# Alcoholic Hepatitis
## The Rising Epidemic

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**KEYWORDS**

• Alcoholic hepatitis • Alcohol use disorder • Alcohol-associated liver disease • AH • AUD • ALD

**KEY POINTS**

- Alcoholic hepatitis is characterized by new onset or worsening jaundice in the setting of heavy alcohol use and has significant short-term and long-term morbidity and mortality.
- Over the last decade, health care burden from alcoholic hepatitis has been increasing, and this has accelerated in the last 2 to 3 years during the COVID-19 pandemic.
- Corticosteroids, the mainstay of treatment for severe alcoholic hepatitis, are a suboptimal treatment, and there is a need for novel therapeutic agents.
- The long-term prognosis of alcoholic hepatitis is determined by alcohol abstinence, and the treatment for the second pathology of alcohol use disorder is critical.

### DISEASE BURDEN AND RISING EPIDEMIC OF ALCOHOLIC HEPATITIS

Alcohol-associated liver disease (ALD) encompasses a spectrum of disease from alcohol-associated steatosis to cirrhosis. Alcohol-associated hepatitis (AH), a unique manifestation on this spectrum, is characterized by new onset or worsening jaundice in the setting of heavy alcohol use with less than 60 days of abstinence before the onset of jaundice.[1] Among patients with severe forms, mortality approaches 20% to 30% at 30 days and 30% to 40% at 6 months.[2] In addition, there is an increased risk of progression to cirrhosis, especially in the setting of continued alcohol use.[3,4]

Over the last decade, since the availability of effective therapy for hepatitis C virus infection, ALD-related hospitalizations and disease burden have been increasing, with ALD currently being the leading indication for liver transplantation (LT). A retrospective study of hospitalized patients in the United States showed a 28.3% increase in AH

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hospitalizations between 2007 and 2014.[5] Taken together, this increasing disease burden results in increased health care utilization, costs, morbidity, and mortality.[6] In 2011 alone, the average cost of a hospitalization for AH was $37,769 with an average length of hospitalization of 6.5 days.[7] More recently, between 2012 and 2016, alcohol-associated cirrhosis accounted for $22.7 billion in hospitalizations costs and an increasing trend has been observed.[6]

These increasing trends are disproportionately increasing in specific demographic populations of young adults, females, and minorities.[5,7,8] For example, a study of 14,547 adolescents and young adults aged 15 to 39 years enrolled in the National Health and Nutrition Examination Survey between 1988 to 2012 showed an increase in the prevalence of ALD from 2.3% between 1988 and 1994 to 5.1% between 2007 and 2012 period.[9] Another similar study of 1,319 adolescents and young adults between 2017 and 2018 showed 8.5% prevalence of excessive alcohol intake in the overall study population and a 56.59% prevalence of ALD among those with excessive drinking.[10] In another study using population-level vital statistics data, the highest average annual increase in cirrhosis-related deaths was observed among individuals aged 25 to 34 years (10.5% during 2009–2016), which was entirely driven by ALD.[11] Similarly, disease burden related to hospitalizations due to AH was shown to be increased by 37.6% among females compared with 22.3% increase among males during the same time period.[5] This and other studies have also shown disproportionate increase in disease burden among Native Americans and Hispanics compared with whites.[5]

The COVID pandemic has further exacerbated the problem by increasing excessive alcohol consumption, alcohol use disorder (AUD), and ALD, particularly among patients younger than 40 years (**Table 1**).[18] A Canadian retrospective study revealed a significant increase in average monthly admissions for AH during the pandemic (22.1/10,000 admissions) compared with the pre-pandemic period (11.6/10,000 admissions).[21] These trends have been corroborated by other studies and are expected to continue, with effects persisting over the coming years.[6,22] For example, a modeling study projected additional 8000 ALD-related deaths and 18,700 cases of decompensated cirrhosis from a 1-year increase in alcohol consumption during the COVID-19 pandemic.[16]

Clearly, physicians, internists, gastroenterologists, and hepatologists will continue to face these patients with advanced ALD and AH over the years to come. Hence, there is a need for an improved understanding on how to evaluate and manage these patients, and this review is timely to meet this educational need. From here on, the authors discuss and provide recent updates on the pathophysiology, diagnosis, and treatment of patients with AH.

## DIAGNOSIS

The clinical syndrome of AH includes a constellation of jaundice, malaise, fever, tender hepatomegaly, and anorexia in the setting of heavy and often active alcohol use.[4] The clinical presentation can vary from mild jaundice, hepatic decompensation, and acute on chronic liver failure with failure of one or more organs in most severe forms. The NIAAA Alcoholic Hepatitis Consortia has proposed clinical criteria (**Fig. 1**) for a probable diagnosis of AH.[1] Patients not meeting one or more of these criteria (possible AH) would need a liver biopsy for diagnosis (definite AH).[23] When a liver biopsy is performed, a transjugular liver biopsy is recommended given frequent coexistence of coagulopathy and/or ascites in these sick patients. The histologic features of AH include hepatocellular ballooning, neutrophilic lobular inflammation, Mallory–Denk bodies, and megamitochondria.[3] Sclerosing hyaline necrosis characterized by

