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Gaps in Knowledge and Research Priorities for Alcoholic Hepatitis

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Alcoholic hepatitis (AH) is a clinical syndrome that was classically characterized by increasing jaundice, hepatomegaly, fever, neutrophilia, and an aspartate aminotransferase (AST):alanine aminotransferase (ALT) ratio of >2 .¹ It is a major cause of liver-related hospitalizations in those with a history of heavy alcohol consumption and is also a leading etiology associated with recurrent hospitalizations.² Unfortunately, despite its clinical relevance, there are many gaps in knowledge related to this syndrome that represent barriers to the development of effective preventive surveillance, early detection, and therapeutic strategies. This article summarizes the gaps in knowledge and identifies research priorities to fill these gaps (Table 1).

Demographics, Epidemiology, and Burden of Disease

In the United States, the total cases of AH-related hospitalization have increased from 249,884 (0.66% of total admission) in 2002 to 326,403 (0.83% of total admission) in 2010.² It is also important to identify whether there are specific populations with a particularly high prevalence. As the baby boomer generation ages, it is also important to determine the spectrum of comorbidities present in those with AH and how they impact outcomes, including the response to therapy. A population that needs much more characterization is those who are repeatedly admitted for AH. It has been shown that recidivism is closely linked to such recurrent bouts of AH.³ Finally, accurate data on overall health care resource utilization along with the financial and social impact of days of work lost and the impact on caregivers and potential employers, as well as from disability are needed to guide health care policy related to reimbursement of preventive and treatment strategies and funding for research.

Conflicts of interest

The authors disclose the following: Arun Sanyal: Clinical trial site PI for NIAAA-industry sponsored trials for alcoholic hepatitis (Conatus, Intercept, Immuron) and Ad hoc consultant to Intercept +Immuron. The remaining authors disclose no conflicts.

Histologic and Clinical Classification

Bringing clarity to the nomenclature and classification of AH is critically needed to evaluate fully the true prevalence and health burden owing to AH and to inform methods to prevent and treat this condition.

ICD-10 Classification

A major gap relates to confusion in nomenclature of the disease. The *International Classification of Diseases*, 10th edition (ICD-10) identifies several phenotypes of alcohol-related liver disease (K70). Specifically, the K70.1 code identifies those with AH. However, several clinical phenotypes are included under this code and include acute and chronic AH with or without cirrhosis. There are additional codes for AH with ascites (K70.11). Although some of these changes from the ICD-9 classification identify specific clinical subsets of patients with potentially variable prognosis, they also confound a clear assessment of the burden of disease, especially given variable billing and coding practice patterns.

Histology

The histologic spectrum of AH, however, includes features not usually seen in nonalcoholic steatohepatitis, such as cholestasis, especially in those with jaundice.⁴ There is an immediate need to reevaluate the histologic spectrum of AH and relate these to clinical phenotypes to allow risk stratification, identification of key mechanisms driving the histology, and the risk of progression. The grading of the severity should be validated further against clinical outcomes. Recent studies linking bilirubinostasis and fibrosis with a poor outcome and neutrophil infiltration to a better outcome are a step in the right direction.⁵ Well-defined criteria will be needed to optimize populations for future clinical trials and to identify the appropriate therapeutic targets in such populations.

Clinical Definitions

The clinical features of those with steatohepatitis can be quite variable and range from an asymptomatic state to jaundice, fever, neutrophilia, and an AST:ALT ratio of >2. One of the most important research priorities in this field is to develop a standard definition of the syndrome that is useful for clinicians to identify the disease, stratify subjects for the risk of mortality and morbidity, and engage in treatment and secondary preventive strategies.

Grading the Severity of AH

Several scoring systems have been developed to risk stratify subjects based on mortality and have been recently reviewed.⁶ Although the widely used Maddrey index and the Model for End-stage Liver Disease score provide information on short-term prognosis, they are less accurate in predicting long-term outcomes. A comprehensive model of the disease including all the factors that independently drive short-term and long-term morbidity and mortality, recidivism, risk of recurrent hospitalization, resource utilization, and failure of medical treatments remains to be developed.

