Abstract: Excessive alcohol consumption is responsible for approximately 50% of all deaths due to cirrhosis. Although the duration and amount of alcohol consumption are the primary factors responsible for the liver injury caused by consuming alcohol, the pathogenesis of the 3 stages of alcohol-associated liver disease (ALD)—fatty liver, alcoholic hepatitis (AH), and cirrhosis—is likely multifactorial. Preexisting obesity, dysbiosis of the gut microbiome, activation of proinflammatory cytokines, and genetic factors can all contribute to the risk of developing ALD. The cornerstone of therapy for all stages of ALD is abstinence from drinking alcoholic beverages. Severe AH, defined by a Maddrey discriminant function greater than 32, warrants additional therapy. The results of multiple studies evaluating the use of glucocorticoids in the treatment of severe AH led to guidelines from international societies that recommend glucocorticoid therapy in patients with severe AH without active infection. Liver transplantation provides an effective treatment option for patients who fail glucocorticoid therapy. Recent advances in understanding the pathogenesis of AH have led to the investigation of potential therapies directed at preventing the development of steatosis, inhibiting the innate immune response, modifying the gut microbiome, and stimulating liver regeneration.

In 2010, the Global Burden of Disease Study estimated that cirrhosis attributable to alcohol consumption was the cause of 493,300 deaths worldwide (0.9% of all deaths). Furthermore, alcohol consumption accounted for 48% of all deaths due to cirrhosis.1 By definition, nonalcoholic fatty liver disease (NAFLD) excludes patients with a history of heavy alcohol consumption, defined as 21 drinks (294 g) per week for men and 14 drinks (196 g) per week for women.2 Alcohol-associated liver disease (ALD) is usually asymptomatic in the early stages and begins in an insidious manner. Although there are some distinctive histologic features, ALD and NAFLD are difficult to distinguish, particularly if the patient has already developed cirrhosis.3 Three overlapping conditions have been found in individuals who drink alcohol excessively: fatty liver, alcoholic hepatitis (AH), and cirrhosis. A precise
Definition of Alcoholic Hepatitis

Although simple steatosis may be reversible with abstinence, AH is a more serious form of acute decompensation of ALD that is characterized clinically by rapid onset of jaundice, abdominal pain, anorexia, malaise, tender hepatomegaly, systemic inflammatory response syndrome (SIRS), and hepatic decompensation, including ascites and encephalopathy.5 Spider nevi, gynecomastia, and temporal wasting may be present, and suggest underlying advanced liver disease. Less common features include enlargement of the parotid and lacrimal glands. Patients with AH are systemically ill with a high risk of nutritional deficiency, infection, acute kidney injury (AKI), variceal bleeding, and development of multiorgan failure (MOF) syndrome.6,7 Most patients with AH have been drinking heavily (>5 drinks/day) for more than 6 months, with less than 2 months of abstinence before becoming jaundiced. In addition to jaundice with a total serum bilirubin greater than 3.0 mg/dL, aspartate aminotransferase (AST) is usually elevated to over 50 IU/L, but usually does not exceed 400 IU/L, in contrast to other liver diseases such as viral hepatitis, acute liver injury from drugs, or hypoperfusion. Alanine aminotransferase (ALT) may be normal or slightly elevated, but is almost always less than 200 IU/L, again in contrast to other liver diseases. The AST/ALT ratio may be greater than 1.0 in NASH (nonalcoholic steatohepatitis) can be difficult. Although the histologic features of AH are identical, jaundice is uncommon in patients with NASH in the absence of acute-on-chronic liver failure. The AST/ALT ratio may be greater than 1.5 in AH. The AST/ALT ratio is characteristically greater than 1.5, more often because of low ALT rather than high AST, and is an important part of the clinical definition of AH.7 Gamma-glutamyl transferase (GGT), red cell mean corpuscular volume, and serum ferritin may be elevated as a consequence of heavy alcohol consumption.8

