REVIEW ARTICLE

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Alcohol-Associated Hepatitis

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Alcohol use disorder is a major cause of advanced liver disease and liver-related hospitalization and death worldwide.[1,2] Globally, alcohol is the cause of 50% of all deaths due to liver disease, and various forms of alcohol-associated liver disease (ALD) will develop in approximately 35% of patients with alcohol use disorder.[3] The natural history of ALD is not well defined and is influenced by periods of heavy alcohol intake and abstinence.[4] The clinical and histopathological forms of ALD range from isolated steatosis to progressive steatohepatitis with fibrosis accumulation to cirrhosis and its complications, culminating in the development of hepatocellular carcinoma.[5]

Most patients with ALD receive a diagnosis at an advanced stage, when the disease becomes symptomatic.[6] A severe clinical profile may develop in patients with underlying ALD and active drinking, characterized by an abrupt onset of jaundice, malaise, decompensated liver disease, and coagulopathy, an entity called alcohol-associated hepatitis.[7] In its severe forms, alcohol-associated hepatitis is associated with bacterial infections and the development of acute-on-chronic liver failure, multiorgan failure, and high short-term mortality (20 to 50% at 3 months).[8,9] Although the prevalence of alcohol-associated hepatitis is not well known, the global incidence is probably increasing, especially among young adults (in their 20s and 30s) and women.[8,10] Its incidence has increased during the coronavirus disease 2019 pandemic.[11,12]

During the past decade, the diagnostic criteria for alcohol-associated hepatitis have been revised. The clinical findings required for its diagnosis, the indications for transjugular liver biopsy, and the diagnostic certainty (possible, probable, and definitive alcohol-associated hepatitis) were defined by a panel of experts from the National Institute on Alcohol Abuse and Alcoholism (NIAAA).[13] Moreover, a specific histologic classification with prognostic significance was developed (Alcoholic Hepatitis Histologic Score [AHHS]).[14] Specific therapy for alcohol-associated hepatitis, however, still relies on the use of glucocorticoids, which improve short-term (30-day) but not long-term survival in selected patients.[15,16] From the early trials in the 1970s until the more recent Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial, glucocorticoids were the only therapy for severe alcohol-associated hepatitis that consistently showed a benefit with respect to short-term survival.[16-18] Translational studies have identified several key mechanisms of alcohol-associated hepatitis involving the microbiome, proinflammatory signals, and factors leading to poor hepatocyte differentiation and function.[19] These discoveries have markedly stimulated the liver-disease and pharmaceutical communities to test new pathophysiological-based therapeutic approaches.[20] Finally, since the transformative study by Mathurin et al.,[21] an increasing number of centers worldwide are offering the possibility of early transplantation to highly selected patients with severe alcohol-associated hepatitis that does not respond to medical therapy.

In this review, we discuss evolving concepts in the diagnosis and prognosis of alcohol-associated hepatitis, the current trend to treat these patients in a holistic

manner involving addiction specialists, ongoing clinical trials testing new targets for therapy, and current selection criteria for early liver transplantation.

PREDISPOSING FACTORS AND PATHOGENESIS

Individual susceptibility to the development of severe forms of ALD varies among heavy drinkers. Although many patients have only mild forms, progressive fibrosis and cirrhosis and its complications develop in others.[22] The factors underlying the development of the abrupt form of liver failure that defines alcohol-associated hepatitis are largely unknown and probably include environmental, genetic, and epigenetic factors.[23] Although most patients presenting with alcohol-associated hepatitis have a history of prolonged and heavy alcohol use, whether the total amount or pattern of alcohol consumption plays a role remains unknown.[24] Sex differences have been observed in alcohol-associated hepatitis, both in the manifestations and severity of liver disease and in the prevalence and severity of alcohol use disorder and relapse potential. Women are more susceptible to alcohol injury and cirrhosis,[25,26] young women constitute the fastest growing population assessed for liver transplantation in the United States,[27] and female sex is independently associated with ALD-related burden and alcohol-related acute-on-chronic liver failure in the United States.[10] Hispanic persons are predisposed to the development of alcohol-associated hepatitis, and genetic factors such as variations in the gene encoding patatin-like phospholipase domain–containing protein 3 (*PNAPL3*) influence disease severity among persons with alcohol-associated hepatitis.[28] Some factors such as coffee consumption and polymorphism in the gene encoding hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) have shown a protective role.[29] Further studies should identify individual characteristics, behaviors, and exposures — alone or in combination — that influence susceptibility to alcohol-associated hepatitis.

The pathogenesis of alcohol-associated hepatitis is incompletely understood (Fig. 1). Earlier studies that focused on animal models that do not reproduce the main features of alcohol-associated hepatitis (i.e., hepatocellular failure and portal hypertension) proposed a central role for tumor necrosis factor α.[30] Subsequent attempts to block this molecule in patients with alcohol-associated hepatitis were unsuccessful and were associated with severe and life-threatening infections, probably due to its role in liver regeneration and protection against bacterial infections.[31] Translational studies have identified new potential cellular and molecular drivers of alcohol-associated hepatitis.[19]

The liver is the main site to metabolize alcohol into acetaldehyde, which forms protein and DNA adducts that promote innate immune response, glutathione depletion, lipid peroxidation, and mitochondrial damage.[32] Injured hepatocytes release danger-associated molecular patterns, such as high-mobility group protein 1, which trigger inflammatory responses by activating the inflammasome–caspase-1 complex.[33] Excessive consumption of alcohol also increases gut permeability by disrupting the tight junctions in the intestinal epithelial cells and induces profound changes in the microbiome, including increased pathogenic bacteria (e.g., *Enterococcus faecalis*) and immunogenic fungi.[34] For example, an exotoxin from *E. faecalis* promotes alcohol-induced liver injury.[35] The subsequent translocation of viable bacteria and microbial products to the liver (pathogen-associated molecular patterns such as lipopolysaccharide) induces inflammation, favors hepatocyte death, and stimulates a fibrotic response. Other inflammatory factors such as CXC chemokines, macrophage migration inhibitory factor, and complement factors are likely to contribute to hepatocellular injury. These processes culminate in the activation of fibrogenic cell types that accumulate extracellular matrix around hepatocytes and sinusoidal cells, forming a "chicken-wire" pattern and favoring the development of portal hypertension.[36,37] The action of upstream regulators such as transforming growth factor β1 leads to impairment of hepatocyte regeneration and hepatocyte dedifferentiation that causes profound synthetic dysfunction and failure of important metabolic liver functions, including defective bilirubin transport, clotting factor synthesis, and glucose metabolization. This effect is largely mediated by an inefficient activation of hepatocyte nuclear factor 4α and aberrant Hippo–yes-associated protein pathway in hepatocytes.[38,39] This failure of differentiation results