**Table 1**
**Studies assessing the effect of COVID-19 on alcohol consumption, alcohol use disorder, alcohol-associated liver disease, and alcoholic hepatitis**

| Author | Outcome | Study Design | Study Findings |
|---|---|---|---|
| Alcohol use disorder | | | |
| Yeo et al,[12] 2022 | AUD-related mortality | Modeling | Outcome increased by 24.7% in 2020 and 21.95% in 2021 vs projected rates. |
| White et al,[13] 2022 | Alcohol-related deaths | Cross-sectional | Outcome increased by 25.9% in 2020 vs 2019. |
| Sharma et al,[14] 2021 | Alcohol withdrawal hospitalizations | Retrospective single-center cohort | 34% increase in hospitalizations related to alcohol withdrawal in 2020 vs same period in 2019. |
| Barbosa et al,[15] 2021 | Alcohol consumption | Cross-sectional survey | 20% increase in harmful alcohol use and 21% increase in binge drinking between 02/2020 and 04/2020. |
| Alcohol-associated liver disease | | | |
| Julien et al,[16] 2021 | ALD-related outcomes | Modeling | Projected 18,700 additional decompensated cirrhosis (including 1000 HCC cases) with 8000 additional deaths between 2020 and 2040 from 1-y increase in alcohol use. |
| Deutsch-Link et al,[17] 2022 | ALD-related mortality | Cross-sectional | Outcomes increased by 21% in males and 27% in females in 2020 vs 2019. |
| Alcoholic hepatitis | | | |
| Sohal et al,[18] 2022 | AH hospitalizations | Retrospective multicenter cohort | Increased AH hospitalizations by 51% in 2020 vs 2019 (100% increase in <40 y age and 125% increase in females). |
| Damjanovska et al,[19] 2022 | AH incidence | Retrospective national database study on over 8 million patients between 06/2020 and 06/2021, and over 6.5 million before 06/2020 | AH diagnosis in 98.5/100,000 between 06/2020 and 06/2021 vs 35.6/100,000 before 06/2020 with highest increase in black patients. |
| Gonzalez et al,[20] 2022 | AH hospitalizations | Retrospective single-center cohort | AH hospitalizations increased by more than 50% in 2020 vs 2016–2019 |

*Abbreviations:* AH, alcoholic hepatitis; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; HCC, hepatocellular carcinoma.

*Adapted from* Deutsch-Link S, Jiang Y, Peery AF, Barritt AS, Bataller R, Moon AM. Alcohol-Associated Liver Disease Mortality Increased From 2017 to 2020 and Accelerated During the COVID-19 Pandemic. Clin Gastroenterol Hepatol. 2022 Sep;20(9):2142-2144.e2. https://doi.org/10.1016/j.cgh.2022.03.017. Epub 2022 Mar 19. PMID: 35314353; PMCID: PMC8933289.

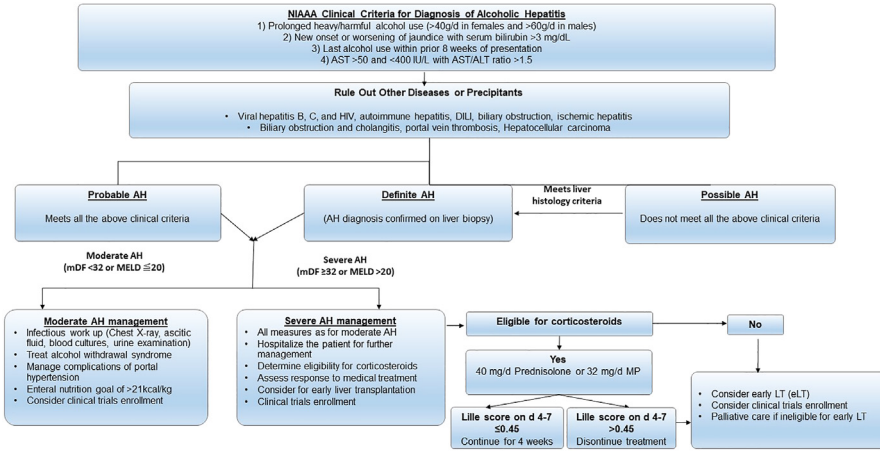


**Fig. 1.** NIAAA Alcoholic Hepatitis Consortia. ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; CXR, chest X-ray; DILI, drug-induced liver injury; HCC, hepatocellular carcinoma; LT, liver transplant; mDF, Maddrey Discriminant Function; MELD, Model for End-Stage Liver Disease; UA, urinalysis; UC, urine culture.

perivenular hepatocyte necrosis and pericellular fibrosis with chicken wire appearance is characteristic findings and is present in most severe cases.[3]

## DETERMINING PROGNOSIS

### *Clinical Models*

Maddrey Discriminant Function (mDF) and Model for End-Stage Liver Disease (MELD) score are most commonly used to stratify disease severity and candidacy for corticosteroid treatment (MELD >20, mDF $\geq$32).[24] Other scores such as Glasgow Alcoholic Hepatitis Score (GAHS) and age, serum bilirubin, International Normalized Ratio (INR), and serum creatinine (ABIC) score have also been used.[25,26] In an international study assessing performance characteristics of prognostication tools, the MELD score demonstrated a higher area under the receiving operating characteristic curve (AUROC) in predicting mortality at 28 and 90 days compared with mDF, MELD-Na, GAHS, and ABIC scores.[27]

Among corticosteroid-treated patients, Lille score at 1 week is used to determine treatment response, with the algorithm factoring mainly change in bilirubin along with several pretreatment variables. With the range of Lille score of 0 to 1, a score of $\leq$0.45 at 1 week defines response to treatment, and corticosteroids are discontinued at 1 week in nonresponders.[28] It has been further stratified to define complete responders (Lille <0.16), partial responders (Lille 0.16–0.56), and null responders (Lille >0.56) with 28-day survival strongly correlated to this stratification (91%, 79%, and 53%, respectively).[29] The Lille score at day 4 can be used if patients are ready for discharge, and its accuracy in determining treatment response is similar to day-7 Lille with a 91.1% agreement ($\kappa = 0.82$, $P < .001$).[30] A combination of a static model with baseline MELD score and a dynamic model with day-7 Lille score is better than mDF + Lille or ABIC + Lille in determining mortality at 2 and at 6 months.[31] As none of the clinical scores is an ideal model with limitations of all scores (**Table 2**),[32] the search for an ideal score continues for an improved diagnostic and prognostic biomarkers.