Biomarker Development

Another area where there has been minimal progress is in the area of biomarker development to identify (1) those at risk for AH, (2) the presence of early phases of the disease, particularly in those who are likely to progress, (3) the optimal molecular targets for therapy, and (4) response to treatment. A recent serum metabolomics analysis of 25 patients with severe AH identified a panel of biomarkers for disease prognosis⁷; however, future studies in larger cohorts of AH patients are required to validate these bio-markers. In addition, the Lille criteria for response to steroids is an important step forward, but is limited by a high likelihood of meeting failure criteria in older subjects with a high baseline bilirubin.⁸

Risk Stratification and Biology of Disease

Despite extensive research on alcoholic liver disease (ALD) over the last 40 years,⁹ the pathogenesis of AH and the mechanisms that trigger AH in patients with chronic ALD remain largely unknown (Figure 1). In fact, there are several critical areas that need to be investigated in the near future.

Drinking Pattern

It is well-documented that the duration and amount of alcohol consumption are important factors contributing to AH.¹⁰ Binge drinking has been linked with the development of AH.¹¹ This notion is also supported by recent studies from animal models that acute binge ethanol feeding exacerbates markedly liver injury in chronically ethanol-fed mice.^{12,13} Future studies are needed to further investigate how irregular binge drinking triggers AH and to identify any other factors that may trigger AH in patients with chronic ALD.

Genetics

Although substantial data on the role of genetics in drinking behavior exist, there is a paucity of data linking genetics to the risk of development of AH. Although many genetic variants have been implicated in linking the susceptibility of ALD development, few have been confirmed.¹⁴ The PNPLA3 mutation is probably the first confirmed genetic risk factor for progression of both alcoholic and nonalcoholic steatohepatitis.¹⁵ Future genome-wide association studies and deep sequencing studies to define the novel genetic determinants of AH and its severity are needed.

Intestinal Contribution to Disease Pathogenesis

The role of the intestinal micro-biome in the development of ALD has been established.¹⁶ However, much remains unknown. Specifically, the linkage of changes in microbial populations to AH and its severity remains unclear. Also, how changes in microbiota contribute to disease pathogenesis is understood only partly. The role of microbiota and its metabolites on gut permeability, activation of systemic inflammatory responses, hepatic macrophage activation, hepatocellular function, and disease progression needs much further clarification. The cross-talk between diet, altered bile acid and biliary physiology, microbiome, and intestinal signaling to the liver and brain in AH also remains largely unknown. Specifically, the role of farnesoid X receptor and Takeda G-protein-coupled bile

acid receptor 5 signaling in the intestine in AH as drivers of altered hepatic microcirculation, bile flow, inflammation, and metabolic responses is an area that warrants active investigation. Another area of active investigation in ALD is modulation of the gut microbiome with the use of probiotics or prebiotics.

Immunologic Mechanisms

Activation of innate immunity is known to play an important role in promoting the development of chronic ALD,¹⁷ but the specific component(s) of innate immunity that triggers AH and contributes to liver failure in AH patients remain obscure. For example, activation of the lipopolysaccharide–Toll-like receptor 4–tumor necrosis factor (TNF)- α pathway is critical for the pathogenesis of ALD in mice.¹⁷ However, anti-TNF- α treatment failed to demonstrate beneficial effects in AH patients,¹⁸ raising a doubt about the key role of this pathway in AH pathogenesis. A recent study reported that interleukin (IL)-1 plays an important role in promoting ALD in mice,¹⁹ and a clinical trial of anti-IL-1 therapy is currently under investigation for the treatment of AH. These clinical trial results will reveal whether IL-1 is a key inflammatory mediator that triggers and promotes AH in patients.

Hepatic neutrophil infiltration is a hallmark of human AH, which is attributable to elevated hepatic expression of a variety of chemokines.²⁰ It has been hypothesized that, in severe forms of AH, neutrophils can produce high levels of oxidative burst that contributes to liver injury. Conversely, their phagocytic capacity is suppressed, which may contribute to increased susceptibility of AH patients to infection.²¹ The pathogenic function of neutrophils was also demonstrated in a mouse model of chronic-plus-binge ethanol feeding.¹² In contrast, a recent study reported that the presence of a marked neutrophil infiltration was associated independently with a favorable outcome, which may be attributed to neutrophil-mediated stimulation of liver regeneration.⁵ Collectively, neutrophils likely play complex roles in the pathogenesis of AH, and further investigation of their precise functions may help design better immune therapy for AH.