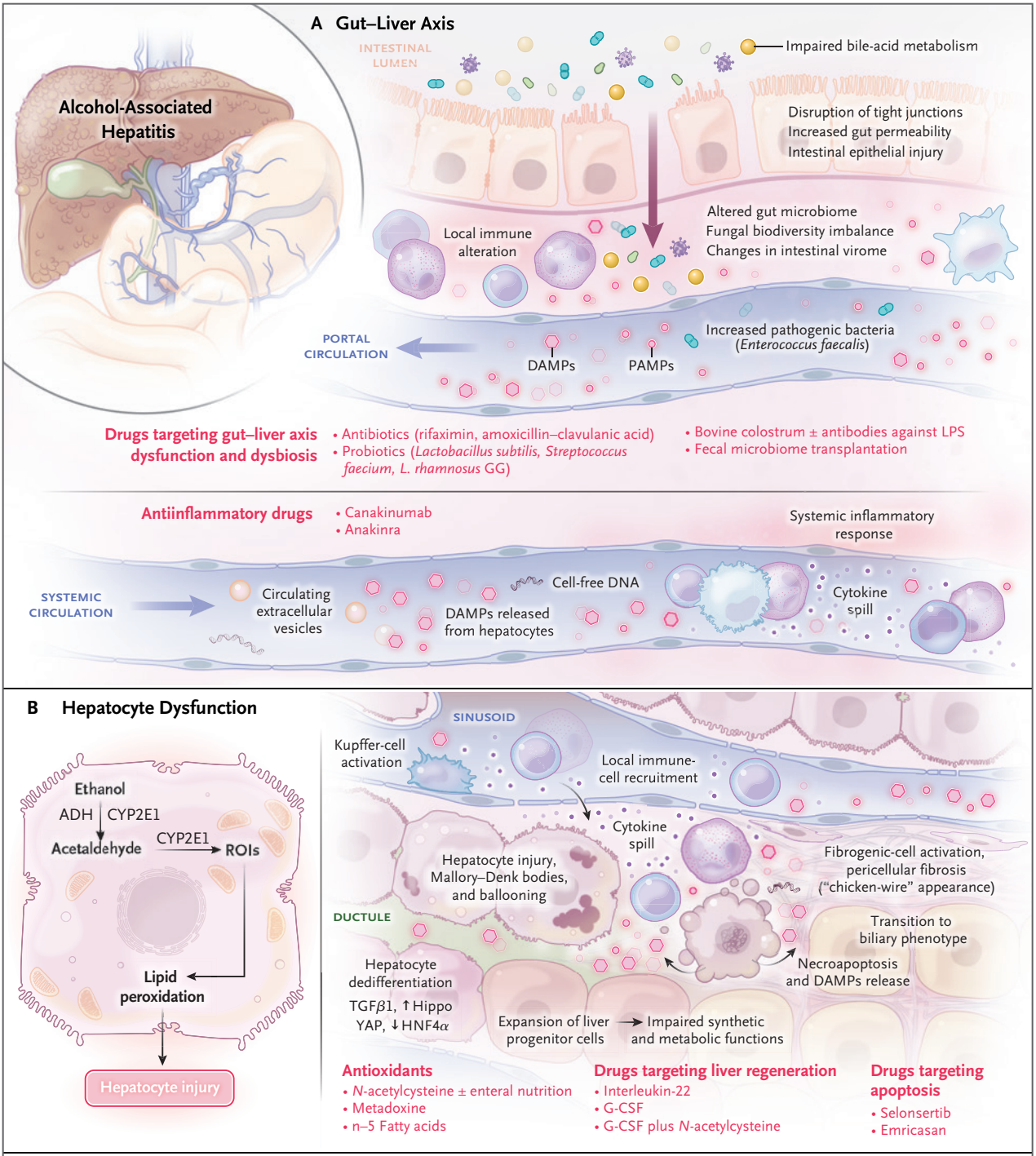

Figure 1 (facing page). Pathogenesis of Alcohol-Associated Hepatitis.

Panel A shows the role of the gut–liver axis; Panel B, the mechanisms involved in hepatocyte dysfunction; and Panel C, the development of liver-related decompensations and multiorgan failure. In Panels A and B, drugs and antioxidants that are being evaluated are shown in red. ADH denotes alcohol dehydrogenase, DAMPs danger-associated molecular patterns, G-CSF granulocyte colony-stimulating factor, HNF4 hepatocyte nuclear factor 4, LPS lipopolysaccharide, PAMPs pathogen-associated molecular patterns, ROIs reactive oxygen intermediates, SIRS systemic inflammatory response syndrome, TGF transforming growth factor, and YAP yes-associated protein.

in a massive expansion of liver progenitor cells (ductular reaction), which represents a futile attempt to regenerate the liver.[40] Systemic inflammatory response syndrome (SIRS) and immune dysfunction often develop, favoring bacterial infections and the development of acute-on-chronic liver failure and multiorgan failure.[41]

Although in some patients the condition rapidly improves after abstinence or responds quickly to glucocorticoids, in others the liver dysfunction progresses; they are at high risk for death unless an early transplantation is performed.[42,43] The livers from patients with these severe forms are characterized by massive ductular reaction and hepatocyte dedifferentiation into a cholangiocyte-like phenotype.[44] Maneuvers that are aimed at reducing this futile ductular reaction, promoting epithelial differentiation of hepatocytes, and attenuating the systemic inflammatory response represent appealing approaches for therapy.

DIAGNOSIS, PROGNOSIS, AND MEDICAL MANAGEMENT

The diagnosis of alcohol-associated hepatitis is usually made on clinical grounds, with the application of criteria derived from clinical history, physical examination, and laboratory findings (Fig. 2). The NIAAA-funded Alcoholic Hepatitis Consortia proposed criteria to clinically define alcohol-associated hepatitis[13]: onset of jaundice within the previous 8 weeks; ongoing consumption of more than 3 drinks (approximately 40 g) per day for women and 4 drinks (approximately 50 to 60 g) per day for men for 6 months or more, with less than 60 days of abstinence before the onset of jaundice; a total serum bilirubin level of more than 3 mg per deciliter (>50 μmol per liter), an aspartate aminotransferase (AST) level of more than 50 IU per liter, and a ratio of AST to alanine aminotransferase of more than 1.5, with both values less than 400 IU per liter; and the ruling out of other liver diseases such as drug-induced liver injury and ischemic hepatitis. This set of criteria is slightly different from previous criteria,[25] particularly in lowering the minimal total bilirubin level from 5 mg per deciliter (85 μmol per liter) to 3 mg per deciliter. This change was intended to identify patients with less severe forms of alcohol-associated hepatitis, sometimes referred to as "nonsevere or moderate alcohol-associated hepatitis." Moderate alcohol-associated hepatitis occurs frequently, and its incidence is probably underestimated as compared with its severe form. Mortality from moderate alcohol-associated hepatitis is up to 3 to 7% in the short-to-medium term (1 to 3 months) and 13 to 20% at 1 year, mainly owing to liver-related complications and severe infections.[45] Furthermore, this disorder is often not recognized, does not necessarily warrant admission to a hospital, and represents a missed opportunity for primary care providers and community gastroenterologists to institute therapy for alcohol use disorder. Long-term abstinence is the main goal of the treatment.[45]

Imaging should rule out biliary obstruction, and an extensive workup for other causes such as viral hepatitis, severe autoimmune liver disease, and Wilson's disease should be performed. Liver biopsy through a transjugular route is recommended in patients with factors that confound diagnosis.[13] Histologically, alcohol-associated hepatitis is characterized by features of alcohol-related steatohepatitis (e.g., ballooned hepatocytes, Mallory–Denk bodies, and neutrophil infiltration), ductular reaction, bilirubinostasis, and pericellular and sinusoidal fibrosis (chicken-wire appearance). Many of these features do not differ from those described in nonalcoholic steatohepatitis (NASH)[46]; thus, it is difficult to differentiate between the two entities on the basis of histologic findings. Liver-biopsy specimens from patients with alcohol-associated hepatitis typically have more megamitochondria, pericellular fibrosis, macrovesicular steatosis, and bilirubinostasis than those from patients with