Several noninvasive biomarkers have been assessed aiming to improve the accuracy of diagnosis and in predicting prognosis of AH (**Table 3**). However, none of these is currently available for routine use in clinical practice.[40]

**Table 2**
**Comparison of prognostic models for alcoholic hepatitis**

| Model | Type of Model | Components<br>*Link to online calculator* | Advantages | Disadvantages |
|---|---|---|---|---|
| mDF | Static | PT, total bilirubin<br>https://www.mdcalc.com/calc/56/maddreys-discriminant-function-alcoholic-hepatitis | • Oldest validated model to assess the disease severity<br>• Commonly used in clinical trials<br>• Simple bedside calculation | • Use of PT, which is not standardized across laboratories<br>• Low specificity (62%)[32] |
| MELD | Static | Total bilirubin, INR, creatinine<br>https://www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/meld-model/itt-20434705 | • Best validated score to predict disease severity<br>• Can be used to determine need for corticosteroids | • Requires online calculator. |
| GAHS | Static | Age, total bilirubin, PT, BUN, WBC<br>https://www.mdcalc.com/calc/680/glasgow-alcoholic-hepatitis-score | • Better performance than mDF<br>• Simple bedside use in clinical practice | • Use of PT, which is not standardized across laboratories<br>• Not validated outside of the United Kingdom. |
| ABIC | Static | Age, total bilirubin, creatinine<br>https://www.mdcalc.com/calc/10136/abic-score-alcoholic-hepatitis | • Uses INR as opposed to PT | • Not frequently used<br>• Not validated outside of Spain |
| AHHS | Static | Fibrosis, bilirubinostasis, PMN infiltration, mega mitochondria<br>https://globalrph.com/medcalcs/alcoholic-hepatitis-histological-score-ahhs/ | • Can help rule out alternative disease processes.<br>• Can highlight features associated with favorable prognosis such as mega mitochondria and marked PMN infiltration | • Biopsy rarely performed<br>• Poor inter-provider reliability on interpretation of overall and different histologic findings.<br>• Accuracy in predicting disease severity lower than clinical scores. |
| Lille | Dynamic | Age, albumin, PT, creatinine, day 1 total bilirubin, day 7 total bilirubin<br>http://www.lillemodel.com/score.asp | • A validated dynamic model to determine response to medical treatment. | • Use of PT, which is not standardized across laboratories<br>• Complex score which requires an online calculator. |

*Abbreviations:* ABIC, age, bilirubin, INR, and creatinine; AHHS, alcoholic hepatitis histologic score; BUN, blood urea nitrogen; GAHS, Glasgow Alcoholic Hepatitis Score; mDF, Maddrey Discriminant Function; MELD, Model for End-Stage Liver Disease; PMN, polymorphonuclear neutrophils; PT, prothrombin time; WBC, white blood count.

**Table 3**
**Emerging biomarkers for alcoholic hepatitis diagnosis, prognosis, and assessment of treatment response**

| Biomarker | Summary | Test Characteristics |
|---|---|---|
| Biomarkers for Diagnosis of AH | | |
| Breath TAP (triethylamine, acetone, and pentane) | Volatile compounds in breath samples, measured by mass spectrometry | 97% sensitivity and 72% specificity for a TAP score of 28%; 80% sensitivity and 86% specificity for a score of 51.[33] |
| Cytokeratin-18 M65 level | Cytokeratin-18 is an intermediate filament protein released from damaged hepatocytes. Measured by ELISA for M65 and M30, which are circulating fragments of cytokeratin-18. | 67% sensitivity and 92% specificity at an M65 > 2000 IU/L; 93% sensitivity and 62% specificity at M65 < 641 IU/L.[34] |
| miRNA-192 | MicroRNAs are small, non-coding segments of RNA involved in regulation of gene expression. Measured by quantitative PCR. | AUC of 0.95 for diagnosis of AH.[35] |
| Biomarkers to predict prognosis of AH patients | | |
| Cytokeratin-18 M30 and M65 level | Measured by ELISA for M65 and M30, which are circulating fragments of cytokeratin-18. | AUROC for M30 was 0.616 and AUROC for M65 was 0.627 for 90-d mortality.[36] |
| Total and conjugated bile acids | Total bile acids and conjugated acids increase in AH due to cholestasis and further propagate liver injury. Measured by mass spectrometry. | Correlates with MELD ($P$ = .06).[37] |
| FGF19 | Negative feedback regulator of bile acid synthesis. Measured by ELISA for serum FGF19. | Correlates with 30-d mortality in patients with MELD $\geq$29.[37] |
| CD163 | Marker of inflammatory macrophage activation. Measured by ELISA for serum CD163. | Independent predictor of 84-d mortality. Correlates with MELD and GAHS ($P$ < .02).[38] |

| | | |
|---|---|---|
| LPS | Marker of bacterial translocation. Measured by a quantitative chromogenic assay. | 3.6% 90-d mortality with serum LPS ≤1.3 EU/mL compared with 50% mortality with serum LPS >1.3 EU/mL ($P < .001$).[39] |
| Treatment response | | |
| Cytokeratin-18 M30 level | Cytokeratin-18 is an intermediate filament protein released from damaged hepatocytes. Measured by ELISA for M65 and M30, which are circulating fragments of cytokeratin-18. | Improved 90-d survival in patients treated with corticosteroids when M30 > 5000 U/L (Odds Ratio [OR] 0.433, $P = .0398$).[36] |
| LPS | Marker of bacterial translocation. Measured by a quantitative chromogenic assay. | 100% of patients with serum LPS ≤1.3 EU/mL responded to corticosteroids, whereas 61.1% of patients with serum LPS >1.3 EU/mL were nonresponder ($P = .006$).[39] |

*Abbreviations:* AUC, area under curve; AUROC, area under receiver operating curve; CD163, Cluster of Differentiation 163; ELISA, enzyme-linked immunosorbent assay; FGF19, fibroblast growth factor 19; LPS, lipopolysaccharide; MELD, Model for End-Stage Liver Disease; miRNA, microribonucleic acid; PCR, polymerase chain reaction.