Liver biopsy can be valuable in confirming the diagnosis of AH and has been shown to have prognostic value in some studies.9 Up to 20% of patients with a clinical diagnosis of AH have another liver disease identified only by biopsy or may have liver injury without the classical findings of alcoholic steatohepatitis (ASH).10 ASH includes evidence of macrovesicular steatosis, neutrophil infiltration, cholestasis (bilirubinostasis), hepatocyte injury (ballooning), Mallory-Denk bodies, megamitochondria, and satellitosis (neutrophils surrounding dying/dead hepatocytes).11 Pericellular fibrosis (PCF) may represent an early stage of fibrosis due to alcohol. Liver biopsies performed in patients with severe AH show underlying cirrhosis in more than 70%, suggesting that a more chronic indolent type of injury precedes clinical manifestations of severe AH.9,11,12 The extent of fibrosis is the histlogic factor with the greatest prognostic value both in patients with AH and in patients with other forms of ALD.8,12 Several studies have shown that both stage of fibrosis and abstinence from alcohol influence outcomes, including mortality, in patients with ALD.5,12,13 In one study, the extent of bridging fibrosis was significantly greater in patients with decompensated vs compensated cirrhosis, whereas there was no significant difference in PCF.12 In this study, the 10-year mortality for patients with stage 3 to 4 fibrosis was 45%, whereas none of the patients with stage 0 to 2 fibrosis died.13 Features of steatohepatitis, including ballooning degeneration, Mallory-Denk bodies, and neutrophil infiltration, were also significantly more common in decompensated cirrhosis. Accumulation of proliferative cells expressing stem cell markers (ductular reaction) also appears to correlate with higher short-term mortality in AH.14,15 Most patients with alcohol-associated cirrhosis had steatohepatitis at an earlier stage in the development of injury, but some investigators have argued that perivenular fibrosis alone can be a precursor of cirrhosis in the absence of steatohepatitis.16

Because AH is a clinicopathologic entity, liver biopsy may be helpful in confirming the diagnosis in some patients and in predicting short-term mortality.9 However, histologic features of AH can persist for up to 18 months even with abstinence from alcohol.17

According to the Alcoholic Hepatitis Working Group, definite AH can be classified as clinically diagnosed and biopsy-proven AH, probable AH as clinically diagnosed AH without confounding factors, and possible AH as clinically diagnosed AH with confounding factors that necessitate liver biopsy for inclusion in trials.7

Separating ASH from nonalcoholic steatohepatitis (NASH) can be difficult. Although the histologic features are identical, jaundice is uncommon in patients with NASH in the absence of acute-on-chronic liver failure. The AST/ALT ratio may be greater than 1.0 in NASH with cirrhosis, but should be greater than 1.5 in AH. The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index (found at http://www.mayoclinic.org/gi-rst/mayo-model10.html) has been proposed as an aid in separating ALD from NAFLD.18

Risk Factors for Alcoholic Hepatitis and Alcohol-Associated Liver Disease

The amount and duration of alcohol consumption are both risk factors for the development of ALD.19,22 Higher daily consumption of alcohol increases the risk of more advanced ALD and cirrhosis-related mortality.19,21,23 A recent meta-analysis of liver biopsies in 3474 hospitalized patients with hazardous levels of drinking and some
clinical evidence of liver disease confirmed fibrosis or cirrhosis in 53%.24

Fatty liver develops rapidly with heavy drinking, as demonstrated by a study in human volunteers showing that consumption of 68 to 130 g of ethanol daily resulted in a significant increase in hepatic triglycerides within 6 to 14 days.25 Although concern has been raised about harm related to binge drinking, daily drinking, particularly outside of meals, appears to be more harmful with regard to developing alcohol-related cirrhosis.20,23,26 In northern Italy, the Dionysos study showed a dose-related increase in the relative risk of noncirrhotic fatty liver disease and cirrhosis related to both alcohol consumption and obesity.20,27 The estimated prevalence of alcohol-associated cirrhosis in patients consuming more than 60 g of ethanol daily. A similar study from Copenhagen reported an absolute risk of cirrhosis of 6% in patients drinking more than 35 drinks per week (~60 g daily).19,26 Although these studies suggest a threshold effect of approximately 30 g of ethanol per day in men, a study from Sweden showed an almost linear increase in the risk of cirrhosis related to daily consumption of alcohol at age 18 years.28 Risk factors for the development of fibrosis and cirrhosis include not only the daily amount of alcohol consumed, particularly outside of meals, and the duration of heavy consumption, but also obesity and cigarette smoking.19,21,29,30

Importantly, the daily alcohol consumption threshold for the risk of ALD is clearly lower in women compared to men (11-20 vs 21-40 g daily).21 While more men than women develop alcohol-related cirrhosis, the risk for women increases at a lower daily intake of alcohol than for men, although the reason remains unclear.23 Obesity is a risk factor for both ALD and NAFLD progressing to cirrhosis.31-34 Many of the same pathways contribute to the pathogenesis of both ALD and NAFLD.35-37 A single nucleotide polymorphism (rs738409G) in patatin-like phospholipase 3 (PNPLA3) is associated with an increased risk of fatty liver and cirrhosis related to ALD and NAFLD.38,41 Furthermore, the risk of developing liver injury in patients with the variant polymorphism is increased by a higher body mass index or higher levels of alcohol consumption.42 Several studies have suggested that patients with the I148M genotype of PNPLA3 have more severe AH.43,44