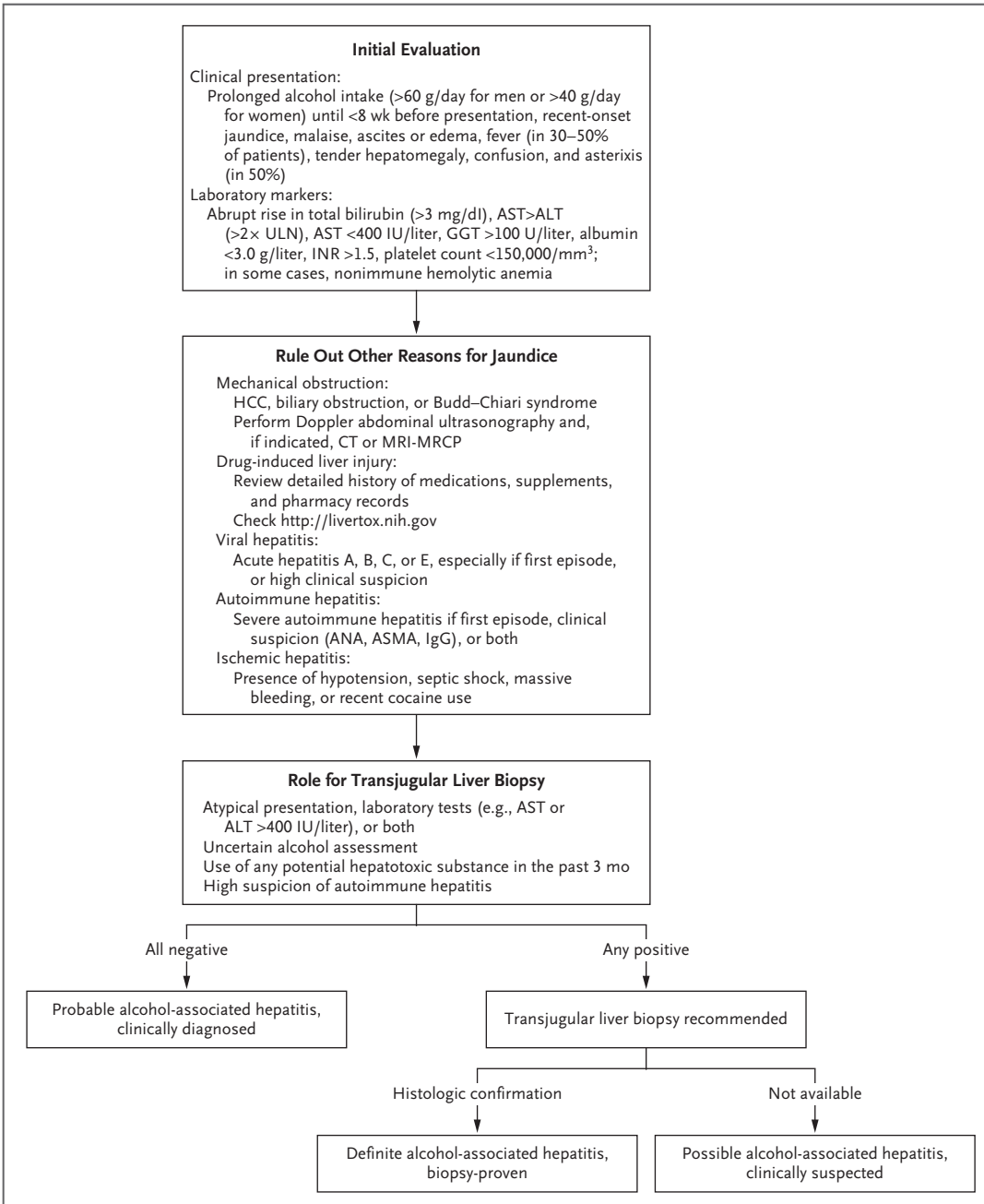

Figure 2. Algorithm for the Diagnosis of Alcohol-Associated Hepatitis.

To convert the value for bilirubin to micromoles per liter, multiply by 17.1. ALT denotes alanine aminotransferase, ANA antinuclear antibodies, ASMA α–smooth-muscle actin antibodies, AST aspartate aminotransferase, CT computerized tomography, GGT γ-glutamyltransferase, HCC hepatocellular carcinoma, INR international normalized ratio, MRI-MRCP magnetic resonance imaging–magnetic resonance cholangiopancreatography, and ULN upper limit of the normal range.

NASH[14,47]; however, none of these features are unique, and prospective studies are needed to better characterize these two conditions.

In addition to its diagnostic role, liver biopsy can provide prognostic information. The AHHS includes four histologic features (the presence of

bridging fibrosis or cirrhosis; hepatocellular, canalicular, or ductular bilirubinostasis; severe neutrophil infiltration; and megamitochondria) that independently predict 90-day mortality.[14] The SALVE (Study of Alcohol-Related Liver Disease in Europe) Histopathology Group recently described a semiquantitative score for alcohol-associated hepatitis (including steatosis, activity [hepatocellular injury and lobular neutrophils], and cholestasis). In both scoring systems, the presence of fully developed cirrhosis confers a bad prognosis in patients with alcohol-associated hepatitis.[47] Because liver biopsy is costly and invasive, there has been interest in developing noninvasive biomarkers with diagnostic and prognostic significance. Serum keratin-18 fragments have been shown to correlate with histologic severity and 90-day mortality and can be useful to predict response to glucocorticoid therapy.[48-50] Other potential biomarkers include circulating extracellular vesicles and microRNA.[51] The development of diagnostic and prognostic biomarkers that define disease subtypes with therapeutic implications represents an unmet need in this field.

At presentation, patients are jaundiced and often have ascites and edema. Some patients present with severe caloric malnutrition and sarcopenia. Hepatic encephalopathy confers a particularly poor prognosis.[52] The diagnosis of encephalopathy can be challenging because patients may have withdrawal syndrome, seizures, or underlying cognitive dysfunction. Patients can present with tender hepatomegaly, and because there is an increase in portal hypertension this can lead to variceal bleeding, especially in patients with underlying cirrhosis.[53] At admission, many patients present with signs of SIRS (e.g., low-grade fever and neutrophilia), and in some cases an infection cannot be diagnosed, which suggests a sterile origin.[41] Most bacterial infections at admission can be controlled with broad-spectrum antibiotics, whereas in-hospital incident infections have a bad prognosis and are often caused by multidrug-resistant bacteria, leading to acute kidney injury and acute-on-chronic liver failure.[54] All patients at admission and after any signs of SIRS or clinical deterioration should be evaluated for infections. The use of biomarkers such as procalcitonin is potentially helpful to differentiate sterile SIRS from infection-associated SIRS.[41] Infections in patients receiving glucocorticoids have a worse prognosis than those in patients not receiving glucocorticoids.[55]

The mortality associated with an episode of alcohol-associated hepatitis warranting hospitalization is approximately 20 to 50% at 90 days.[17] The current models that are used to predict short-term mortality include the Maddrey's modified discriminant function[56]; the Model for End-Stage Liver Disease (MELD)[57]; the age, serum bilirubin, international normalized ratio, and serum creatinine (ABIC) score[58]; and the Glasgow alcoholic hepatitis score.[59] At baseline, the MELD score has been shown to be the best static scoring system at a global level, and current guidelines recommend its use for patient risk stratification.[60,61] The Lille score is a dynamic score that is useful to assess prognosis and to define nonresponse to glucocorticoids; it is calculated at day 7, but it may be alternatively calculated at day 4.[62,63] In addition, the presence of SIRS predicts multiorgan failure and acute-on-chronic liver failure.[41]