## TREATMENT

### *Nutrition*

Malnutrition is a frequent complication in AH patients as this is a catabolic condition due to systemic inflammation. In an observational study among hospitalized veterans with AH, an in-hospital mortality of over 90% was observed with a daily caloric intake of below 1000 kilocalories (kcal) and everyone survived the hospitalization if the daily caloric intake was over 3000 kilocalories. A randomized trial comparing corticosteroids vs. enteral nutrition supplementation of 2000 kcal/d via nasogastric did not show any significant difference in 28-day mortality.[41] In another randomized controlled trial, 174 patients with biopsy-proven severe AH were randomized to enteral nutrition for 14 days as an adjunct to corticosteroid therapy versus corticosteroids alone. Although there was no difference in mortality at 1 or 6 months in this study, daily caloric intake below 21.5 kcal/kg/d, irrespective of the study arm, was associated with higher 6-month mortality (65.8% vs 33.1%, $P < .001$).[42] In addition, almost half of the patients were unable to tolerate the nasogastric tube for the entirety of the planned 14-day treatment duration. Clearly, a daily caloric intake should be monitored among hospitalized patients who are suspected of poor oral intake and nutritional supplementation recommended for those with daily intake below 1200 calories. Oral route is preferred, and a parenteral route is used if oral route is not possible.[43]

### *Pharmacological Therapies*

Corticosteroid (prednisolone 40 mg/d or methylprednisolone 32 mg/d) is recommended as the first-line treatment of severe AH patients.[43–45] However, the efficacy of corticosteroids in AH has remained conflicting across studies since the first report of a randomized controlled trial in 1971.[46] The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) study randomized 1103 severe AH patients but could only demonstrate a modest 28-day survival benefit of prednisolone of 86.2% compared with 82% survival among placebo-treated patients, $P = .056$.[47] Two separate meta-analyses, including the STOPAH study confirmed that prednisolone improves the 28-day survival by 46% and 36%, respectively. However, none of these meta-analyses showed any benefit of corticosteroids at 3 or 6 months.[29,48]

Apart from the limited survival benefit, 30% to 40% of patients remain ineligible for corticosteroids due to relative contraindications such as active bacterial infection, gastrointestinal bleeding, and hepatorenal syndrome. Further, only 40% to 50% of those treated with corticosteroids can complete the full 28-day regimen, as the treatment has to be discontinued in 40% to 50% of nonresponders at 1 week of treatment due to increased risk of bacterial and fungal infections in these with continuation of treatment without any benefit and unpredictable response to treatment in 50% to 60% patients.[28,49] Moreover, corticosteroids are not recommended for patients with moderate AH (MELD score 11–20), a disease with up to 10% 3-month mortality.[50] These limitations of corticosteroid therapy result in their heterogeneous use, with only 25% of providers reported to use these drugs in severe AH patients.[51,52]

The use of corticosteroids can be optimized with simple biomarkers with personalized use in those likely to respond to these medications. For example, serum levels of bacterial DNA at baseline among patients enrolled in the STOPAH study were associated with a risk of bacterial infection after exposure to corticosteroids. In a retrospective, multicenter international cohort of 3,380 patients with severe AH, benefit of corticosteroids was observed between MELD scores of 21 and 51, with the maximum benefit among those with MELD scores between 25 and 39 (Hazard Ratio [HR] 0.61;

95% CI 0.39–0.95; $P = .027$).[24] Based on these data, corticosteroids can be personalized in eligible patients with MELD scores between 25 and 39 for the maximum survival benefit.

Pentoxifylline, a phosphodiesterase inhibitor has historically been used for the treatment of severe AH based on its documented survival benefit in the initial seminal study.[53] However, based on the lack of benefit in the STOPAH study and subsequent meta-analyses, this is currently not recommended as a treatment option for patients with severe AH.[54] Antagonists of Tumor Necrosis Factor-Alpha (TNF-$\alpha$) such as infliximab and etanercept also failed and in fact were associated with worse survival in the intervention arm due to the development of infection with these drugs. Extracorporeal cellular therapy (ELAD), which uses hepatoblastoma-derived C3A cells expressing anti-inflammatory proteins in addition to growth factors, has been studied as an ancillary treatment modality for severe AH. In a trial randomizing patients with standard of care therapy (corticosteroids or pentoxifylline) versus standard of care therapy in addition to 3 days of ELAD, overall survival was not different between the two groups at 91 days with a 47.9% mortality rate in the ELAD group and 47.7% mortality rate in the control group (HR 1.03; 95% CI 0.69–1.53).[55]

## *Emerging Therapies*

Given the limitations of currently existing treatment options, treatment strategies focusing on multiple targets (**Fig. 2**) are currently being investigated as potential therapies for patients with AH.[56,57]

### *Therapies targeting gut dysbiosis*

Alcohol consumption is associated with intestinal bacterial overgrowth with reduced alpha diversity, disruption of the intestinal tight junctions with bacterial translocation to the portal circulation, and impaired Kupffer cell clearance of lipopolysaccharide (LPS).[58] Pathogen-associated molecular patterns such as LPS are recognized by toll-like receptor 4 on the surface of Kupffer cells and other hepatic cells leading to cytokine signaling and activation of inflammatory pathways.