Determining Prognosis in Alcoholic Hepatitis

Laboratory parameters have proven to be more predictive of outcome in AH than clinical features such as ascites and encephalopathy.8 Serum bilirubin, creatinine, and prolongation of the international normalized ratio (INR) are indicators of the severity of AH.9 The Maddrey discriminant function (MDF), Model for End-Stage Liver Disease (MELD) score, ABIC (age, serum bilirubin, INR, creatinine) score, and Glasgow Alcoholic Hepatitis score utilize these laboratory parameters to predict short-term mortality with a high degree of accuracy45-48 (Table 1). Many of the other clinical features of AH are related to SIRS. This syndrome and the serum level of endotoxin independently predict development of MOF and short-term mortality in AH.5 Patients with AH may present with or quickly develop AKI, ascites, coagulopathy, and hepatic encephalopathy, with AKI being the strongest predictor of in-hospital mortality.49,50 Infections are a frequent complication of AH, developing in up to 60% of hospitalized patients.51-54 Furthermore, infections acquired during hospitalization may trigger MOF, leading to higher mortality.5 A pattern of dysbiosis and intestinal bacterial overgrowth has been described in patients with ALD and could be a risk factor for infections in patients with AH.55-58 Patients with AH also have fungal dysbiosis with a lower diversity of organisms, predominantly Candida species.59 Glucocorticoid treatment may not increase the risk of infection during treatment, but following therapy, the risk of serious infection, including fungal infections, is higher.51,53,54,60 Mortality at 90 days was higher in AH patients who have levels of anti-Saccharomyces cerevisiae antibodies greater than 34 IU/mL compared to patients who have lower levels, suggesting that fungal dysbiosis may be an important risk factor for poor outcomes.59

Although short-term mortality in AH is determined by the severity of liver disease at the time of presentation, the long-term prognosis of AH and ALD is dependent on abstinence.51-60 All patients who have fatty liver disease should be screened for quantity and frequency of alcohol consumption as well as for alcohol use disorders (AUDs). The AUDIT (Alcohol Use Disorders Identification Test) questionnaire is a very effective tool, with over 90% sensitivity and over 80% specificity for AUDs in hospitalized patients.64 The adverse effect of continued alcohol consumption on mortality of ALD patients emphasizes the importance of treatment of AUDs.65 However, there are relatively few safe and effective drugs that are currently available for treating AUDs in patients with ALD. Treatment of AUDs is, therefore, a major unmet need in the field of ALD.

Pathogenesis of Alcoholic Hepatitis

The mechanism of liver injury from alcohol is almost certainly multifactorial. Development of alcohol-related
steatosis has been linked to production of reactive oxygen species as well as dietary fat intake, adipose tissue, fatty acid transporters, hepatic lipid synthesis, and cytokines. Overexpression of the steroid response binding protein-1c (SREBP-1c) and induction of the glucose-responsive transcription factor, carbohydrate-responsive element binding protein, have been implicated in alcohol-associated steatosis. Additional regulators of steatosis include the liver X receptor (LXR) and the farnesoid X receptor (FXR). Peroxisome proliferator-activated receptor (PPAR) α is inhibited by alcohol and downregulates PPARα-regulated genes that, in turn, regulate SREBP-1c. Alcohol-related induction of hypoxia-inducible factor-1α (HIF-1α) may be another important factor in steatosis, as suggested by research in HIF-1α knockout mice.

ASH includes features of both cell death and inflammation, as previously noted. Although many clinical factors have been associated with the development of AH, the specific events (mechanisms) that trigger an episode of acute AH in a patient with otherwise stable ALD remain uncertain. There is increasing evidence that dysbiosis of the gut microbiome may stimulate release of proinflammatory cytokines such as tumor necrosis factor (TNF) α or interleukin (IL) 1-β within the liver. These cytokines trigger an inflammatory cascade and/or affect transcription factors that can interfere with liver regeneration. Direct toxicity from microbial exotoxins represents another potential mechanism of injury for which evidence is accumulating. Cytolysin, an exotoxin produced by Enterococcus faecalis, causes hepatic injury in mice. In AH patients who had cytolysin-positive stool samples, mortality was 50% at 90 days and 85% at 180 days compared to less than 5% in AH patients without cytolysin-positive stool samples. In patients with AH who had fecal samples positive for candidalysin, an exotoxin that is hepatotoxic in mice, mortality at 90 days was higher than in patients with AH without candidalysin in their stool. Not surprisingly, mortality due to Clostridium difficile infection is higher in patients with alcohol-associated cirrhosis compared to patients without liver disease. Taken together, these findings suggest that specific changes in the microbiome may increase mortality and the risk of complications in patients with AH.