The main factor influencing long-term prognosis after an episode of alcohol-associated hepatitis is prolonged alcohol abstinence. Unfortunately, many patients have early alcohol relapse, and more than half the patients resume alcohol drinking.[64] In this context, repeated episodes of alcohol-associated hepatitis can occur. Alcohol relapse is frequent after an episode of alcohol-associated hepatitis, even among patients who have undergone liver transplantation. The reported incidence of post-transplantation alcohol relapse among recipients with ALD ranges from 15 to 50%.[65-68] However, management of alcohol use disorder in these patients has improved. A recent study from the United States showed that at 5 years after liver transplantation, 16.3% of the participants had a relapse with respect to any alcohol use and 8.2% had a relapse with respect to high-dose drinking.[69] It is currently recommended that the care of these patients is managed within a multidisciplinary clinic involving addiction specialists.[70] The identification of underlying psychiatric conditions (e.g., depression or post-traumatic stress disorder) and early referral to addiction programs are highly recommended.

The use of alcohol anticraving drugs has not been rigorously tested in the context of alcohol-associated hepatitis. On the basis of available evidence, although disulfiram is contraindicat-

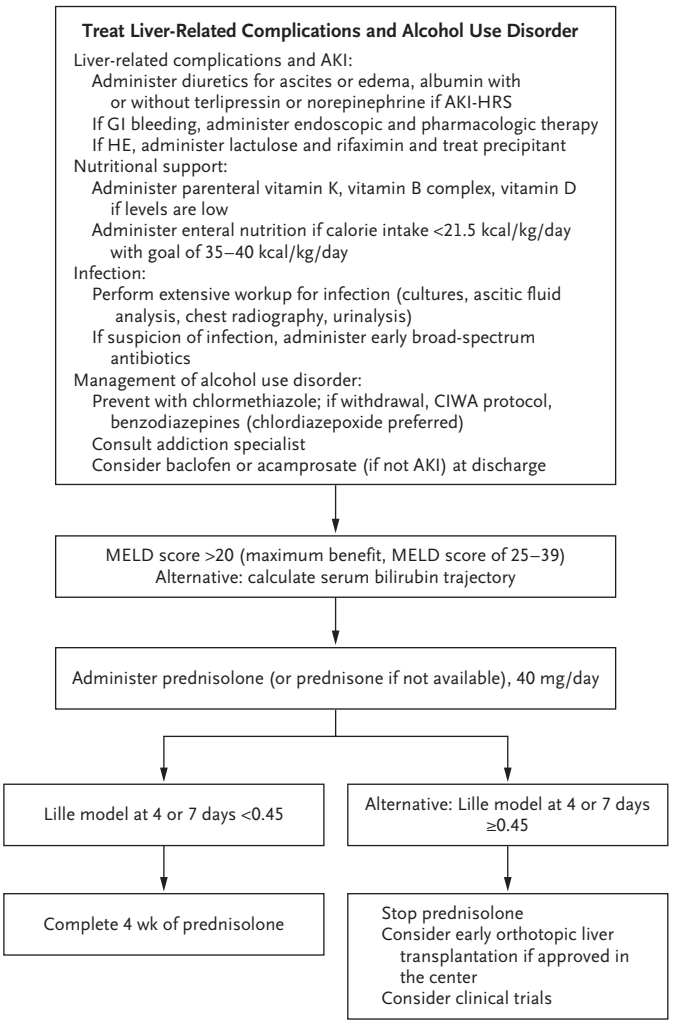

Figure 3. Algorithm for the Management of Alcohol-Associated Hepatitis.

Model for End-Stage Liver Disease (MELD) scores range from 6 to 40, with higher scores indicating a higher risk of death at 3 months. AKI denotes acute kidney injury, AKI-HRS AKI–hepatorenal syndrome, CIWA Clinical Institute Withdrawal Assessment for Alcohol, GI gastrointestinal, and HE hepatic encephalopathy.

ed, the use of baclofen is probably safe in patients with advanced ALD.[71] Acamprosate should be used cautiously in patients with renal failure, and naltrexone should be avoided in patients with decompensated cirrhosis and profound liver dysfunction or concomitant opioid use; otherwise, patients with moderate alcohol-associated hepatitis may be candidates for this drug.[70] Other drugs, such as topiramate (which should be avoided if hepatic encephalopathy is present), gabapentin (which may be a good option if there is concomitant chronic pain), and varenicline, are used off-label, and further studies are needed. Furthermore, the initiation of addiction therapy during inpatient treatment for severe alcohol-associated hepatitis with outpatient follow-up soon after discharge reduces the risk of hospital readmission, alcohol relapse, and death and should be considered as a quality indicator in the management protocol of hospitalized patients with alcohol-associated hepatitis.[72] However, there are data showing that gastroenterologists and hepatologists in North America are reluctant to treat alcohol use disorder in patients with ALD.[73,74] Indeed, a recent study showed that although 60% of providers reported referring patients with alcohol use disorder for behavioral therapy, 71% never prescribed pharmacotherapy because they were less than comfortable doing so (84%).[73] Another study involving a Veterans Health Administration cohort showed that more than 90% of patients with cirrhosis and coexisting alcohol use disorder did not receive behavioral therapy or pharmacotherapy for alcohol use disorder during a 6-month follow-up.[74] Whether there are regional or geographic differences across the globe is not well known. However, recent studies have shown that patients with ALD who receive treatment for alcohol use disorder have lower rates of progression than those who do not.[75,76] This information can be useful to increase awareness of the disease and improve training among primary care providers and specialists to treat alcohol use disorder in patients with ALD.

With respect to specific treatment, glucocorticoids have a transient beneficial effect in patients with severe alcohol-associated hepatitis[18,77,78] (Fig. 3). A large randomized, controlled trial showed a trend toward improved 1-month survival but increased infections.[15] A 2018 meta-analysis showed improved 30-day survival, without improvement in 60- or 90-day mortality.[16] More recently, a study involving a large international cohort of 3380 patients identified the appropriate therapeutic window for the use of glucocorticoids with respect to the MELD score. Glucocorticoids improved 30-day survival among patients with MELD scores of more than 20, with maximum benefit (defined as ≥20% survival benefit) at MELD scores of 25 to 39.[17] Cur-

rently, there is enough evidence to show the futility of pentoxifylline.[15,16] Some promising results have been shown by adding *N*-acetylcysteine (a powerful antioxidant) to prednisolone. The combination of *N*-acetylcysteine with prednisolone improved 1-month survival and reduced the incidence of infections. However, when survival was analyzed at 6 months, no differences were found between the combination and prednisolone alone. Further studies are needed before recommending its use.[79]