Fecal microbiota transplant (FMT) is a promising tool for modulating the gut-liver axis and improving the alpha diversity of the gut microbiome. In a pilot study of 195 patients with ALD, the use of FMT among eight steroid ineligible patients was associated with improved survival compared with historical controls treated with standard of care (87.5% vs 33.3%; $P = .018$).[59] In a phase 1 double-blinded randomized control trial, the use of FMT was associated with a significant reduction in alcohol craving among a higher proportion of treated patients compared with placebo (90% vs 30%).[60] Another retrospective analysis comparing long-term outcomes in patients with corticosteroid-responsive severe AH receiving healthy-donor FMT via nasoduodenal tube for 7 days compared with corticosteroids found a significantly lower incidence of alcohol relapse was in the FMT group (28.6% vs 53.8%; $P = .04$).[61] In addition, FMT treatment was associated with significantly lower incidence of hepatic encephalopathy, ascites, infections, and reduced risk of hospitalization.

### *Therapies targeting inflammatory pathways*

Anakinra is an interleukin (IL)-1 receptor antagonist that targets IL-1, a major cytokine in the pathogenesis of AH. Randomized controlled trial from the Defeat Alcoholic Steatohepatitis compared combination of Anakinra (IL-1 receptor antagonist), pentoxifylline, and zinc oxide against corticosteroids alone in severe AH. This was a negative trial with no survival benefit at 28, 90, or 180 days in the intervention arm.[62] However, the risk of fungal infection was lower in the intervention arm (0% vs 5%, $P = .02$).

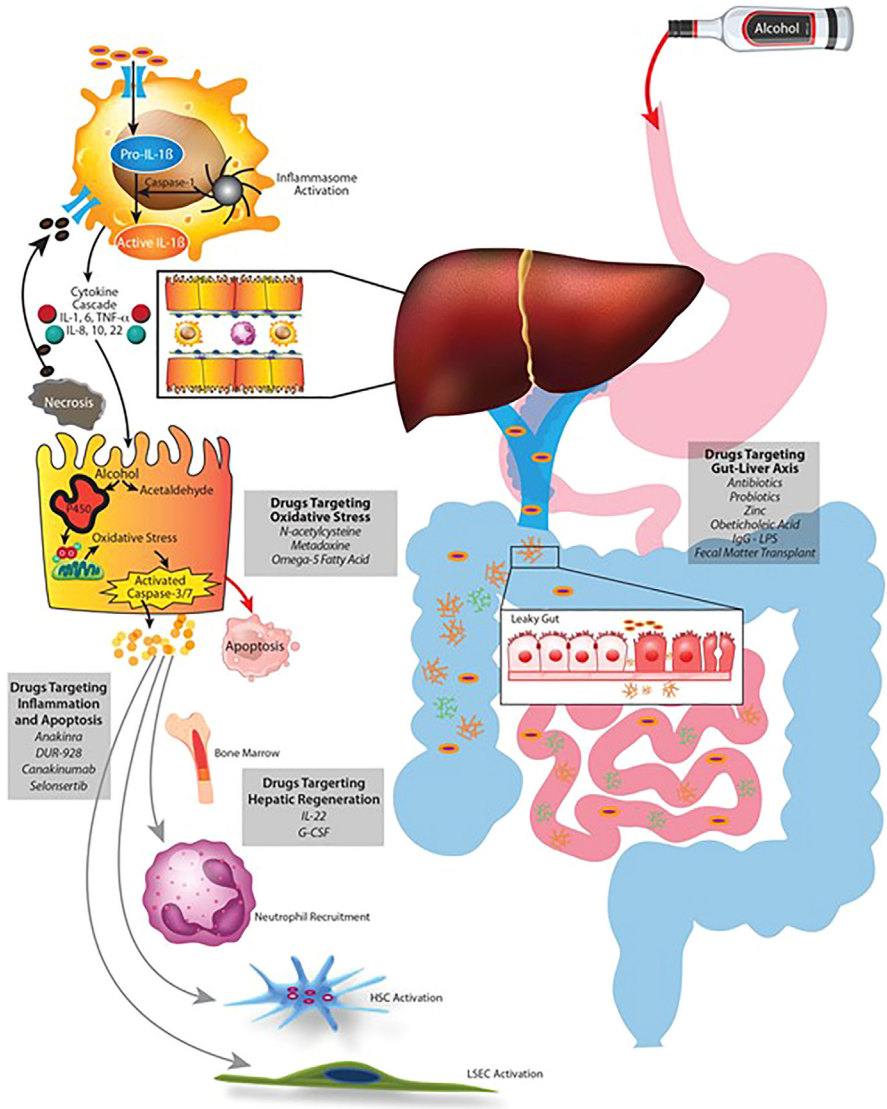


**Fig. 2.** Diagnosis and treatment of alcoholic hepatitis.

Another double-blind randomized placebo-controlled trial of adults with severe AH (MELD 20–35) compared anakinra combined with zinc with prednisone. This trial was terminated early due to reduced survival and higher occurrence of acute kidney injury in the active arm of anakinra (69.9% vs 91%, $P = .003$ and 41% vs 21%, $P = .005$, respectively).[63]

DUR-928 is an endogenous sulfated oxysterol which reduces the expression of pro-inflammatory cytokines, regulates lipid metabolism, and stimulates cell survival. In a Phase 2a study on 18 patients with moderate and severe AH, there was an 89% response rate as reflected by a Lille score on day 7 of treatment.[57] There was a significant decrease in MELD at Day 28 in all patients ($P = .005$) and in those with baseline

MELD 21 to 30 ($P = .051$). None of the enrolled patients died during the study period of 28 days. DUR-928 was also found to be safe and well-tolerated.[64]

***Therapies targeting oxidative stress***

N-acetylcysteine (NAC) is an antioxidant that replenishes glutathione levels and attenuates free radical-induced injury. NAC combined with corticosteroids in one study reduced mortality at 1 month (8% vs 24%; $P = .006$), however, failed to meet the primary outcome of 6-month survival.[65] However, NAC was beneficial in reducing the risk of infection and of hepatorenal syndrome.