Recent research suggests that epithelial transformation during liver regeneration leads to dedifferentiation of hepatocytes. Expression of transforming growth factor β is enhanced in patients with severe AH through epigenetic modifications that alter expression of hepatocyte nuclear factor 4α. In addition, inflammatory cytokines (TNFα and IL-1β) suppress expression of epithelial splicing protein, transforming adult hepatocytes into more proliferative fetal-like cells in patients with severe AH. The consequence of epithelial mesenchymal transformation is dedifferentiation of hepatocytes and loss of functions, including bilirubin transport, detoxification of ammonia, and synthesis of clotting factors. These new

Table 1. Scores Determining Prognosis in Alcoholic Hepatitis

<table>
<thead>
<tr>
<th>Name of Score</th>
<th>Components of Score</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maddrey Discriminant Function</td>
<td>Serum bilirubin PT/INR</td>
<td>Prognosis</td>
</tr>
<tr>
<td>MELD Score</td>
<td>Serum bilirubin INR Creatinine</td>
<td>Prognosis</td>
</tr>
<tr>
<td>ABIC Score</td>
<td>Serum bilirubin INR Creatinine Age</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Glasgow Alcoholic Hepatitis Score</td>
<td>Serum bilirubin INR Creatinine Age WBC</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Hepatitis Histologic Score</td>
<td>Bilirubinostasis Megamitochondria Fibrosis PMN infiltration</td>
<td>Prognosis</td>
</tr>
<tr>
<td>Lille Score</td>
<td>Serum bilirubin and change in serum bilirubin at day 7 PT/INR Creatinine Age Determination of response to glucocorticoid therapy</td>
<td></td>
</tr>
</tbody>
</table>

ABIC, age, serum bilirubin, INR, creatinine; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PMN, polymorphonuclear leukocyte; PT, prothrombin time; WBC, white blood cells.
insights into basic mechanisms responsible for inflammation and liver failure in patients with severe AH may be valuable in developing new approaches to the treatment of this disease.

**Current Standard of Care for Severe Alcoholic Hepatitis**

Initial evaluation of patients with AH should include a careful history of alcohol consumption, including recent use, quantity, and frequency of intake. The cornerstone of therapy for all stages of ALD is abstinence from drinking alcoholic beverages. However, formal treatment programs are often not accessible to patients with AH. Features of SIRS (fever, tachycardia, tachypnea, and elevated white blood cells) in patients with AH indicate a higher probability of MOF syndrome as well as the possibility of infection. Analysis of blood and urine cultures and ascites should be performed in patients with suspected AH regardless of whether they have fever because infection can lead to decompensation. Urinary tract infection, bacteremia, spontaneous bacterial peritonitis, and *C difficile* colitis are the most frequent sites of infection. Prophylactic coverage with antibiotics should be considered while awaiting results of cultures. If identified, active infections require treatment prior to initiating therapy for AH that can impair the immune response.

A recent study of practice patterns in the United States indicated that currently available therapies for AH are used infrequently and inconsistently. The vast majority of patients do not receive the recommended treatment for AH, suggesting either a lack of recognition or a lack of confidence in the available treatment for this condition. Although short-term mortality has improved, overall mortality may still reach 30% to 50% within 90 days of the diagnosis of severe AH.

**Glucocorticoids**

Glucocorticoids were first used to treat AH almost 50 years ago, primarily because of the inflammatory features of the illness. Since then, more than 20 randomized, controlled trials of glucocorticoids have been conducted in patients with severe AH as defined by an MDF greater than 32. The 1989 US multicenter trial of methylprednisolone vs placebo for the treatment of severe AH reported a significantly lower 28-day mortality rate in patients treated with methylprednisolone compared with standard care. Subsequent trials from France reported similar findings. Two meta-analyses that included primarily high-quality studies concluded that there is a benefit to treatment, whereas a third did not. More recently, a meta-analysis using primary data from 11 trials concluded that glucocorticoids reduce 28-day mortality of severe AH but did not affect 6-month mortality. A 2019 systematic review of 16 trials using the Cochrane methodology concluded that there was no benefit from glucocorticoids and that 15 of the 16 trials had a high probability of bias.

The STOPAH trial is the largest randomized, controlled trial in patients with severe AH. The trial randomized 1103 patients with severe AH in Europe between 2011 and 2014 to receive prednisolone 40 mg (equivalent to 32 mg of methylprednisolone) daily, pentoxifylline (PTX) 400 mg 3 times daily, the combination of prednisolone and PTX, or placebo. The odds ratio for mortality at 28 days for patients receiving prednisolone (including the combination with PTX) was 0.72 (95% CI, 0.52-1.01) but was not statistically significant (*P*=.06), and the odds ratio for all patients receiving PTX was 1.07 (95% CI, 0.77-1.49), which was also not statistically significant. The mortality rate was 30% at 90 days and 56% at 1 year, and was similar in all 4 groups. Although no differences were observed in the development of AKI, the groups treated with prednisolone had more infections (10%) than the groups not treated with prednisolone (6%) after treatment was concluded (*P*=.024). The 28-day mortality rate for placebo, which was lower in this study compared to that in other studies, adversely impacted the calculated power analysis and may explain why the effects of prednisolone narrowly missed achieving statistical significance for improvement in short-term mortality. Furthermore, treatment of AKI with agents such as terlipressin was left to the discretion of the investigator and could be a confounding factor influencing the overall outcomes.