Given the high prevalence of malnutrition among patients with alcohol-associated hepatitis, it is important to assess the nutritional status and ensure adequate caloric and protein intake. Usual goals for enteral nutrition are 35 to 40 kcal per kilogram of body weight per day, with 1.5 g of protein content per kilogram per day.[80] Furthermore, because infections are common, especially among those who do not have a response to glucocorticoids, they should be actively ruled out and treated.[55] In the STOPAH trial, 12.5% of the patients had an infection at baseline, 23.0% during treatment, and 8.2% after treatment. Early detection and treatment of infection may reduce the associated mortality.[54] Controlled infections are not contraindications to the use of glucocorticoids. Besides bacterial infections, fungal infections are common in patients with severe alcohol-associated hepatitis (with an incidence of up to 16%) and carry a high risk of death.[81] Indeed, fungal infections are frequently underdiagnosed. A younger age, a higher MELD score, and glucocorticoid therapy are independently associated with invasive fungal infection.[82] Finally, acute kidney injury occurs frequently, is present in up to a third of the patients with severe alcohol-associated hepatitis, and is associated with an increase in 90-day mortality by a factor of 9.[52] The use of albumin and vasoconstrictors may be indicated if criteria for hepatorenal syndrome are met. Renal-replacement therapy could be indicated, although its use is hampered by concerns of futility in patients who are not deemed to be candidates for transplantation.[83] Studies that identify diagnostic and prognostic biomarkers of renal failure in patients with alcohol-associated hepatitis are needed. Consultation with palliative care is appropriate for some patients who have severe alcohol-associated hepatitis that is unresponsive to medical therapy and for whom liver transplantation is not an option.[84]

EARLY LIVER TRANSPLANTATION

Traditionally, patients with severe forms of alcohol-associated hepatitis who did not have a response to medical therapy were ineligible for salvage liver transplantation owing to the lack of a minimum period of sobriety. In 2011, a landmark Franco–Belgian study represented a paradigm shift in the management of these patients' care. A total of 26 carefully selected patients with severe alcohol-associated hepatitis who had not had a response to glucocorticoids underwent early liver transplantation. The cumulative 6-month survival was much higher among patients who received early liver transplantation than that in a historical series of patients with similarly severe disease (77% vs. 23%).[21] After this initial study, numerous transplantation centers across the globe have accepted this new indication. Figure 4A summarizes the studies[21,85-91] evaluating early liver transplantation for severe alcohol-associated hepatitis that did not respond to glucocorticoids, and Figure 4B shows survival after liver transplantation in patients with alcohol-associated hepatitis and ALD.

Follow-up studies, including the American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) study, have confirmed the benefits of early liver transplantation in selected patients with severe alcohol-associated hepatitis.[85-87,92] Moreover, a recent follow-up study from the Franco–Belgian group showed that the 2-year survival was similar in the early-transplantation group and the standard-transplantation group.[90] The main concern of this approach is the potential for a high incidence of alcohol relapse (Fig. 4C). Studies in both the European and American cohorts have shown a higher incidence of relapse than among other transplant recipients with advanced ALD (20 to 35% in the early-transplantation groups, as compared with 10 to 25% in the standard-transplantation groups). However, there are differences in relapse ascertainment among the different studies. Few studies use biomarkers or other robust means of assessing alcohol use beyond patient report and patient interview.[93] In addition, even among patients with presumed nonalcoholic fatty liver disease, 25 to 29% had positive biomarkers of alcohol consumption.[94]

Although sustained alcohol use after early transplantation is infrequent (10% at 1 year and

A Characteristics of the Studies

Study	Inclusion Criteria	Primary End Point	Location
Mathurin et al., 2011[21]	Severe AH not responding to glucocorticoids or rapid worsening of liver function No previous episodes of AH, supportive family members, no severe psychiatric conditions, commitment to alcohol abstinence	Survival at 6 mo	France Belgium
Im et al., 2016[85]	Severe AH not responding to medical therapy	Survival at 6 mo	United States
Lee et al., 2017[86]	Severe AH as first liver decompensation	Survival at 6 mo	United States
Lee et al., 2018[87]	Severe AH and no previous diagnosis of liver disease or episodes of AH	Survival and AUD after liver transplantation	United States
Cotter et al., 2021[88]	Severe AH and no previous diagnosis of liver disease or episodes of AH	Survival at 1 and 5 yr	United States
Lee et al., 2022[89]	Retrospective analysis of UNOS database of patients undergoing liver transplantation for AH	Survival at 1 and 5 yr	United States
Louvet et al., 2022[90]	Patients with severe AH who did not have a response to medical treatment and were eligible for eLT according to social and addiction evaluation	Alcohol relapse and survival at 2 yr	France Belgium
Germani et al., 2022[91]	Severe AH according to NIAAA criteria, not responding to medical therapy	Survival at 6, 12, and 24 mo	Italy

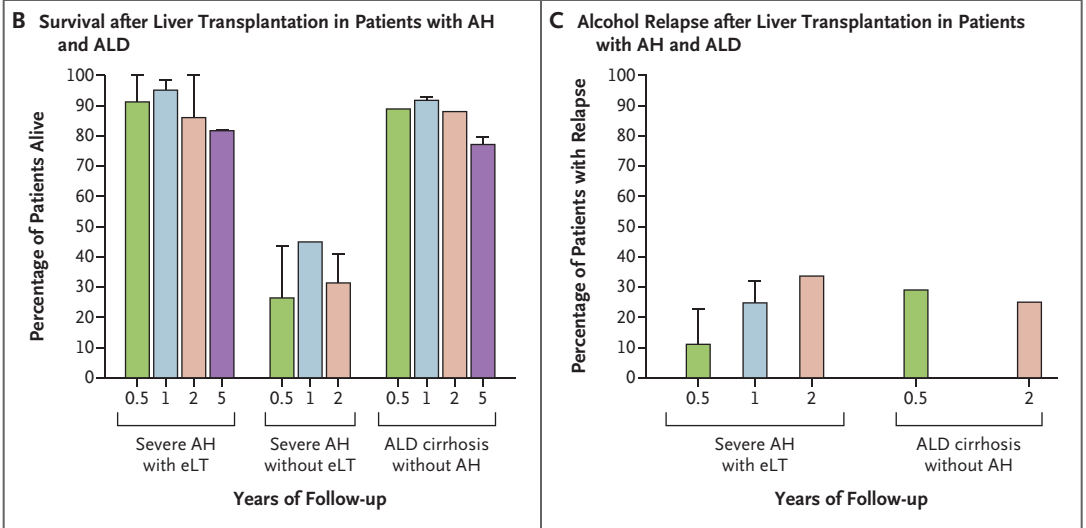

Figure 4. Summary of Studies Assessing Early Liver Transplantation (eLT) for Severe Alcohol-Associated Hepatitis (AH).
In Panels B and C, I bars indicate standard deviations. ALD denotes alcohol-associated liver disease, AUD alcohol use disorder, NIAAA National Institute on Alcohol Abuse and Alcoholism, and UNOS United Network for Organ Sharing.

nearly 20% at 3 years), it is associated with increased mortality.[87] Identifying risk factors for poor outcomes after liver transplantation is key in the selection process. The ACCELERATE-AH recently developed the Sustained Alcohol Use Post–Liver Transplant (SALT) score, which is useful is determining a lower risk of relapse (owing to its high negative predictive value).[92] The SALT score includes four variables: more than 10 drinks per day at the time of the initial hospitalization, multiple previous rehabilitation attempts, previous alcohol-related legal issues, and previous illicit substance abuse. There have been efforts to develop new predictive scores, including with the use of artificial intelligence.[95] Because excessive consumption of alcohol is heavily influenced by

genetic, cultural, and socioeconomic factors, it is plausible that factors predicting relapse vary among different cultures across the globe.

