

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 β 1 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 metabolism. This effect is largely mediated by an inefficient activation of hepatocyte nuclear factor 4 α and aberrant Hippo–yes-associated protein pathway in hepatocytes.^{38,39} This failure of differentiation results

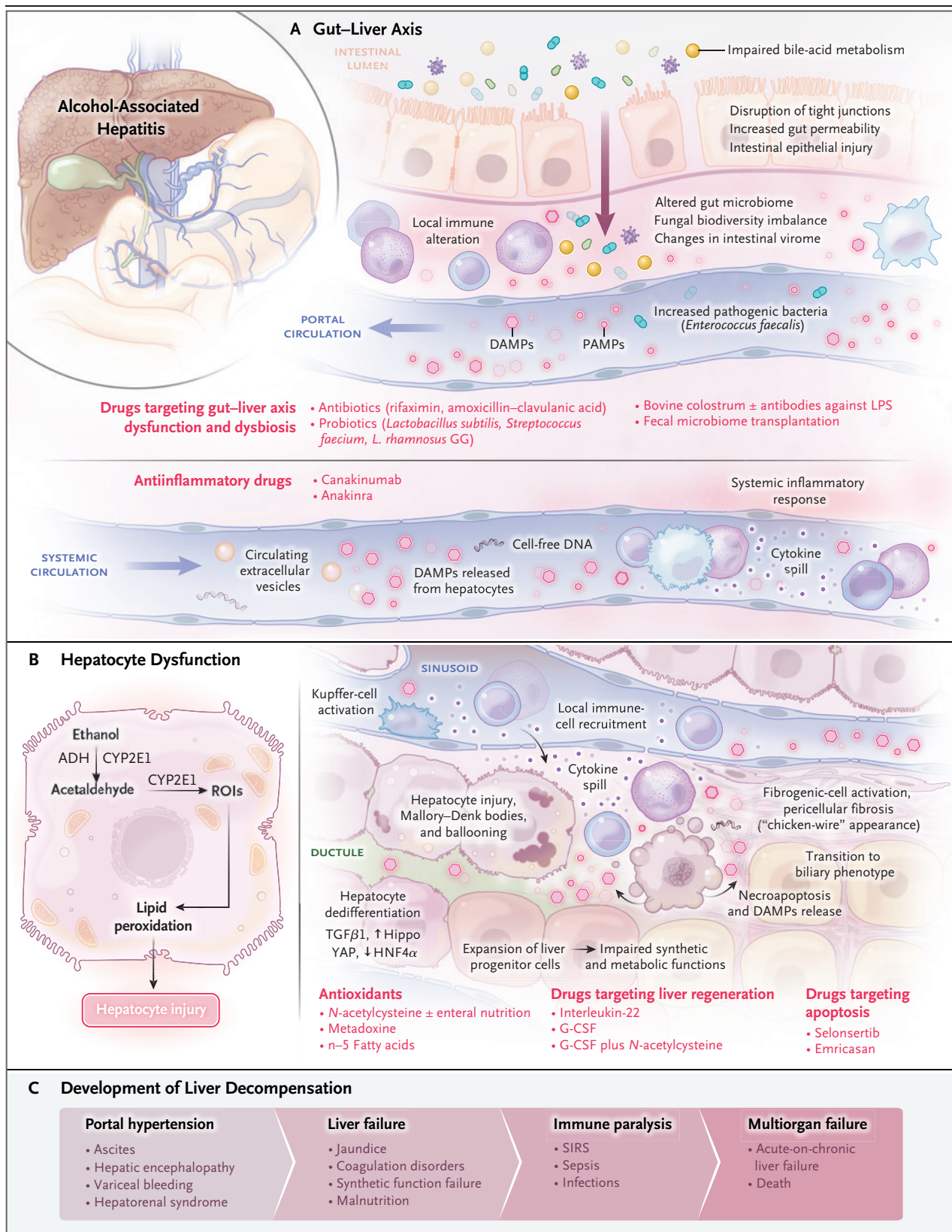


Figure 1 (facing page). Pathogenesis of Alcohol-Associated Hepatitis.

