone is not currently recommended in AUD

Table 2. Pros and Cons of Available Biomarkers of Alcohol Consumption

Method	Pros	Cons
Indirect biomarkers		
- GGT, AST[58]	Inexpensive and readily available; AST to ALT ratio is a good indicator of chronic excessive alcohol use.	Low specificity particularly in patients with liver dysfunction or on multiple drug therapy
- Mean corpuscular volume[72]	Widely available, marker of chronic consumption.	Low specificity
- Carbohydrate-deficient transferrin (CDT)[73]	Useful marker for the monitoring of an alcohol relapse in patients after transplantation for alcoholic cirrhosis.	Low specificity. Does not appear to be useful as a pre-transplant screening.
Direct biomarkers		
Ethyl glucuronide (EtG)[57] Ethyl sulfate (EtS)[74]	Detected in urine up to 90 hours after alcohol ingestion; their performance is not influenced by the presence of liver disease. Metabolites are detectable in urine for 4–5 days after alcohol consumption, sensitivity of 62%–89% and specificity of 93%–99%.	High cost and low availability
Phosphatidylethanol (PEth)[75]	Can detect alcohol consumption in the last 28 days with a reported sensitivity of 90%–99% and specificity of 100%	High cost and low availability

patients with ALD because of the concern of potential risk of hepatotoxicity related to its metabolism.[59] In the past, the Food and Drug Administration issued a black box warning discouraging the use of naltrexone in patients with ALD. However, over the years, several studies showed the absence of hepatotoxicity in patients treated with the standard dose of naltrexone,[62,63] so the Food and Drug Administration black box has been removed. Currently, pharmacologic options in patients with AUD and ALD are very limited, and evidence about the side effects of naltrexone on the liver is rare and outdated. Therefore, in a benefit-risk approach, naltrexone could be evaluated and suggested in these patients.[58]

Nalmefene is a drug approved to reduce alcohol intake. Patients with ALD should have the goal of total alcohol abstinence; therefore, this medication is not recommended in advanced ALD. However, nalmefene could be used in patients with early stages of liver disease who are not still able to maintain alcohol abstinence, with the aim of harm reduction.[64]

Sodium oxybate is an alcohol-mimetic anti-craving drug approved for the treatment of alcohol withdrawal syndrome; it is effective to promote alcohol abstinence and relapse prevention in AUD patients.[65] Although sodium oxybate has a liver metabolism, its short half-life (4–5 hours) could make it safe and manageable in patients with ALD. In cirrhotic patients, an increase in half-life could be present; however, it seems not to be enough to cause drug accumulation and/or toxicity in these patients. RCTs are needed to confirm efficacy and safety of sodium oxybate in patients with ALD; at present EMA suggests halving the dose in patients with hepatic impairment, and response to dose increments should be strictly monitored.

Baclofen is able to modulate alcohol-stimulated dopamine release. Baclofen has low liver metabolism (less than 15%) and is mainly eliminated unmodified by the kidney. Currently, baclofen is the only medication formally tested in RCTs in AUD patients with severe liver damage.[66] The safety of baclofen in patients with advanced liver disease was supported by several cohort studies in which more than 300 AUD patients with advanced ALD were successfully and safely treated with baclofen.[64] At present, the off-label use of baclofen may be considered a first-line treatment in AUD patients with advanced ALD.[67]

In combination with pharmacologic treatments, psychosocial intervention is strongly recommended in these patients. Psychosocial support for AUD includes different options:

(1) brief intervention (sessions of 5–30 minutes motivational interview, to reinforce the subject's motivation to achieve abstinence or to reduce alcohol consumption);

(2) motivational enhancement therapy (MET) (brief treatment approach provided by individual counseling sessions approach, based on the resolution of psychological ambivalence by promoting the knowledge of potential harmful consequences associated with persistent drinking);

(3) cognitive-behavioral therapy (CBT) (weekly individual sessions of psychotherapy with the goal to increase the patient's ability to manage alcohol craving and to develop effective coping strategies, to reduce the risk of relapse);

(4) mutual help or peer support groups (ie, Alcoholics Anonymous) represent one of the most