In contrast with the extensive research on innate immunity in ALD, activation of adaptive immunity has not been reported in rodent models of ALD. Interestingly, accumulating clinical evidence suggests that activation of adaptive immunity plays a role in promoting liver inflammation and injury in patients with AH,²² but its precise role remains obscure and needs further studies.

Cellular and Molecular Mechanisms of Injury

Historically, hepatocyte injury in ALD has been linked to the direct effects of alcohol, altered redox potential, exposure to toxic metabolic byproducts of alcohol, and inflammatory cytokines.⁹ The role of autophagy, unfolded protein response, notch signaling, and activation of hedgehog signaling in AH remains to be explored in detail. The role of micro-RNAs in regulating the metabolic, cell injury, and regenerative response remains relatively unknown and worthy of further investigation. Another important area of investigation includes the role of altered bile acid metabolism in hepatotoxicity and the metabolic reprogramming of cell function, structure, and fate. It is recognized that those with the greatest hepatic dysfunction from AH are often also severely malnourished. The role of underlying nutritional status and

cross-talk between the liver, striated muscle, adipose tissue, and the intestine in determining the development and severity of AH is yet another area of great importance that warrants further research. The role of lipotoxicity and the specific mechanisms by which cellular and extracellular signals converge of cell death pathways to sensitize and produce liver injury in AH is also understood only partially. The contribution of specific cell death pathways in the ultimate loss of hepatocytes and liver function needs to be clarified.

Impairment of Liver Repair

It is generally accepted now that impairment of liver regeneration (hepatocyte proliferation) is an important mechanism contributing liver failure in AH patients.²³ In contrast with impaired hepatocyte proliferation, AH is associated with significant ductular reaction and increased expression of liver progenitor cell (LPC) markers. These markers correlate positively with disease severity and short-term mortality in AH patients.²³ Presently, the mechanisms underlying impaired hepatocyte proliferation and increased ductular reaction/LPC proliferation in AH patients are understood poorly. The role of this ductular reaction/LPC proliferation remains unknown. Identification of these mechanisms and the function of ductular reaction/LPC proliferation may help to design a therapy for promoting liver regeneration in AH patients.

Impact of Underlying Comorbidities

Viral hepatitis, chronic alcohol consumption, and obesity are the 3 major factors causing liver diseases worldwide and often coexist. There are few studies that investigate the interaction of AH and viral hepatitis or obesity. Naveau et al^{24,25} reported that excess overweight is a risk factor for acute AH, yet diagnosis of acute AH in these studies, which was based on liver histology, was questionable because the clinical features of AH in these patients were not described. It is important to determine whether obesity is a risk factor for the development of clinical features of human AH.

Patient-Centered Outcomes for AH

Patient outcomes in AH are generally poor unless patients stop alcohol use in an early phase of the disease. In patients with fatty liver, continued alcohol drinking leads to cirrhosis in about 20% of patients. The 30-day mortality is about 20% in mild and moderate AH but it is >40% in severe AH. Long-term survival at 5 and 10 years varies from 0% to 80%.² About two-thirds of patients present with decompensated liver disease and 15% develop hepatocellular cancer.

Knowledge gaps in the natural history and cofactors in the progression of AH exist and need attention. There is an urgent need to identify predictors of disease progression and response to therapy. The greater predisposition of women to disease progression warrants further research. Definition of short- and long-term clinically meaningful outcomes in AH should facilitate and improve clinical trial design in this population.

Factors Affecting Outcomes

Patient outcomes in AH are affected by many factors, particularly behavioral elements, addiction, severity of the disease, and other comorbid conditions. Recent studies indicate that sepsis is the major cause of acute-on-chronic liver failure²⁶; the role of infection in AH needs to be confirmed in prospective studies. The study of the role of systemic inflammatory responses and microcirculatory dysfunction in driving severe AH has just begun,²⁷ and merits further attention. Furthermore, the potential relevance of dysalbuminemia and impaired capacity of albumin to buffer toxic hydrophobic compounds has not been studied. These should inform future strategies to prevent infection, early detection of infection, and management of infection as adjunctive or mainline treatment of AH.