Metadoxine, an antioxidant, increases hepatic glutathione and adenosine triphosphate levels. In a randomized controlled trial, metadoxine in combination with prednisolone versus prednisolone alone improved patient survival in severe AH patients at 3 months (68.6% vs 20%, $P = .0001$) and at 6 months (48.6% vs 20%, $P = .003$).[66] Interestingly, patients receiving metadoxine maintained greater abstinence compared with those receiving placebo (74.5% vs 59.4%, $P = .02$). Larger trials are needed to validate these results.

***Therapies enhancing liver regeneration***

IL-22, a cytokine of IL-10 family, is known to provide hepatoprotective effects to improve oxidative stress and fibrosis, in turn promoting liver repair and regeneration.[56,67] A phase 2 trial in 24 patients with moderate and severe AH (MELD 11–28) showed an excellent safety profile of two infusions on days 1 and 7 of F-652, a recombinant fusion protein combining IL-22 and immunoglobulin G2. This was a dose-escalating study of 10, 30, and 45 mcg/kg of the active drug, with three patients enrolled with moderate and three with severe AH at each of three different doses. The drug significantly improved the MELD score and serum aminotransferases at days 28 and 42 from baseline, $P < .005$. A total of 83% patients enrolled in the study responded as determined by Lille score at day 7 of treatment, as compared with 6% to 12% of untreated cohorts and 56% in a prospective cohort treated with corticosteroids.[68] The drug was associated with reduction in the levels of circulating extracellular vesicles at 28 days and of cytokine levels at days 28 and 42[68].

Granulocyte-colony stimulating factor (G-CSF) is a glycoprotein which stimulates the bone marrow to release neutrophils and stem cells into the circulation, subsequently stimulating hepatocyte regeneration as well as proliferation of hepatocyte progenitor cells. A meta-analysis pooling data from seven randomized controlled trials (five from Asia and two from Europe) demonstrated an overall 90-day survival benefit in the G-CSF treated group (OR 0.28; 95% CI 0.09–0.88).[69] However, there was a high degree of heterogeneity with the Asian cohort demonstrating the majority of the benefit, whereas there was a trend toward worse outcomes in the G-CSF group in the European cohort (OR 1.89; 95% CI 0.90–3.98). Studies are in progress to substantiate the role of G-CSF in the United States, in the management of patients with severe AH (**Table 4**).

## *Early Liver Transplantation*

Traditionally, transplant centers until a decade ago required a minimum 6-month abstinence period before consideration for LT.[70,71] However, several studies have shown that minimum abstinence period of 6 months to be a poor predictor of recurrence of alcohol use after LT.[72,73] More consistent and accurate predictors are younger age, psychosomatic status, psychiatric comorbidities, failed previous rehabilitation attempts, and family history of alcoholism.[74,75] The 6-month rule was challenged in a prospective study from the Franco-Belgian group, with the use of early LT (eLT) in

**Table 4**
**Active or recently completed trials of emerging therapeutic agents for alcoholic hepatitis**

| Therapeutic Agent | Mechanism | Study Design | Disease Severity | Primary Endpoint | Trial Identifier | Current Status |
|---|---|---|---|---|---|---|
| Therapies Targeting Oxidative Stress | | | | | | |
| N-acetylcysteine (NAC) | Antioxidant | • RCT: NAC + CS vs CS<br>• RCT: NAC + CS vs CS | • mDF ≥32<br>• mDF ≥32 | • All-cause mortality at 6 mo<br>• Improvement in monocyte oxidative burst | • NCT05294744<br>• NCT03069300 | • Not yet recruiting<br>• Phase 3 recruiting |
| Metadoxine | Antioxidant | RCT: CS, PTX, metadoxine + CS, metadoxine + PTX | mDF ≥32 | Survival at 30 d | NCT02161653 | Phase 4 completed, improved survival at 3 and at 6 mo as well as improved abstinence |
| Omega 5 fatty acid | Peroxisome Proliferator Activated-Receptor (PPAR) gamma agonist | Placebo controlled RCT: Omega 5 fatty acid + SOC vs placebo + SOC | mDF ≥32 | 30-d survival | NCT03732586 | Recruiting |
| Therapies Targeting Hepatic Inflammation | | | | | | |
| DUR-928 (endogenous sulfated oxysterol) | Hepatic regeneration, inflammatory response, cell survival | Placebo-controlled RCT: DUR-928 30 mg vs DUR 928 90 mg vs placebo + SOC | MELD 21–30 and mDF ≥32 | Difference in 90-d mortality or liver transplant | NCT04563026 | Phase 2 recruiting |
| Anakinra | IL-1 receptor antagonist | RCT: anakinra + zinc + pentoxifylline vs CS | mDF ≥32 and MELD >20 | Survival at 6 mo | NCT04072822 | Phase 2 completed, no difference in survival, but lower rate of fungal infection in the active arm |