A network meta-analysis using results from 22 recent trials involving 2621 patients with severe AH showed that treatment with glucocorticoids alone or in combination with PTX or the antioxidant N-acetylcysteine (NAC) reduced 28-day but not 90-day mortality compared to standard care based on moderate-quality evidence. Although in previous studies an antioxidant cocktail including NAC and vitamin E showed little benefit in severe AH, the combination of prednisolone plus NAC given intravenously over the first 5 days of the trial resulted in the most significant improvement in 1-month mortality (8% vs 24% for prednisolone alone) of the studies included in the network meta-analysis. Patients treated with the combination had fewer infections (19%) than patients treated with prednisolone alone (42%) (*P*<.001) and a lower incidence of hepatorenal syndrome (HRS) (12% vs 25%; *P*<.02). These important findings await confirmation by additional studies. The results of these studies collectively were used to formulate the current guidelines of both the American Association for
the Study of Liver Diseases and the European Association for the Study of the Liver that recommend glucocorticoid treatment for patients with severe AH without active infections.\textsuperscript{94,105}

All of the reported controlled trials of glucocorticoids have used similar doses and duration of treatment. Methylprednisolone 32 mg is equivalent to 40 mg of prednisolone or prednisone. Many studies favored prednisolone or methylprednisolone to avoid potential confounding of variability in hepatic conversion of prednisone to prednisolone. There are no published studies that evaluated different doses or duration of treatment with glucocorticoids, so the optimal dose and duration of treatment remain uncertain. Almost all trials employed a 28-day regimen, although, in 2007, Louvet and colleagues developed a prognostic model now known as the Lille score to predict response to continuing glucocorticoids beyond 7 days.\textsuperscript{106} Using a cutoff of 0.45, the Lille score predicted 75% of the observed deaths at 6 months in patients who were treated for 28 days. Forty percent of patients in their original cohort were classified as nonresponders to glucocorticoids. Subsequent research by this group showed that combining the initial MELD score with the Lille score at 7 days was more effective at predicting survival than either score alone.\textsuperscript{107} The Lille score for complete responders (0.16) with the initial MELD score (15–45) predicted a 6-month mortality of 8.5% to 49.7% compared to a 6-month mortality of 16.4% to 75.2% for nonresponders (Lille score, 0.45) with a similar initial MELD score. Given the lack of data regarding the ideal dose and duration of glucocorticoid therapy, the Lille score is useful in identifying patients who have a lower probability of benefit from extending treatment with glucocorticoids beyond 7 days. This issue is relevant given the potential risk of infections in patients treated with glucocorticoids, although some studies have linked the risk of infection to a lack of response to glucocorticoids.\textsuperscript{53,54} Infections that begin after initiation of treatment with glucocorticoids have a worse outcome than infections present before treatment.\textsuperscript{53}

**Therapies Lacking Evidence for Efficacy in the Treatment of Alcoholic Hepatitis**

**Pentoxifylline**

Although PTX was reported to reduce mortality in patients with severe AH (MDF >32),\textsuperscript{108-110} studies combining PTX with glucocorticoids did not show any benefit in the survival of patients with severe AH.\textsuperscript{94,99,111} Two meta-analyses and 1 network meta-analysis concluded that there were no differences in short-term mortality related to PTX.\textsuperscript{100,112,113} Based on these findings, PTX is not recommended for use in patients with severe AH.

**Anti–Tumor Necrosis Factor α Therapy**

Levels of TNFα are often elevated in patients with severe AH.\textsuperscript{114,115} Although preliminary evidence suggested that anti-TNFα therapy might be beneficial in severe AH,\textsuperscript{116,117} subsequent larger trials of etanercept (antibody to TNFα receptor) and the combination of anti-TNFα therapy with glucocorticoids led to a higher risk of infections and a higher mortality rate than standard care.\textsuperscript{118,119} These trials have generally led to an abandonment of anti-TNFα therapy in AH.

**Novel Therapies for Alcoholic Hepatitis**

Understanding the pathogenesis of AH provides the potential to develop new therapies based on the mechanism(s) of injury. As noted previously, there are 3 overlapping pathways or mechanisms of injury that provide potential targets for future therapy: development of steatosis; inflammation mediated primarily by the innate immune system stimulated, in part, by gut dysbiosis and translocation of bacterial products; and reprogramming of adult hepatocytes to a more fetal, regenerative state leading to loss of critical functions such as detoxification of ammonia, transport of bilirubin, and production of clotting factors. Some of the studies that are currently enrolling patients are listed in Table 2.