Prospective studies should define the precise timing and indications of early liver transplantation in patients with alcohol-associated hepatitis, identify predictors of spontaneous recovery or futility and more refined predictors of alcohol relapse, and test different motivational and pharmacologic approaches that favor prolonged abstinence after transplantation. In addition, it is important to consider that currently most patients with alcohol-associated hepatitis never get referred for liver transplantation, and it is very likely that stigma plays a part in this phenomenon.[96] Indeed, an increasing number of studies have shown that patients with ALD are more likely to be denied placement on the transplant waiting list than those with non–alcohol-related liver disease who undergo evaluation, even though patients with ALD have higher MELD scores.[97] The main reason for denial is the psychosocial evaluation; thus, efforts to decrease the stigma and selection bias regardless of the cause of liver disease are needed.[98]

EMERGING THERAPIES

The number of clinical trials testing new pathophysiologically oriented drugs in patients with alcohol-associated hepatitis has markedly increased in recent years.[20] Most studies are aimed at promoting effective liver regeneration, blocking inflammatory pathways, restoring a normal microbiome, or a combination of these. A pilot study of a recombinant fusion protein of human interleukin-22, an antiinflammatory and proregenerative cytokine, showed favorable outcomes as determined by Lille and MELD scores, a reduction in markers of inflammation, and increased expression of markers of hepatic regeneration.[99] In addition, two open-label, randomized trials comparing granulocyte colony-stimulating factor (G-CSF) plus standard medical therapy with standard medical therapy alone in patients with severe alcohol-associated hepatitis showed an improvement in 3- and 6-month survival and a lower incidence of bacterial infections.[100] A more recent European study, however, failed to show a benefit with G-CSF in patients with severe alcohol-associated hepatitis.[101]

The role of gut microbiota in the pathogenesis of alcohol-associated hepatitis is another area of development. A promising pilot study showed that fecal microbiome transplantation from healthy donors was associated with lower mortality than in a historical cohort.[102] A study of interleukin-1 inhibition by anakinra, pentoxifylline, and zinc showed an acceptable side-effect profile, but 180-day survival did not differ significantly between the combination therapy and glucocorticoid therapy.[103] Several clinical trials are now examining the role of probiotics, rifaximin, and fecal microbiome transplantation in patients with alcohol-associated hepatitis. Other targeted trials under way involve the use of antiinflammatory drugs (interleukin-1β inhibition by canakinumab), drugs targeting gut–liver axis dysfunction and dysbiosis (broad-spectrum antibiotics and bovine colostrum), antioxidants (*N*-acetylcysteine, metadoxine, and n–5 fatty acids), drugs targeting apoptosis (selonsertib and emricasan), phage therapy, and supplemental nutrition strategies.[104]

FUTURE DIRECTIONS

To reduce the burden of ALD including alcohol-associated hepatitis, excessive consumption of alcohol should be targeted with the use of a holistic societal approach; thus, more efficient public health policies are needed — for example, increasing taxes or raising the minimum price of a unit of alcohol.[105,106] Furthermore, efforts must be aimed to assess the determinants of the increasing prevalence of ALD, in particular the severe forms in young women. In addition, to promote the development of new therapies, drug companies, regulatory agencies, and liver researchers should reach consensus on key determinants of outcomes and on the new end points for clinical trials. More translational research is needed to better characterize moderate alcohol-associated hepatitis and its early identification, to develop new prognostic biomarkers of alcohol-associated hepatitis, and to identify molecular subtypes for personalized medicine and response to therapy. The development of human-based experimental models could be useful to test new therapies. For patients who do not have a response to medical therapy, the timing and indications for early liver transplantation should be

better defined. Digital transformation of health care offers care opportunities for ALD through remote health, analytics, and artificial intelligence techniques for the management of both alcohol use disorder and ALD. Finally, more efforts should be paid to define new holistic multidisciplinary approaches to treat the underlying alcohol use disorder and promote prolonged alcohol abstinence.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Jepsen P, Younossi ZM. The global burden of cirrhosis: a review of disability-adjusted life-years lost and unmet needs. J Hepatol 2021;75:Suppl 1:S3-S13.
2. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1015-35.
3. Stein E, Cruz-Lemini M, Altamirano J, et al. Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. J Hepatol 2016;65:998-1005.
4. Parker R, Aithal GP, Becker U, et al. Natural history of histologically proven alcohol-related liver disease: a systematic review. J Hepatol 2019;71:586-93.
5. Arab JP, Roblero JP, Altamirano J, et al. Alcohol-related liver disease: clinical practice guidelines by the Latin American Association for the Study of the Liver (ALEH). Ann Hepatol 2019;18:518-35.
6. Shah ND, Ventura-Cots M, Abraldes JG, et al. Alcohol-related liver disease is rarely detected at early stages compared with liver diseases of other etiologies worldwide. Clin Gastroenterol Hepatol 2019;17(11):2320-2329.e12.
7. Singal AK, Louvet A, Shah VH, Kamath PS. Grand rounds: alcoholic hepatitis. J Hepatol 2018;69:534-43.
8. Singal AK, Mathurin P. Diagnosis and treatment of alcohol-associated liver disease: a review. JAMA 2021;326:165-76.
9. Sersté T, Cornillie A, Njimi H, et al. The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. J Hepatol 2018;69:318-24.
10. Singal AK, Arsalan A, Dunn W, et al. Alcohol-associated liver disease in the United States is associated with severe forms of disease among young, females and Hispanics. Aliment Pharmacol Ther 2021;54:451-61.
11. Bloom PP, Fontana RJ. With alcohol as the fuel, COVID is the match: liver transplantation for alcohol-associated liver disease is increasing in the United States. Hepatology 2021;74:2948-51.
12. Cholankeril G, Goli K, Rana A, et al. Impact of COVID-19 pandemic on liver transplantation and alcohol-associated liver disease in the USA. Hepatology 2021;74:3316-29.
13. Crabb DW, Bataller R, Chalasani NP, et al. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology 2016;150:785-90.
14. Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology 2014;146(5):1231-1239.e1.
15. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619-28.
16. Louvet A, Thursz MR, Kim DJ, et al. Corticosteroids reduce risk of death within 28 days for patients with severe alcoholic hepatitis, compared with pentoxifylline or placebo — a meta-analysis of individual data from controlled trials. Gastroenterology 2018;155(2):458-468.e8.
17. Arab JP, Díaz LA, Baeza N, et al. Identification of optimal therapeutic window for steroid use in severe alcohol-associated hepatitis: a worldwide study. J Hepatol 2021;75:1026-33.
18. Porter HP, Simon FR, Pope CE II, Volwiler W, Fenster LF. Corticosteroid therapy in severe alcoholic hepatitis — a double-blind drug trial. N Engl J Med 1971;284:1350-5.
19. Mandrekar P, Bataller R, Tsukamoto H, Gao B. Alcoholic hepatitis: translational approaches to develop targeted therapies. Hepatology 2016;64:1343-55.
20. Singal AK, Shah VH. Current trials and novel therapeutic targets for alcoholic hepatitis. J Hepatol 2019;70:305-13.
21. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790-800.
22. Anstee QM, Seth D, Day CP. Genetic factors that affect risk of alcoholic and nonalcoholic fatty liver disease. Gastroenterology 2016;150(8):1728-1744.e7.
23. Stickel F, Moreno C, Hampe J, Morgan MY. The genetics of alcohol dependence and alcohol-related liver disease. J Hepatol 2017;66:195-211.
24. Ventura-Cots M, Argemi J, Jones PD, et al. Clinical, histological and molecular profiling of different stages of alcohol-related liver disease. Gut 2022;71:1856-66.
25. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med 2009;360:2758-69.
26. Roerecke M, Vafaei A, Hasan OSM, et al. Alcohol consumption and risk of liver cirrhosis: a systematic review and meta-analysis. Am J Gastroenterol 2019;114:1574-86.
27. Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2021;19(3):580-589.e5.
28. Whitfield JB, Schwantes-An T-H, Darlay R, et al. A genetic risk score and diabetes predict development of alcohol-related cirrhosis in drinkers. J Hepatol 2022;76:275-82.
29. Liangpunsakul S, Beaudoin JJ, Shah VH, et al. Interaction between the patatin-like phospholipase domain-containing protein 3 genotype and coffee drinking and the risk for acute alcoholic hepatitis. Hepatol Commun 2017;2:29-34.
30. Enomoto N, Ikejima K, Bradford BU, et al. Role of Kupffer cells and gut-derived endotoxins in alcoholic liver injury. J Gastroenterol Hepatol 2000;15:Suppl:D20-D25.
31. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology 2008;135:1953-60.
32. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 2011;141:1572-85.
33. Saha B, Tornai D, Kodys K, et al. Biomarkers of macrophage activation and immune danger signals predict clinical outcomes in alcoholic hepatitis. Hepatology 2019;70:1134-49.
34. Fairfield B, Schnabl B. Gut dysbiosis as a driver in alcohol-induced liver injury. JHEP Rep 2020;3:100220.
35. Duan Y, Llorente C, Lang S, et al. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. Nature 2019;575:505-11.
36. Dominguez M, Miquel R, Colmenero J, et al. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. Gastroenterology 2009;136:1639-50.
37. Liu M, Cao S, He L, et al. Super enhancer regulation of cytokine-induced chemokine production in alcoholic hepatitis. Nat Commun 2021;12:4560.
38. Argemi J, Latasa MU, Atkinson SR,