| | | | | | | |
|---|---|---|---|---|---|---|
| Canakinumab | IL-1β antagonist | Placebo controlled RCT: canakinumab vs placebo | mDF ≥32 and MELD ≦27 | Improvement in AHHS after 28 d | NCT03775109 | Phase 2 completed, no improvement in survival |
| Selonsertib | ASK-1 antagonist | Placebo-controlled RCT: selonsertib + CS vs selonsertib + placebo | mDF ≥32 | Safety and SAE at 28 d + 30 d | NCT02854631 | Phase 2 completed, no improvement in survival or in liver function |
| Emricasan | Pan-caspase inhibitor | Placebo controlled RCT: Emricasan vs placebo | MELD 21–34 or MELD 35–40 if SOFA <10 | Survival at 28 d | NCT01912404 | Phase 2 terminated due to concerns of Pharmacokinetics / Pharmacodynamics (PK/PD) concerns |
| Therapies Enhancing Hepatic Regeneration | | | | | | |
| G-CSF | Hepatic regeneration | Placebo-controlled RCT: prednisolone + G-CSF vs prednisolone vs G-CSF | mDF≥ 32 | Survival at 90 d | NCT04066179 | Unknown recruitment status |
| IL-22/F-652 | Regeneration, antioxidant, anti-inflammatory | Open-label, dose-escalating trial | MELD 11–28 | Safety and SAE at 42 d | NCT02655510 | Phase 2 completed, demonstrated safety |
| Therapies Targeting Gut-Liver Axis | | | | | | |
| FMT | Modulation of gut microbiome | • Placebo-controlled RCT: FMT + SOC vs placebo + SOC<br>• RCT: FMT vs SOC (steroid-ineligible patients) | • MELD >15 and/ or mDF ≥32<br>• mDF ≥32 and MELD ≥20 | • Survival at 12 mo, change in microbiome at different time points<br>• Survival at 3 mo and transplant-free survival | • NCT05006430<br>• NCT05285592 | • Phase 1 recruiting<br>• Recruiting |

(*continued on next page*)

**Table 4**
**(*continued*)**

| Therapeutic Agent | Mechanism | Study Design | Disease Severity | Primary Endpoint | Trial Identifier | Current Status |
|---|---|---|---|---|---|---|
| Purified bovine colostrum | Immunoglobulin G (IgG) antibodies against LPS | Placebo-controlled RCT: bovine colostrum vs placebo | mDF ≥32 and MELD ≥21 | Survival at 3 mo | NCT02473341 | Phase 3 recruiting |
| Augmentin | Antibiotic | Placebo-controlled RCT: augmentin + CS vs CS | mDF ≥32 and MELD ≥21 | Survival at 2 mo | NCT02281929 | Phase 3 completed, pending final results |
| Rifaximin | Antibiotic | Case control: rifaximin + SOC vs SOC | mDF ≥32 | Development of any bacterial infection | NCT02116556 | Phase 2 completed, significant decrease in infection and liver-related complications |
| *Lactobacillus rhamnosus* GG | Probiotic | Placebo-controlled RCT: Lactobacillus vs placebo | MELD<20 | Change in MELD | NCT01922895 | Phase 2 terminated due to lack of funding |
| Obeticholic acid (OCA) | FXR agonist; bile acid agonist, anti-inflammatory | Placebo-controlled RCT: OCA vs placebo | MELD 12–19 | Change in MELD at 6 wk | NCT02039219 | Phase 2 terminated due to post-marketing reports of hepatotoxicity |

*Abbreviations:* AHHS, alcoholic hepatitis histologic score; ASK, apoptosis signaling kinase; CS, corticosteroid; FMT, fecal microbiota transplant; FXR, Farnesoid X receptor; G-CSF, granulocyte-colony stimulating factor; IL, interleukin; LPS, lipopolysaccharide; mDF, Maddrey discriminant function; MELD, Model for End-Stage Liver Disease; NCT, clinical trial identifier; PTX, pentoxifylline; RCT, randomized-controlled trial; SAE, serious adverse event; SOC, standard of care; SOFA, sequential organ failure assessment.

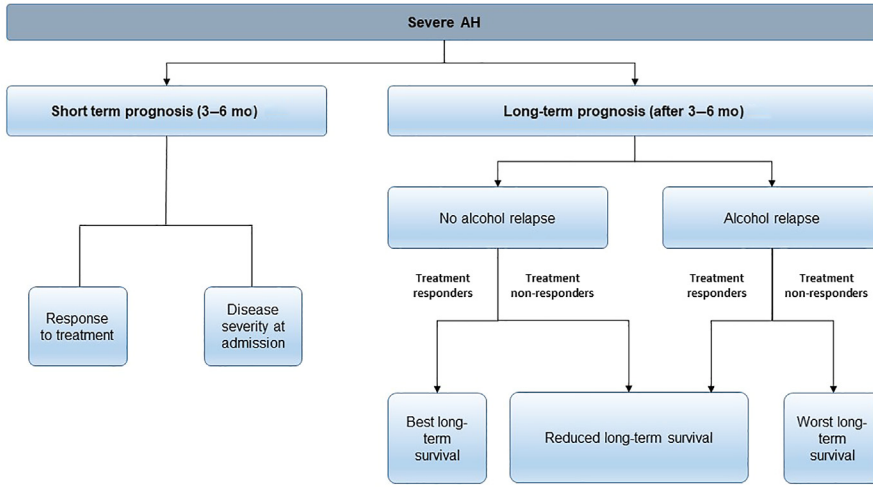


**Fig. 3.** Determinants of short-term and long-term prognosis in severe alcoholic hepatitis.

selected 26 severe AH patients with their first AH episode who did not respond to corticosteroids and had excellent psychosocial status. Compared with matched 26 patients who did not meet the selection criteria, eLT provided survival benefit with patient survival of 77% at 6 months compared with 23% survival among non-transplanted patients at same time points. Recurrence of alcohol use was acceptable in three patients at 2 years, two of these patients engaging in harmful alcohol use. Further, all the deaths in the patients in the study were within first 6 months, confirming that these patients cannot afford to wait for 6 months to meet with the requirement of minimum of 6 months abstinence.[50] Since then, other studies have shown similar benefit with eLT in severe AH patients.[76–79] In a retrospective study of patients who underwent eLT for severe AH, 1-year survival (94%) and 3-year survival (84%) were found to be similar to LT for other indications. The cumulative incidence of alcohol use post-LT was 25% at 1 year and 34% at 3 years with the only predictor for alcohol use post-LT being younger age on multivariable analysis.[76] In a meta-analysis including 11 studies, similar rates of relapse were observed between patients with severe AH undergoing eLT compared with those with cirrhosis undergoing elective transplantation (OR = 1.68, 95%CI = 0.79–3.58, $P$ = .2). Furthermore, 6-month survival rates were similar between both groups (OR = 2.00, 95% CI = 0.95–4.23).[80] Currently, eLT is recommended among highly selected patients with severe AH.[43–45]