**Prevention of the Development of Steatosis**

**Obeticholic Acid**

Obeticholic acid (Ocaliva, Intercept), a bile acid derivative with anticholestatic and hepatoprotective properties, acts via the FXR pathway. FXR controls bile acid synthesis and transport, lipid metabolism, and glucose homeostasis, and, thus, is a promising therapeutic target for the treatment of NAFLD.\textsuperscript{120,121} Given the similarities between ALD and NAFLD, obeticholic acid could lower the severity of alcoholic steatosis and prevent downstream effects. Studies are currently underway to evaluate the role of obeticholic acid in AH.

**5-Cholesten-3b, 25-Diol 3-Sulfate**

5-cholest-en-3b, 25-diol 3-sulfate (25HC3S), a novel oxysterol synthesized by oxysterol sulfation from 25-hydroxycholesterol, downregulates lipid metabolism and inflammatory responses acting through decreases in LXR and SREBP-1c activity and increases in PPARγ.\textsuperscript{122} The downregulation of LXR by 25HC3S is in contrast to the upregulation of LXR by 25-hydroxycholesterol. The changes in activity of these key enzymes decrease triglyceride synthesis and reduce expression of proinflammatory cytokines when challenged by lipopolysaccharide (LPS) and TNFα.\textsuperscript{122} 25HC3S (also known as DUR-928) was evaluated in an open-label study of patients with both moderate and severe AH. Seventeen of 19 patients dosed with up to
Table 2. Select Studies on Clinicaltrials.gov Currently Enrolling Patients With Alcoholic Hepatitis

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Clinicaltrials.gov Identifier</th>
<th>Trial Name</th>
<th>Investigational Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of Steatosis</td>
<td>NCT03917407</td>
<td>DUR-928 in Patients With Alcoholic Hepatitis (DUR-928/AH)</td>
<td>5-cholesten-3b, 25-diol 3-sulfate (25HC3S)</td>
</tr>
<tr>
<td></td>
<td>NCT03452540</td>
<td>Efficacy and Safety of Orally Administered DS102 in Patients With Acute Alcoholic Hepatitis</td>
<td>15-hydroxy eicosapentaenoic acid ethyl ester (Epeleuton)</td>
</tr>
<tr>
<td>Modulation of Inflammation</td>
<td>NCT03732586</td>
<td>Effect of Omega 5 Fatty Acid as an Adjuvant Treatment to Prednisone in Patients With Severe Alcoholic Hepatitis</td>
<td>Omega-5 fatty acid (punicic acid)</td>
</tr>
<tr>
<td></td>
<td>NCT03775109</td>
<td>IL-1 Signal Inhibition in Alcoholic Hepatitis (ISAIAH)</td>
<td>Canakinumab</td>
</tr>
<tr>
<td></td>
<td>NCT03703674</td>
<td>G-CSF in Alcoholic Hepatitis</td>
<td>G-CSF</td>
</tr>
<tr>
<td></td>
<td>NCT04072822</td>
<td>Trial of Anakintra (Plus Zinc), G-CSF, or Prednisone in Patients With Severe Alcoholic Hepatitis (AlcHepNet)</td>
<td>Prednisone, G-CSF, Anakinra</td>
</tr>
<tr>
<td></td>
<td>NCT02776059</td>
<td>Pegfilgrastim in Patients With Alcoholic Hepatitis</td>
<td>Pegfilgrastim</td>
</tr>
<tr>
<td></td>
<td>NCT02442180</td>
<td>Efficacy and Safety of G-CSF in Patients With Severe Alcoholic Hepatitis With Null or Partial Response to Steroid (GraCiAH)</td>
<td>G-CSF, prednisolone</td>
</tr>
<tr>
<td></td>
<td>NCT03829683</td>
<td>Vitamin C Infusion for Treatment in Sepsis and Alcoholic Hepatitis (CITRIS-AH)</td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td>NCT03069300</td>
<td>N-acetylcysteine to Reduce Infection and Mortality for Alcoholic Hepatitis (NACAH)</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Modification of the Microbiome</td>
<td>NCT01922895</td>
<td>Novel Therapies in Moderately Severe Acute Alcoholic Hepatitis (NTAH-Mod)</td>
<td>Lactobacillus rhamnosus GG</td>
</tr>
<tr>
<td></td>
<td>NCT03827772</td>
<td>Fecal Microbiota Transplantation in Severe Alcoholic Hepatitis—Assessment of Impact on Prognosis and Short-Term Outcome</td>
<td>Fecal microbiota transplantation</td>
</tr>
<tr>
<td></td>
<td>NCT02281929</td>
<td>Efficacy of Antibiotic Therapy in Severe Alcoholic Hepatitis Treated With Prednisolone (AntibioCor)</td>
<td>Amoxicillin, prednisolone</td>
</tr>
<tr>
<td></td>
<td>NCT02473341</td>
<td>Comparison of Bovine Colostrum Versus Placebo in Treatment of Severe Alcoholic Hepatitis: A Randomized Double Blind Controlled Trial (BASH)</td>
<td>Bovine Colostrum</td>
</tr>
</tbody>
</table>

G-CSF, granulocyte-colony stimulating factor; IL, interleukin.