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

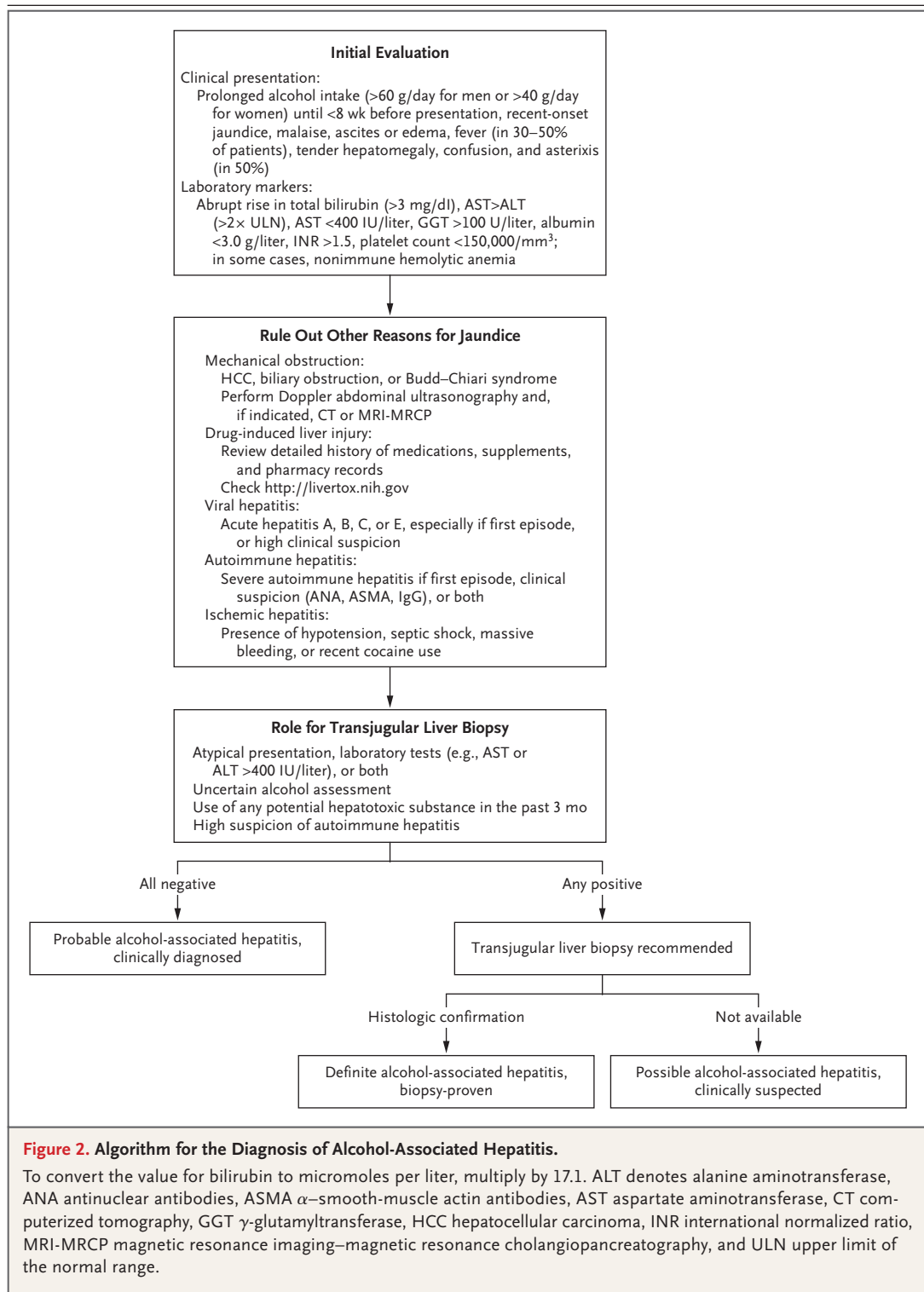
Although in some patients the condition rapidly improves after abstinence or responds quickly to glucocorticoids, in others the liver dysfunction progresses; they are at high risk for death unless an early transplantation is performed.^{42,43} The livers from patients with these severe forms are characterized 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 hepatitis¹³: 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 ($>50 \mu\text{mol}$ 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 ($85 \mu\text{mol}$ 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



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.