The awareness on benefits of eLT has increased enthusiasm within the transplant community with an increasing use of eLT for severe AH patients. However, the fairness of allocating organs to patients with AH has been questioned, as these patients may be perceived as having played a role in the evolution of their disease by some individuals, whereas others consider a more empathetic approach to them and consider dual pathology in these patients of liver disease and of AUD.[81,82] However, ethical implications of using a scarce resource for AH, risk of recurrent alcohol use questioning the utility of LT, and lack of accurate objective scores in predicting candidates at high risk for alcohol recurrence after LT have resulted in a significant heterogeneous use of eLT across providers and transplant centers.[83–85] Clearly, multicenter prospective studies are needed to refine selection criteria and develop a protocol which can be uniformly followed across centers for candidate selection for eLT in AH patients.

### *Treatment of Alcohol Use Disorder*

Alcohol abstinence is the single most important determinant of long-term patient survival among patients surviving the initial AH episode (**Fig. 3**).[86–88] In a prospective study following patients for a maximum duration of 12 years after a diagnosis of AH, alcohol relapse of greater than 30 g per day was associated with an increased risk of death (HR 3.9, 95% CI 2.61–5.82) 6 months after the time of initial AH diagnosis.[89] However, maintaining abstinence is difficult with only 45% and 37% patients enrolled in the STOPAH study remaining abstinent at 3 months and at 1 year respectively.[47] Clearly, treatment of comorbid AUD becomes crucial in ALD patients using behavioral therapies (cognitive behavioral therapy, motivational interviewing, and support groups such as Alcoholics Anonymous) and/or pharmacologic therapies. FDA-approved medications (disulfiram, naltrexone, and acamprosate) to treat AUD have not been studied in randomized studies among patients with ALD. In a retrospective study on 160 (100 with liver disease of which 47 had decompensated cirrhosis) patients, naltrexone use was safe as evaluated by changes in liver aminotransferases. Further, 2 years risk of hospitalization was reduced with naltrexone use of 30 days or more.[90] Of the non-FDA-approved therapies, baclofen has been studied in the context of ALD and AH. In a retrospective study, the use of baclofen in 35 AH patients once serum bilirubin level has reduced to below 10 mg/dL and encephalopathy has resolved was safe with 97% of patients remaining abstinent over a mean follow-up period of 5.8 months.[91] Currently, baclofen and gabapentin are recommended treatment options for advanced ALD patients including those with AH.[43–45,92]

However, in the real world, AUD treatment is rarely used.[93] In a large study of 35,682 veterans with a diagnosis of AUD and cirrhosis, only 14% received AUD treatment, with pharmacotherapy used in only 1.4%.[93] Several barriers at the level of patients (reduced awareness, perception of stigma with ALD diagnosis, focus on liver disease and not on AUD), clinicians (lack of time and training in addiction medicine), and administration (lack of initiative, focus on other drug and substance use disorders, and siloed practices of addiction and hepatology specialists) limit addressing AUD in ALD patients.[94,95] Further, several administrative and system wide barriers related to billing, cost, and resources limit establishing multidisciplinary integrated care models to address the dual pathology of liver disease by hepatologists and AUD by addiction team under one roof in a collocated clinic.[94,96] Strategies are needed to overcome these barriers are needed to promote and establish integrated care of ALD patients with hepatology and addiction teams during pre-transplant as well as post-transplant care, with improvement in long-term outcomes and survival of patients with ALD and AH.

## SUMMARY

The rising health care burden related to AH during the last decade and acceleration during the COVID-19 era has resulted in this disease entity emerging as an epidemic, especially in young individuals at the prime of their life. Further, in the background, there is a potential for high short-term mortality in most severe forms, whereas there is a lack of effective therapies, AH currently is an area of urgent attention from researchers to develop effective therapies, and from public health officials to derive strategies targeting to reduce the availability of alcohol in the community, especially through increase prices and higher taxation on alcohol. Several therapeutic targets are being examined, with some of these such as FMT, interleukin-22, DUR-928, and G-CSF being of potential promise. Early LT, in select cases, is emerging as a acceptable form of life-saving intervention. Although efforts are ongoing to develop newer

pharmacotherapies and strategies targeting alcohol use, it is critical to promote integrated multidisciplinary care models for control of alcohol use and improvement in long-term outcomes of patients with ALD and AH.

## CLINICS CARE POINTS

- Alcoholic hepatitis is characterized by new onset or worsening jaundice in the setting of heavy alcohol use and has significant short-term and long-term morbidity and mortality.
- Over the last decade, health care burden from alcoholic hepatitis has been increasing, and this has accelerated in the last 2 to 3 years during the COVID-19 pandemic.
- Corticosteroids, the mainstay of treatment for severe alcoholic hepatitis, is a suboptimal treatment, and there is a need for novel therapeutic agents.
- Several therapeutic targets are being examined, with some of these especially fecal microbiota transplant, interleukin-22, DUR-928, and granulocyte-colony stimulating factor (G-CSF) being of potential promise.
- Long-term prognosis of alcoholic hepatitis is determined by alcohol abstinence, and the treatment of the dual entities of liver disease and alcohol use disorder is critical.
- Integrated multidisciplinary care models with hepatology and addiction teams should be promoted to control alcohol use and improve long-term outcomes of patients with alcohol-associated liver disease and alcoholic hepatitis.

## DISCLOSURES

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