There are also no well-defined and validated clinical models that are ready for clinical use for long-term risk stratification. The social, economic, behavioral, and organic factors that influence disease progression need to be clarified further; specifically, future research should focus on identification of key factors that can be targeted to reduce recurrent hospitalization and mortality, and improve the quality of life and functional status of individual patients. Such approaches need to be combined with additional strategies to reintegrate these subjects in to the mainstream of society.

Treatment of AH

Steroids have been the mainstay of treatment for those with severe AH, particularly in the presence of hepatic encephalopathy. However, they are contraindicated in the presence of infections, which are often concomitantly present. A recent, large, multicenter trial of pentoxifylline did not show any benefits over placebo. Therefore, the treatment of AH remains largely unsatisfactory.

Therapeutic Targets

There are a large number of potential therapeutic targets for AH. These include the microbiome, intestinal barrier, systemic and hepatic inflammatory responses, pathways involved in hepatocyte injury, cholestasis, and hepatic regeneration.²⁸ The recent initiative by the National Institute on Alcohol Abuse and Alcoholism to tackle several such targets in early phase clinical trials is hoped to validate these for more advanced phase clinical trials.⁶

Clinical Trials, End Points, and Regulatory Issues

A major gap in knowledge relates to study populations, trial design, and the identification of clinically meaningful endpoints for AH beyond mortality. Such trials should include consideration of changes in the placebo arms as a result of altered drinking behavior owing to participation in a clinical trial. The clinical trials must be integrated with strategies to prevent relapse and enhance long-term abstinence.

It is also unfortunate that AH largely remains an orphan condition in terms of involvement of the pharmaceutical sector for therapeutic development. The current paradigms for drug development and standards set by the Food and Drug Administration are a major barrier to therapeutic development for conditions like AH, which have a major negative impact on the

health of the people, but for which there is little enthusiasm in the pharmaceutical sector for drug development. There remains a great need for new policies to correct this situation.

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References

1. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med*. 2009; 360:2758–2769. [PubMed: 19553649]
2. Jinjavadia R, Liangpunsakul S. for the Translational Research and Evolving Alcoholic Hepatitis Treatment Consortium. Trends in alcoholic hepatitis-related hospitalizations, financial burden, and mortality in the United States. *J Clin Gastroenterol*. 2014 Jun 25. [Epub ahead of print].
3. Potts JR, Howard MR, Verma S. Recurrent severe alcoholic hepatitis: clinical characteristics and outcomes. *Eur J Gastroenterol Hepatol*. 2013; 25:659–664. [PubMed: 23628964]
4. Yeh MM, Brunt EM. Pathological features of fatty liver disease. *Gastroenterology*. 2014; 147:754–764. [PubMed: 25109884]
5. Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. *Gastroenterology*. 2014; 146:1231–1239. e1–6. [PubMed: 24440674]
6. Singal AK, Kamath PS, Gores GJ, et al. Alcoholic hepatitis: current challenges and future directions. *Clin Gastroenterol Hepatol*. 2014; 12:555–564. [PubMed: 23811249]
7. Rachakonda V, Gabbert C, Raina A, et al. Serum metabolomic profiling in acute alcoholic hepatitis identifies multiple dysregulated pathways. *PLoS One*. 2014; 9:e113860. [PubMed: 25461442]
8. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology*. 2007; 45:1348–1354. [PubMed: 17518367]
9. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology*. 2011; 141:1572–1585. [PubMed: 21920463]
10. Altamirano J, Higuera-de laTijera F, Duarte-Rojo A, et al. The amount of alcohol consumption negatively impacts short-term mortality in Mexican patients with alcoholic hepatitis. *Am J Gastroenterol*. 2011; 106:1472–1480. [PubMed: 21556041]
11. Barrio E, Tome S, Rodriguez I, et al. Liver disease in heavy drinkers with and without alcohol withdrawal syndrome. *Alcohol Clin Exp Res*. 2004; 28:131–136. [PubMed: 14745311]
12. Bertola A, Park O, Gao B. Chronic plus binge ethanol feeding synergistically induces neutrophil infiltration and liver injury in mice: a critical role for E-selectin. *Hepatology*. 2013; 58:1814–1823. [PubMed: 23532958]
13. Lazaro R, Wu R, Lee S, et al. Osteopontin deficiency does not prevent but promotes alcoholic neutrophilic hepatitis in mice. *Hepatology*. 2015; 61:129–140. [PubMed: 25132354]
14. Stickel F, Hampe J. Genetic determinants of alcoholic liver disease. *Gut*. 2012; 61:150–159. [PubMed: 22110053]
15. Krawczyk M, Portincasa P, Lammert F. PNPLA3-associated steatohepatitis: toward a gene-based classification of fatty liver disease. *Semin Liver Dis*. 2013; 33:369–379. [PubMed: 24222094]
16. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology*. 2014; 146:1513–1524. [PubMed: 24440671]
17. Szabo G, Petrasek J, Bala S. Innate immunity and alcoholic liver disease. *Dig Dis*. 2012; 30(Suppl 1):55–60.

18. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. *Gastroenterology*. 2008; 135:1953–1960. [PubMed: 18848937]
19. Petrasek J, Bala S, Csak T, et al. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *J Clin Invest*. 2012; 122:3476–3489. [PubMed: 22945633]
20. Dominguez M, Miquel R, Colmenero J, et al. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. *Gastroenterology*. 2009; 136:1639–1650. [PubMed: 19208360]
21. Mookerjee RP, Stadlbauer V, Lidder S, et al. Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology*. 2007; 46:831–840. [PubMed: 17680644]
22. Albano E. Role of adaptive immunity in alcoholic liver disease. *Int J Hepatol*. 2012; 2012:893026. [PubMed: 22229098]
23. Sancho-Bru P, Altamirano J, Rodrigo-Torres D, et al. Liver progenitor cell markers correlate with liver damage and predict short-term mortality in patients with alcoholic hepatitis. *Hepatology*. 2012; 55:1931–1941. [PubMed: 22278680]
24. Naveau S, Giraud V, Borotto E, et al. Excess weight risk factor for alcoholic liver disease. *Hepatology*. 1997; 25:108–111. [PubMed: 8985274]
25. Naveau S, Cassard-Doulcier AM, Njike-Nakseu M, et al. Harmful effect of adipose tissue on liver lesions in patients with alcoholic liver disease. *J Hepatol*. 2010; 52:895–902. [PubMed: 20399524]
26. Altamirano J, Fagundes C, Dominguez M, et al. Acute kidney injury is an early predictor of mortality for patients with alcoholic hepatitis. *Clin Gastroenterol Hepatol*. 2012; 10:65–71.e3. [PubMed: 21946124]
27. Michelena J, Altamirano J, Abralles JG, et al. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology*. 2015 Mar 11. [Epub ahead of print].
28. Xu M, Chang B, Mathews S, et al. New drug targets for alcoholic liver disease. *Hepatol Int*. 2014; 8:S475–S480.

Figure 1.

The pathogenesis of AH. The pathophysiological complexity of alcoholic hepatitis (AH). Cross-talk between the intestine and the liver plays an important role in the genesis of AH. Alcohol and nutrients are absorbed from the small intestine. The microbiota, endogenous compounds such as bile acids and alcohol breakdown products impair the intestinal barrier and activate the innate and adaptive immune systems, sensitizing hepatic macrophages to endotoxin. The role of other gut constituents on endocrine signaling from the intestine is being clarified; specifically cross-talk between pathways activated in obesity and by alcohol consumption need further clarification. Cell-cell interactions, cytokines, dietary, hormonal influences converge on the hepatocyte and cause metabolic dysregulation leading to oxidative stress, metabolic reprogramming, mitochondrial injury, activation of cellular process such as unfolded protein response, altered miRNA profiles and cholestasis which determine the balance between survival and death. The resultant read out is accumulation of lipid, cell death, inflammation, fibrosis and eventual resolution by tissue repair or progression to cirrhosis.