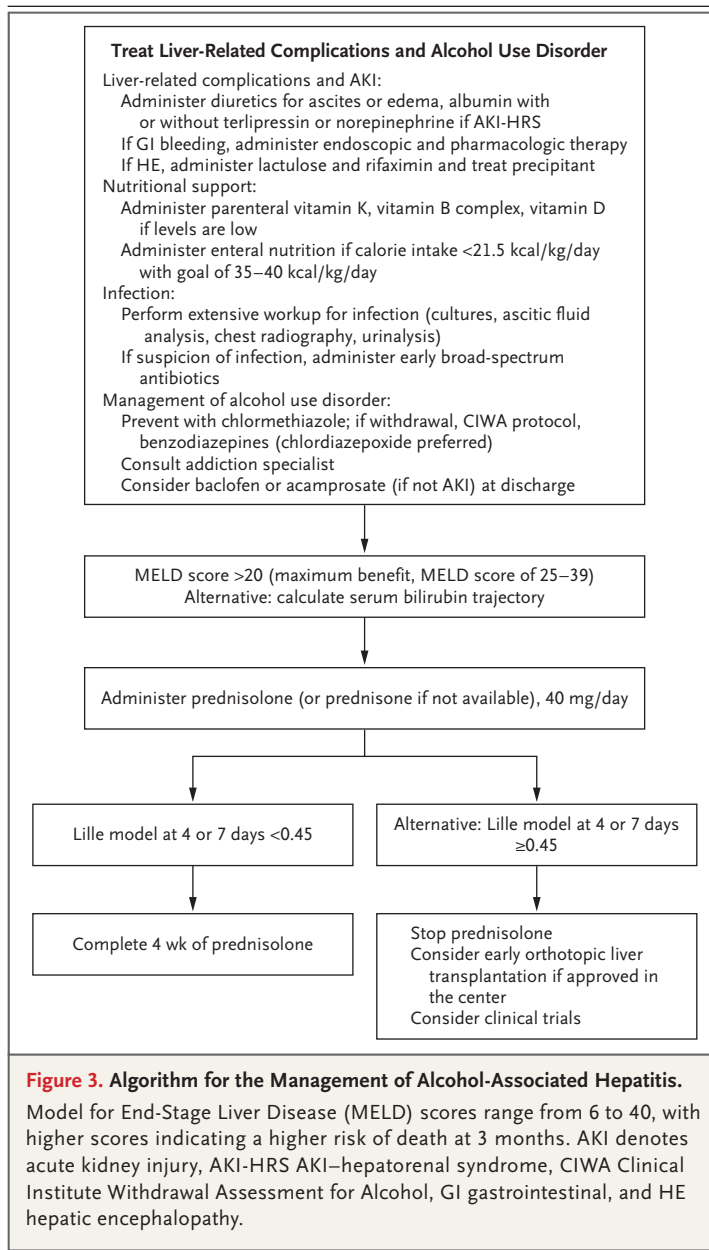
At presentation, patients are jaundiced and often have ascites and edema. Some patients present with severe caloric malnutrition and sarcopenia. Hepatic encephalopathy confers a particularly poor prognosis.⁵² The diagnosis of encephalopathy can be challenging because patients may have withdrawal syndrome, 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 glu-

cocorticoids 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 function⁵⁶; the Model for End-Stage Liver Disease (MELD)⁵⁷; the age, serum bilirubin, international normalized ratio, and serum creatinine (ABIC) score⁵⁸; 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 non-response 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-



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 $\geq 20\%$ 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