Table 3. Pharmacologic Management of AUD in the Setting of ALD

Drug	Approved country	Mechanism of action	Dose	Available data on efficacy and safety in AUD patients with ALD	Main side effects
Acamprosate	US and EU	Glutamate receptor modulation	1.3 g/day (weight <60 kg) and 2 g/day (weight >60 kg) in 3 daily administrations	Only 1 day administration study in Child A-B liver cirrhosis	Diarrhea
Baclofen	France	GABA-B agonist	10 mg 3 times a day in patients with liver disease	In Child A-C liver cirrhosis	Sedation with high doses, hypotonia
Disulfiram	US and EU	Inhibitor of aldehyde dehydrogenase	800–1200 mg/day for 3–4 days, then 400 mg/day until the 7th day, after 200 mg/day	NO	Hepatotoxicity (particularly in patients with liver disease), sleepiness, headache
Nalmefene	EU	Selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor	18 mg per day "on demand"	NO	Insomnia, headache, nausea
Naltrexone	US and EU	Opiate antagonist with the highest affinity for the μ receptor	50–100 mg/day	NO	Headache, sedation, nausea/ vomiting
Sodium oxibate (GHB)	Italy, Austria, Kazakhstan	GABA-B/ GHB receptor agonist	50 mg/kg divided into 3 or 6 daily administrations	Only 1 case report (see ref 99)	Dizziness, headache, nausea, vertigo

NOTE. Effective medications approved in different countries for the treatment of alcohol use disorder.
GABA-B, gamma aminobutyric acid ionotropic receptor family B.

acknowledged and historical sharing programs of approach to alcohol problems, to find a personalized motivational and psychological support.

In these settings, AUD patients with ALD represent a particular population, because their physical limitations (eg, muscle weakness, ascites), cognitive impairment (eg, encephalopathy), and repeated hospitalizations due to the complications of advanced ALD severely limit the ability of ALD patients to attend regular psychosocial support treatment programs. A recent systematic review[68] showed that in AUD patients with ALD any psychosocial intervention alone was not effective, whereas the combination of psychosocial interventions (CBT and MET) integrated with medical management significantly increased alcohol abstinence and reduced alcohol relapse.

Integrative Care

AUD patients with ALD are a special population suffering from a dual pathology. AUD is a chronic disease characterized by harmful alcohol intake from mild to severe and impaired ability to stop or to control alcohol consumption, despite adverse health and social consequences.[58] The inability to stop drinking is related to tolerance and to mitigate alcohol craving and withdrawal symptoms. The long-term prognosis of ALD is strictly related to the persistence of alcohol consumption[29]; therefore, alcohol abstinence is mandatory for ALD patients.

Considering the dual nature of ALD and the outcome of treatment, AUD patients with ALD should be managed by an integrated model characterized by the presence of the AUD addiction specialists' team

within the Liver Unit rather than to use external consultants (Figure 2). The integration of addiction interventions with medical care could engage patients who would not accept an external referral for AUD treatment, whereas they willingly come back for medical visit with the hepatologist in the Liver Unit.[69] The integrated model was found effective to increase alcohol abstinence, to reduce the prevalence of alcohol relapses, and alcohol-associated mortality even after LT,[3,59] regardless of the period of alcohol abstinence before the LT, to identify patients at risk for severe relapse in the pre-LT period,[3] to early identify recurrences to alcohol after LT, and to improve survival.[70] The integrated model has several advantages. Particularly, the AUD team integrated in the Liver Unit can manage simultaneously pharmacotherapies to treat AUD in patients with advanced ALD and impaired liver function, being aware of all aspects related to liver disease and its complications. Finally, the AUD team could properly manage AUD patients listed for LT, closely monitoring the patient and minimizing the risk of alcohol relapse.[58]