150 mg of DUR-928 had Lille scores of less than 0.45 by day 7 after treatment. The Lille scores in these patients were significantly better than those of historically matched glucocorticoid-treated patients. This compound may have more than 1 mechanism of action, but at the doses used, no serious adverse events were reported. A phase 2b study is now underway.

Metadoxine Metadoxine is an ion pair salt of pyridoxine and pyrrolidone carboxylate. There is some evidence
that metadoxine increases glutathione levels and reduces steatosis in animals fed alcohol and may act as an antioxidant.\textsuperscript{124} One study showed a statistically significantly improved 90-day survival in patients treated with a combination of metadoxine and either PTX or prednisone compared to PTX or prednisone alone.\textsuperscript{125}

\textbf{Inflammation Mediated by the Innate Immune Response}

\textbf{Interleukin 1 Receptor Blockers} In patients with severe AH, combination therapy may be warranted. Results were recently presented from a randomized, controlled trial of combination therapy (IL-1 receptor inhibitor anakinra [Kineret, Sobi] to reduce inflammation, zinc supplementation to improve gut barrier function, and PTX to prevent HRS) compared to standard of care with methylprednisolone in patients with severe AH.\textsuperscript{126} The therapy combination was chosen based on validated basic science studies, successful animal models, and patient observations.\textsuperscript{127,128} Anakinra has a better safety profile than anti-TNF\textsubscript{α} therapy, as seen in other inflammatory conditions such as arthritis, and, therefore, potentially avoids the increased risk of infection associated with anti-TNF\textsubscript{α} therapy. In patients with severe AH defined by a MELD score over 20 and an MDF greater than 32, the combination of anakinra for 14 days plus zinc for 180 days plus PTX for 28 days resulted in similar survival at 28 days and a 22% better survival at 90 and 180 days compared to patients treated with methylprednisolone; however, the difference was not statistically significant.\textsuperscript{126} The trial was initially powered to detect a difference of 50% between the 2 groups, so the number enrolled was inadequate to detect a statistical difference of 25%.

\textbf{Caspase Inhibitors} In the sterile inflammation pathway activated by LPS/Toll-like receptor (TLR) 4, caspase-1 ultimately initiates cell death. Hence, caspase inhibitors are of interest for both AH and NAFLD. Emricasan, a pan–caspase inhibitor, successfully lowered fibrosis levels in a murine model of NASH.\textsuperscript{129} However, this medication was withdrawn from clinical trials after several adverse events were reported. A phase 2 trial in patients with NAFLD showed promise for selonsertib, an apoptosis signal-regulating kinase inhibitor,\textsuperscript{130} but a subsequent trial in patients with severe AH failed to show any significant difference between prednisolone plus selonsertib and prednisolone.\textsuperscript{131}

\textbf{Modification of the Microbiome}

\textbf{Probiotics} In a small study of patients with mild-moderate AH, short-term supplementation of \textit{Bifidobacterium bifidum} and \textit{Lactobacillus plantarum} 8PA3 restored gut flora and improved laboratory markers of liver injury (AST, ALT, GGT, lactate dehydrogenase, serum bilirubin).\textsuperscript{132} \textit{Lactobacillus rhamnosus} GG supplements may improve mucosal integrity, inhibit endotoxin activation of TLR4, reduce TNF\textsubscript{α} production, and, thus, lower alcohol-mediated inflammation.\textsuperscript{133,134} Additional studies of \textit{Lactobacillus} in moderate AH are ongoing.

\textbf{Fecal Microbiota Transplantation} Fecal microbiota transplantation (FMT) has been used successfully to treat refractory \textit{C difficile} infection and is being evaluated for the treatment of other gastrointestinal disorders in which there is dysbiosis.\textsuperscript{135} Several small studies have reported efficacy of FMT in treating AH patients.\textsuperscript{136,137} Although this approach holds promise, concern about potential unexpected infections (including bacteremia), particularly in a population at risk for infections, limits enthusiasm for treatment outside of carefully controlled trials.\textsuperscript{138}