Table 1**Gaps in Knowledge and Research Priorities for AH**

Area of study	What we know and do not know	Potential approaches to filling gaps
Histology	AH histology is very similar to NASH histology; some unique features of AH histology are reported. It is not known if specific histologic subsets are linked to specific molecular pathways and distinct clinical outcomes	Studies to determine if there are distinct histologic subsets of AH, eg, classic steatohepatitis versus steatohepatitis with cholestasis with or without fibrosis.
Clinical AH definition	AH is diagnosed based on clinical syndrome. The natural history of these clinical variants is not well-characterized.	Longitudinal cohort studies are needed to classify the clinical variants of AH and relate them to outcomes and specific molecular targets for therapy.
Grading AH severity	Many score systems have been generated to assess the severity of AH. Their ability to comprehensively model disease severity and outcomes in a validated manner is modest.	Prospective studies with adjudicated outcomes to develop models that will provide more accurate short-term, intermediate-term, and long-term risk stratification.
Biomarker	There are no biomarkers for diagnosis of early stages of ALD or AH.	There is an urgent need for biomarker development in the context of longitudinal studies and clinical trials to identify the risk, diagnosis, and therapeutic response for AH.
Genetics	Female gender and PNPLA3 mutations are genetic risk factors for AH. The role of other gene variants and combinations of SNPs remains unknown.	GWAS and deep sequencing in well-defined clinical cohorts where genetic variants and combinations of variants can be linked to the risk of AH, severity of AH, and response to treatments.
Intestinal factors	Gut bacterial overgrowth, dysbiosis, and increased gut permeability contribute to the pathogenesis of ALD/AH. The mechanisms by which this occurs is not fully understood.	Studies of the sterol and bile acid biome, both unbiased and hypothesis-driven mechanistic studies to define the role of the microbiome and the intestinal barrier in AH.
Innate immunity	Activation of LPS–TLR–4–TNF- α , activation of Kupffer cells and neutrophils contribute to the pathogenesis of ALD/AH. The role of specific macrophage phenotypes and modulation of injury versus repair by the innate immune system are not fully understood.	Hypothesis-driven mechanistic studies to define the role of individual cell types and the potential roles of neutrophils in causing injury and also promoting repair.
Adaptive immunity	Evidence suggests adaptive immunity is activated in AH. Its role in AH is incompletely understood.	Specific hypothesis-driven mechanistic studies to clarify the role of adaptive immunity in AH.
Impairment of liver regeneration	Hepatocyte proliferation is suppressed while ductular reaction/liver progenitor cell proliferation is markedly increased in AH. The metabolic, cellular, and molecular basis for this is partly understood.	Factors driving the repair response and potential impairment of the repair response such as stem cell activation, proliferation, differentiation factors, and bone marrow need clarification in focused mechanistic studies.
Therapeutic targets	Many potential therapeutic targets against inflammation have been identified. Some of hepatoprotective targets are also discovered. It is not known if “one size fits all” in terms of therapeutic targets.	Pathophysiologic studies are needed to clarify the molecular homogeneity versus heterogeneity of AH and to determine if there are common targets or variable activation of injury pathways.
Clinical trials	Several trials are now in early phases. However, beyond steroids the evidence base to support other drugs for AH is scant.	Multitude of proof-of-concept studies to validate various therapeutic targets followed by larger efficacy and safety trials, validation of endpoints in prospective cohort studies, and identification of more homogeneous patient populations. Studies are particularly required in those with a Maddrey index of 20–31 who are currently not considered for drug treatment but still have an unacceptably high mortality.
Long-term outcomes	Continued alcohol consumption has been linked to recurrent hospitalization and mortality. However, the social behavioral economic factors driving this have not been clarified and leveraged to improve long-term outcomes.	Development of comprehensive models of care that include behavioral approaches, social and financial support have to be combined with pharmacologic therapies to improve outcomes of AH.

AH, alcoholic hepatitis; ALD, alcoholic liver disease; GWAS, genome-wide association studies; LPS, lipopolysaccharide; NASH, nonalcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; SNPs, single nucleotide polymorphisms; TLR, Toll-like receptor; TNF, tumor necrosis factor.