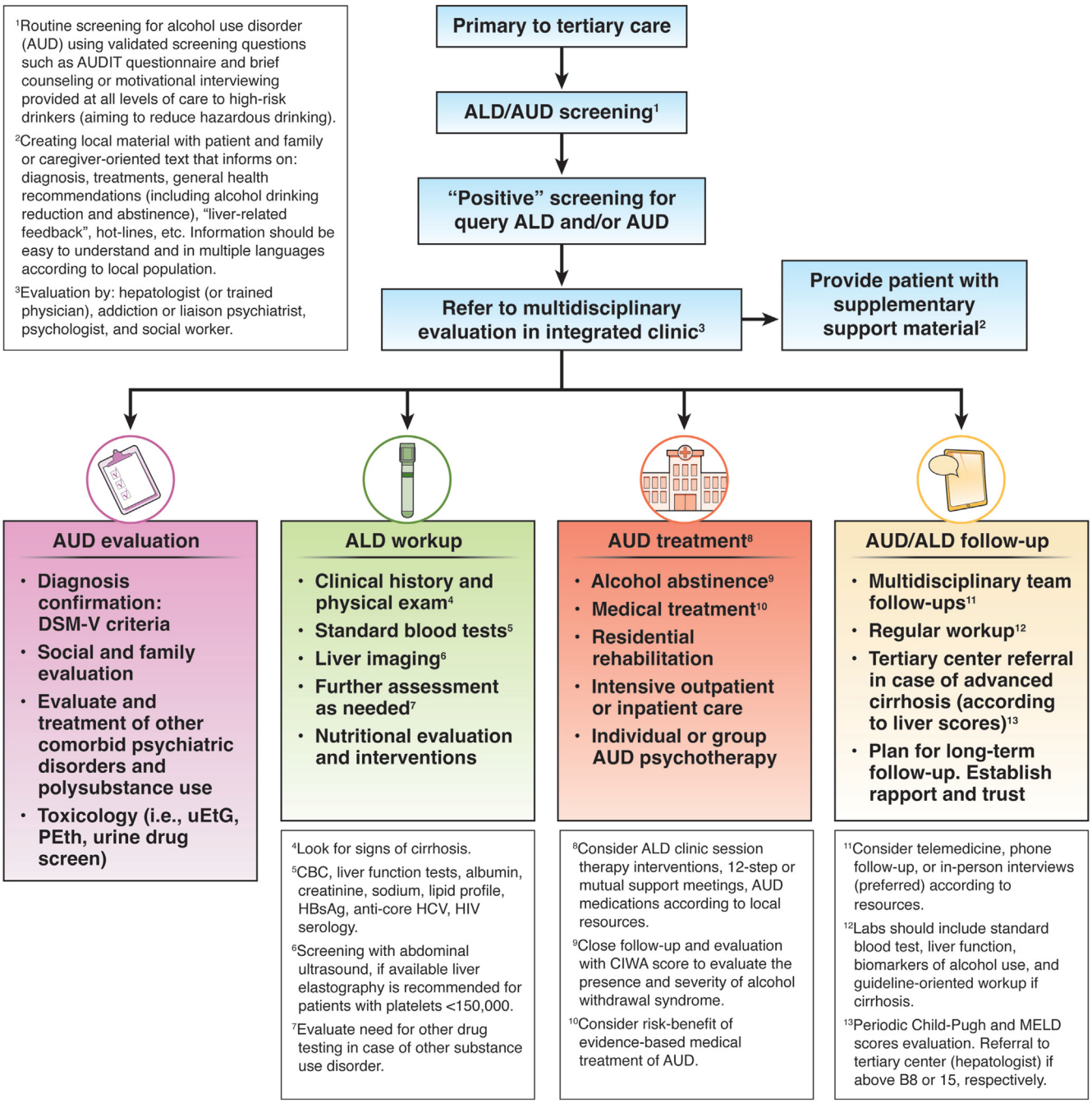

Figure 2. Key components of a multidisciplinary clinic for ALD/ALD treatment. Proposed composition and workflow of a multidisciplinary clinic to treat AUD in the setting of ALD. ALD, alcohol-associated liver disease; AUD, alcohol use disorder.

Conclusions and Future Perspectives

ALD remains a major public health issue because 2 billion people in the world consume alcohol and 2 million die each year from ALD. Around 50% of liver mortality is attributable to alcohol, making ALD one of the top 30 causes of death.[47] In 2010, the worldwide rate of alcohol-attributable cirrhosis death was 7.2 per 100,000 people (4.6 in women and 9.7 in men). Basic and translational studies will improve our understanding of the pathogenesis of the disease, deciphering the mechanisms that drive ALD progression and identifying new biomarkers and targets for intervention.[71]

Late diagnosis of ALD is the most important clinical issue because it significantly contributes to the elevated mortality. Around 75% of patients with fatal cirrhosis are unaware of their disease until they are referred to the emergency department. An innovative, noninvasive screening approach is required for an earlier diagnosis of extensive fibrosis. Such approach could provide new perspectives for early diagnosis of cirrhosis and screening strategy in patients at risk of liver-threatening events.[47]

In advanced ALD patients, integrated combination therapy provided by hepatologists and addiction specialists (the so-called integrated model) is an effective approach, but it is unfortunately not available in most hospitals. Progress has recently been made in the management of patients with severe AH, who have improved survival through better understanding of the concept of response to medical treatment, improved survival prediction, and the advent of early LT. Soon, experts and health agencies should make recommendations for design of phase I and II trials to target AH patients with a slight competitive risk of mortality to ensure sufficient exposure time of the tested drugs.

The emerging concept is that listing for transplantation a patient with severe ALD could lead to adjusting the duration of abstinence according to the severity and evolution of liver dysfunction and the patient's addictive profile.

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