\textbf{Potential Microbial Phage Therapy} Bacteriophages are viruses that are highly selective for specific strains of bacteria. They inject the viral genome into bacterial cells, halting reproduction of the bacteria and producing more phages. Phage therapy was used experimentally to treat a drug-resistant \textit{Acinetobacter baumannii} infection.\textsuperscript{139} Recent research demonstrated that oral administration of cytolysin-positive \textit{E faecalis} produced more severe steatohepatitis than cytolysin-negative \textit{E faecalis} in a mouse model of ethanol-related injury.\textsuperscript{140} The authors also demonstrated that bacteriophages specific for the cytolysin-positive strain of \textit{E faecalis} were able to reduce the severity of steatohepatitis in this mouse model. Recognizing the association between cytolysin-positive \textit{E faecalis} and mortality in patients with AH, using an approach to selectively target this organism may hold promise. A similar approach might be considered for patients harboring candidalysin-positive organisms.

\textbf{Stimulation of Liver Regeneration}

\textbf{Granulocyte-Colony Stimulating Factor} Administration of granulocyte-colony stimulating factor (G-CSF) (10 µg/kg/day × 5 days) was shown to increase the number of CD34+ cells, levels of hepatocyte growth factor, and hepatic progenitor cells in patients with alcohol-associated cirrhosis and steatohepatitis.\textsuperscript{140} This observation suggested that G-CSF may stimulate liver regeneration in patients with severe AH. A subsequent pilot study of G-CSF plus standard care, including PTX, showed improved survival of 78.3%, compared to 30.4% (\(P<.001\)) in patients treated with standard care alone at 90 days.\textsuperscript{141} A larger follow-up study showed statistically significant improvement in survival at 90 days in patients treated with either G-CSF alone or in combination with NAC for 5 days compared to standard care.\textsuperscript{142} The high mortality in the
control group was noted as a potential confounder to these findings. G-CSF was also reported to improve 90-day survival in glucocorticoid nonresponders (Lille score >0.45). Mortality was 35.7% in glucocorticoid nonresponders treated with 12 doses of G-CSF 300 µg over 30 days compared to 70.4% in patients treated with standard medical care. Infections were lower, and the MELD score decreased more significantly in survivors treated with G-CSF.

Interleukin 22 A phase 2 trial of IL-22 (F-652) showed improved Lille scores at 7 days and MELD scores at 28 and 42 days, along with upregulation of markers of regeneration and downregulation of markers of inflammation in 18 patients with AH. No serious adverse events were reported in this population of patients with AH.

Immunoglobulin-Rich Bovine Colostrum Immunoglobulin-rich bovine colostrum has been shown to have immunomodulatory effects, lower serum endotoxin levels in animal studies, and improve gut permeability in critically ill patients. A pilot study combining glucocorticoids with bovine colostrum is underway.

Liver Transplantation

Liver transplantation (LT) offers excellent short-term survival for the treatment of patients with severe AH who, based on Lille criteria, have failed a trial of medical therapy. Over the last 15 years, the number of liver transplant recipients with ALD has increased. The increase in the number of transplants for ALD between 2010 and 2016 coincides with the initial report from France and Belgium in 2011 showing excellent results in carefully selected patients with AH followed by confirmation in US patients with AH. Several studies found that the likelihood of relapse to drinking in patients transplanted for ALD is related to factors other than a specific duration of abstinence. Late deaths following LT for ALD are most often due to cancer, infections, and relapse to harmful levels of drinking. Concern that patients may relapse to harmful levels of drinking is a primary reason why LT remains controversial. Several scoring systems have been developed to predict risk of relapse to harmful drinking in patients with ALD. These scoring systems share some common elements, including the degree of excessive use, continued use despite legal or major social consequences, and failure of previous attempts to quit drinking at harmful levels. The need to treat the underlying AUD underscores the importance of including addiction psychiatrists, social work, and family counselors in the transplant team evaluation process and posttreatment care of patients with AH.

Conclusion

AH is a systemic inflammatory disorder resulting in major decompensation in liver function that carries a potentially high risk of mortality in the first 90 to 180 days. Glucocorticoid therapy improves survival of severe AH at 28 days and remains the current standard of care despite lack of improved survival at 90 days or beyond. New approaches to treatment that reduce the inflammatory component and increase regeneration of the liver while maintaining differentiated liver functions are needed. The complexity of the pathogenesis of AH will likely require combination therapy to make a significant improvement in recovery from this illness. Rapid expansion of knowledge and understanding of this problem should facilitate development of new treatments. A large multicenter trial (AlcHepNet) sponsored by the National Institute on Alcohol Abuse and Alcoholism is currently enrolling patients with severe AH to compare the benefits of anakinra and zinc, G-CSF, and prednisone on 90-day survival (NCT04072822). There are a number of other new studies that are also enrolling patients with AH (Table 2). The results of these studies are likely to contribute significant new understanding to both the pathogenesis and treatment of this illness.

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