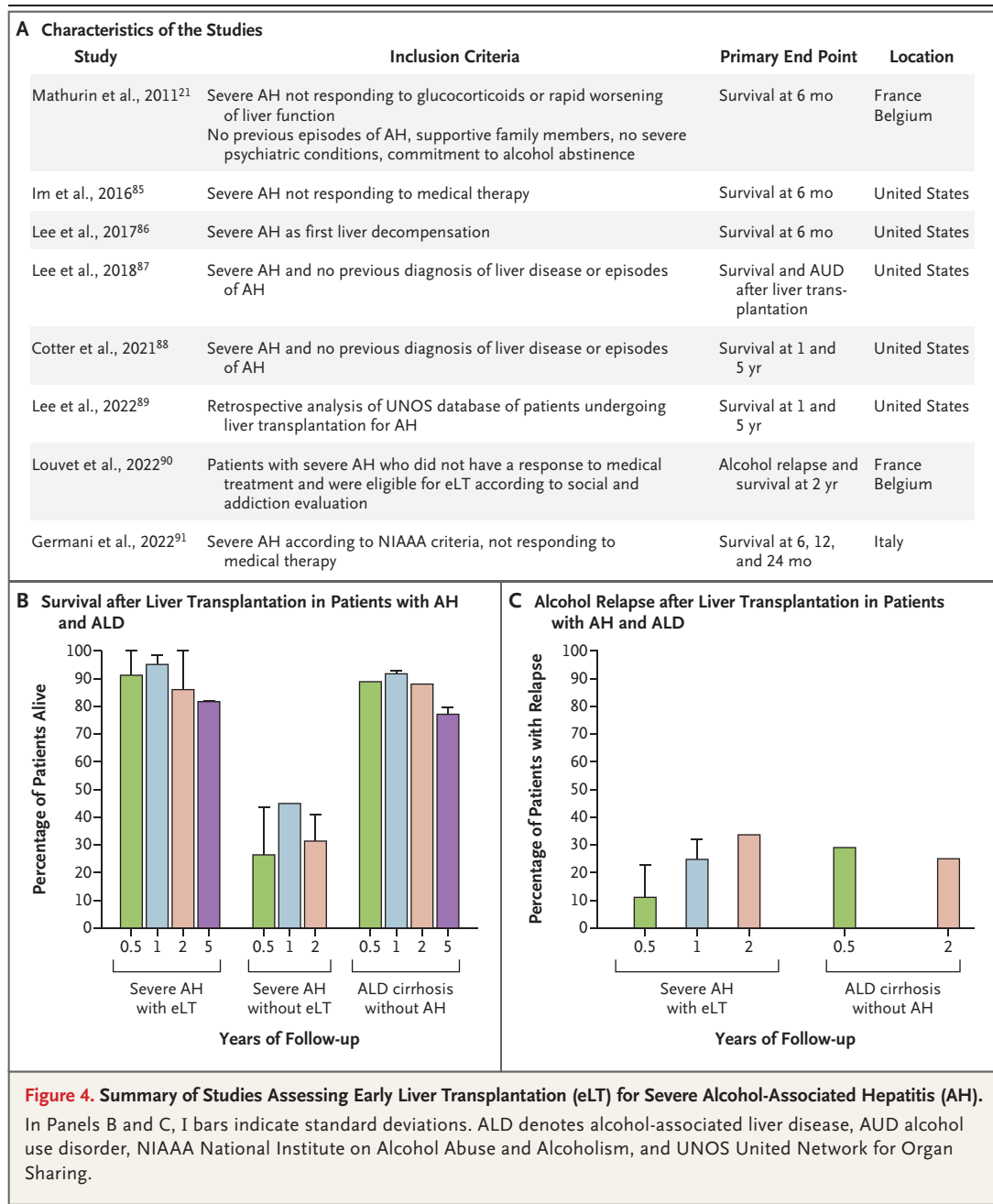
Given the high prevalence of malnutrition among patients with alcohol-associated hepatitis, it is important to assess the nutritional status and ensure adequate caloric and protein intake. Usual goals for enteral nutrition are 35 to 40 kcal per kilogram of body weight per day, with 1.5 g of protein content 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



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 in 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 pro-regenerative 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 anti-inflammatory drugs (interleukin-1 β 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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