et al. Defective HNF4alpha-dependent gene expression as a driver of hepatocellular failure in alcoholic hepatitis. Nat Commun 2019;10:3126.
39. Bou Saleh M, Louvet A, Ntandja-Wandji LC, et al. Loss of hepatocyte identity following aberrant YAP activation: a key mechanism in alcoholic hepatitis. J Hepatol 2021;75:912-23.
40. Sancho-Bru P, Altamirano J, Rodrigo-Torres D, et al. Liver progenitor cell markers correlate with liver damage and predict short-term mortality in patients with alcoholic hepatitis. Hepatology 2012;55:1931-41.
41. Michelena J, Altamirano J, Abraldes JG, et al. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. Hepatology 2015;62:762-72.
42. Parker R, Cabezas J, Altamirano J, et al. Trajectory of serum bilirubin predicts spontaneous recovery in a real-world cohort of patients with alcoholic hepatitis. Clin Gastroenterol Hepatol 2022;20(2):e289-e297.
43. Musto J, Stanfield D, Ley D, Lucey MR, Eickhoff J, Rice JP. Recovery and outcomes of patients denied early liver transplantation for severe alcohol-associated hepatitis. Hepatology 2022;75:104-14.
44. Dubuquoy L, Louvet A, Lassailly G, et al. Progenitor cell expansion and impaired hepatocyte regeneration in explanted livers from alcoholic hepatitis. Gut 2015;64:1949-60.
45. Clemente-Sánchez A, Oliveira-Mello A, Bataller R. Moderate alcoholic hepatitis. Clin Liver Dis 2021;25:537-55.
46. Kleiner DE, Brunt EM. Nonalcoholic fatty liver disease: pathologic patterns and biopsy evaluation in clinical research. Semin Liver Dis 2012;32:3-13.
47. Lackner C, Stauber RE, Davies S, et al. Development and prognostic relevance of a histologic grading and staging system for alcohol-related liver disease. J Hepatol 2021;75:810-9.
48. Atkinson SR, Grove JI, Liebig S, et al. In severe alcoholic hepatitis, serum keratin-18 fragments are diagnostic, prognostic, and theragnostic biomarkers. Am J Gastroenterol 2020;115:1857-68.
49. Bissonnette J, Altamirano J, Devue C, et al. A prospective study of the utility of plasma biomarkers to diagnose alcoholic hepatitis. Hepatology 2017;66:555-63.
50. Vatsalya V, Cave MC, Kong M, et al. Keratin 18 is a diagnostic and prognostic factor for acute alcoholic hepatitis. Clin Gastroenterol Hepatol 2020;18:2046-54.
51. Sehrawat TS, Arab JP, Liu M, et al. Circulating extracellular vesicles carrying sphingolipid cargo for the diagnosis and dynamic risk profiling of alcoholic hepatitis. Hepatology 2021;73:571-85.
52. Sujan R, Cruz-Lemini M, Altamirano J, et al. A validated score predicts acute kidney injury and survival in patients with alcoholic hepatitis. Liver Transpl 2018;24:1655-64.
53. Laswi H, Attar B, Abusalim A-R, Khoshbin K, Shaka H. Trends of readmissions for gastrointestinal bleeding after alcoholic hepatitis: analysis of the nationwide readmission database. Gastroenterology Res 2022;15:136-41.
54. Louvet A, Wartel F, Castel H, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137:541-8.
55. Vergis N, Atkinson SR, Knapp S, et al. In patients with severe alcoholic hepatitis, prednisolone increases susceptibility to infection and infection-related mortality, and is associated with high circulating levels of bacterial DNA. Gastroenterology 2017;152(5):1068-1077.e4.
56. Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr., Mezey E, White RI Jr Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75:193-9.
57. Dunn W, Jamil LH, Brown LS, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology 2005;41:353-8.
58. Dominguez M, Rincón D, Abraldes JG, et al. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. Am J Gastroenterol 2008;103:2747-56.
59. Forrest EH, Evans CD, Stewart S, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 2005;54:1174-9.
60. Forrest EH, Atkinson SR, Richardson P, et al. Application of prognostic scores in the STOPAH trial: discriminant function is no longer the optimal scoring system in alcoholic hepatitis. J Hepatol 2018;68:511-8.
61. Morales-Arráez D, Ventura-Cots M, Altamirano J, et al. The MELD score is superior to the Maddrey discriminant function score to predict short-term mortality in alcohol-associated hepatitis: a global study. Am J Gastroenterol 2022;117:301-10.
62. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45:1348-54.
63. Garcia-Saenz-de-Sicilia M, Duvoor C, Altamirano J, et al. A day-4 Lille model predicts response to corticosteroids and mortality in severe alcoholic hepatitis. Am J Gastroenterol 2017;112:306-15.
64. Altamirano J, López-Pelayo H, Michelena J, et al. Alcohol abstinence in patients surviving an episode of alcoholic hepatitis: prediction and impact on long-term survival. Hepatology 2017;66:1842-53.
65. DiMartini A, Day N, Dew MA, et al. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. Liver Transpl 2006;12:813-20.
66. Dew MA, DiMartini AF, Steel J, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl 2008;14:159-72.
67. DiMartini A, Dew MA, Day N, et al. Trajectories of alcohol consumption following liver transplantation. Am J Transplant 2010;10:2305-12.
68. Rogal S, Shenai N, Kruckenberg K, Rosenberger E, Dew MA, DiMartini A. Post-transplant outcomes of persons receiving a liver graft for alcoholic liver disease. Alcohol Alcohol 2018;53:157-65.
69. Schneekloth TD, Arab JP, Simonetto DA, et al. Factors having an impact on relapse and survival in transplant recipients with alcohol-induced liver disease. Mayo Clin Proc Innov Qual Outcomes 2021;5:1153-64.
70. Arab JP, Izzy M, Leggio L, Bataller R, Shah VH. Management of alcohol use disorder in patients with cirrhosis in the setting of liver transplantation. Nat Rev Gastroenterol Hepatol 2022;19:45-59.
71. Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 2007;370:1915-22.
72. Peeraphatdit TB, Kamath PS, Karpyak VM, et al. Alcohol rehabilitation within 30 days of hospital discharge is associated with reduced readmission, relapse, and death in patients with alcoholic hepatitis. Clin Gastroenterol Hepatol 2020;18(2):477-485.e5.
73. Im GY, Mellinger JL, Winters A, et al. Provider attitudes and practices for alcohol screening, treatment, and education in patients with liver disease: a survey from the American Association for the Study of Liver Diseases alcohol-associated liver disease special interest group. Clin Gastroenterol Hepatol 2021;19(11):2407-2416.e8.
74. Rogal S, Youk A, Zhang H, et al. Impact of alcohol use disorder treatment on clinical outcomes among patients with cirrhosis. Hepatology 2020;71:2080-92.
75. Vannier AGL, Przybyszewski EM, Shay J, et al. Psychotherapy for alcohol use disorder is associated with reduced risk of incident alcohol-associated liver disease. Clin Gastroenterol Hepatol 2022 August 11 (Epub ahead of print).
76. Vannier AGL, Shay JES, Fomin V, et al. Incidence and progression of alcohol-associated liver disease after medical therapy for alcohol use disorder. JAMA Netw Open 2022;5(5):e2213014.
77. Mathurin P, Louvet A, Duhamel A, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe

alcoholic hepatitis: a randomized clinical trial. JAMA 2013;310:1033-41.
78. Mathurin P, O'Grady J, Carithers RL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut 2011;60:255-60.
79. Nguyen-Khac E, Thevenot T, Piquet M-A, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365:1781-9.
80. Moreno C, Langlet P, Hittelet A, et al. Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: a randomized multicenter controlled trial. J Hepatol 2010;53:1117-22.
81. Gustot T, Maillart E, Bocci M, et al. Invasive aspergillosis in patients with severe alcoholic hepatitis. J Hepatol 2014;60:267-74.
82. Otero Sanchez L, Karakike E, Njimi H, et al. Clinical course and risk factors for infection in severe forms of alcohol-associated liver disease. Hepatology 2021;74:2714-24.
83. Jones BE, Allegretti AS, Pose E, et al. Renal replacement therapy for acute kidney injury in severe alcohol-associated hepatitis as a bridge to transplant or recovery. Dig Dis Sci 2022;67:697-707.
84. Rogal SS, Hansen L, Patel A, et al. AASLD practice guidance: palliative care and symptom-based management in decompensated cirrhosis. Hepatology 2022;76:819-53.
85. Im GY, Kim-Schluger L, Shenoy A, et al. Early liver transplantation for severe alcoholic hepatitis in the United States — a single-center experience. Am J Transplant 2016;16:841-9.
86. Lee BP, Chen PH, Haugen C, et al. Three-year results of a pilot program in early liver transplantation for severe alcoholic hepatitis. Ann Surg 2017;265:20-9.
87. Lee BP, Mehta N, Platt L, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. Gastroenterology 2018;155(2):422-430.e1.
88. Cotter TG, Sandikçi B, Paul S, et al. Liver transplantation for alcoholic hepatitis in the United States: excellent outcomes with profound temporal and geographic variation in frequency. Am J Transplant 2021;21:1039-55.
89. Lee BP, Im GY, Rice JP, et al. Patterns of alcohol use after early liver transplantation for alcoholic hepatitis. Clin Gastroenterol Hepatol 2022;20(2):409-418.e5.
90. Louvet A, Labreuche J, Moreno C, et al. Early liver transplantation for severe alcohol-related hepatitis not responding to medical treatment: a prospective controlled study. Lancet Gastroenterol Hepatol 2022;7:416-25.
91. Germani G, Angrisani D, Addolorato G, et al. Liver transplantation for severe alcoholic hepatitis: a multicenter Italian study. Am J Transplant 2022;22:1191-200.
92. Lee BP, Vittinghoff E, Hsu C, et al. Predicting low risk for sustained alcohol use after early liver transplant for acute alcoholic hepatitis: the Sustained Alcohol Use Post-Liver Transplant score. Hepatology 2019;69:1477-87.
93. Lee BP, Terrault NA. Return to alcohol use after liver transplant: patterns and surveillance. Clin Liver Dis (Hoboken) 2019;12:160-4.
94. Staufer K, Huber-Schönauer U, Strebinger G, et al. Ethyl glucuronide in hair detects a high rate of harmful alcohol consumption in presumed non-alcoholic fatty liver disease. J Hepatol 2022;77:918-30.
95. Lee BP, Roth N, Rao P, et al. Artificial intelligence to identify harmful alcohol use after early liver transplant for alcohol-associated hepatitis. Am J Transplant 2022;22:1834-41.
96. Schomerus G, Leonhard A, Manthey J, et al. The stigma of alcohol-related liver disease and its impact on healthcare. J Hepatol 2022;77:516-24.
97. Daniel KE, Matthews LA, Deiss-Yehiely N, et al. Psychosocial assessment rather than severity of liver failure dominates selection for liver transplantation in patients with alcohol-related liver disease. Liver Transpl 2022;28:936-44.
98. Wadhwani SI, Lai JC, Gottlieb LM. Medical need, financial resources, and transplant accessibility. JAMA 2022;327:1445-6.
99. Arab JP, Sehrawat TS, Simonetto DA, et al. An open-label, dose-escalation study to assess the safety and efficacy of IL-22 agonist F-652 in patients with alcohol-associated hepatitis. Hepatology 2020;72:441-53.
100. Singh V, Sharma AK, Narasimhan RL, Bhalla A, Sharma N, Sharma R. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. Am J Gastroenterol 2014;109:1417-23.
101. Marot A, Singal AK, Moreno C, Deltenre P. Granulocyte colony-stimulating factor for alcoholic hepatitis: a systematic review and meta-analysis of randomised controlled trials. JHEP Rep 2020;2(5):100139.
102. Philips CA, Pande A, Shasthry SM, et al. Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: a pilot study. Clin Gastroenterol Hepatol 2017;15:600-2.
103. Szabo G, Mitchell M, McClain CJ, et al. IL-1 receptor antagonist plus pentoxifylline and zinc for severe alcohol-associated hepatitis. Hepatology 2022;76:1058-68.
104. Sehrawat TS, Liu M, Shah VH. The knowns and unknowns of treatment for alcoholic hepatitis. Lancet Gastroenterol Hepatol 2020;5:494-506.
105. Díaz LA, Idalsoaga F, Fuentes-López E, et al. Impact of public health policies on alcohol-associated liver disease in Latin America: an ecological multinational study. Hepatology 2021;74:2478-90.
106. Neufeld M, Rovira P, Ferreira-Borges C, et al. Impact of introducing a minimum alcohol tax share in retail prices on alcohol-attributable mortality in the WHO European region: a modelling study. Lancet Reg Health Eur 2022;15:100325.