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TOPIC HIGHLIGHT

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Alcoholic hepatitis: A comprehensive review of pathogenesis and treatment

Maneerat Chayanupatkul, Suthat Liangpunsakul

Maneerat Chayanupatkul, Department of Medicine, Albert Einstein Medical Center, Philadelphia, PA 19141, United States
Suthat Liangpunsakul, Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University Medical Center, Indianapolis, IN 46202, United States
Suthat Liangpunsakul, Roudebush Veterans Administration Medical Center, Indianapolis, IN 46202, United States
Author contributions: Chayanupatkul M reviewed the manuscript and revised this paper; Liangpunsakul S contributed to the concept, write, and edited the article.
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Correspondence to: Suthat Liangpunsakul, MD, MPH, Associate Professor of Medicine and Public Health, Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University Medical Center, 550 N University Blvd, UH 4100, Indianapolis, IN 46202,
United States. sliangpu@iupui.edu
Telephone: +1-317-2781630 Fax: +1-317-9883180
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Abstract

Alcoholic hepatitis (AH) is an acute hepatic inflammation associated with significant morbidity and mortality. Current evidence suggests that the pathogenesis is the end result of the complex interplay between ethanol metabolism, inflammation and innate immunity. Several clinical scoring systems have been derived to predict the clinical outcomes of patients with AH; such as Child-Turcotte-Pugh score, the Maddrey discriminant function, the Lille Model, the model for end stage liver disease scores, and the Glasgow alcoholic hepatitis score. At present, Corticosteroids or pentoxifylline are the current pharmacologic treatment options; though the outcomes from the therapies are poor. Liver transplantation as the treatment of alcoholic hepatitis remains controversial, and in an era of organ shortage current guidelines do not recommend transplantation as the treatment option. Because of the limitations in the therapeutic options, it is no doubt that there is a critical need for the newer and more effective pharmacological agents to treat AH.

Key words: Alcoholic hepatitis; Pathogenesis; Treatment; Model for end stage liver disease; Discriminant function; Lille Model; Glasgow alcoholic hepatitis score; Liver transplantation

Core tip: Alcoholic hepatitis (AH) is still a major problem in the United States due to significant morbidity and mortality. Currently, corticosteroids or pentoxifylline are the main pharmacological treatment options; though the outcomes from the therapies are poor. Because of the limitations in the therapeutic options, it is no doubt that there is a critical need for the newer and more effective pharmacological agents to treat AH.

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INTRODUCTION

Alcoholic liver disease (ALD) represents a spectrum of conditions ranging from reversible fatty liver to alcoholic hepatitis (AH), and cirrhosis. AH is an acute hepatic inflammation associated with significant morbidity and mortality that occurs in a subset of patients who con-

sume excessive amounts of alcohol[1]. According to our recent study, there were 56809 hospital admissions with the primary diagnosis of AH, which accounted for 0.71% of all admission in the United States in 2007[1]. The average total charges during hospitalization for AH were $37769; which was higher than that from acute myocardial infarction, acute cerebrovascular disease, and acute pancreatitis[1]. Hospitalized AH patients result in significant healthcare cost and utilization[1]. In severe cases, patients have a very poor prognosis, with short term mortality around 30%-50%[2]. A typical patient with AH provides a history of an average daily consumption of over 80 g of ethanol for over 5 years[3].

PATHOGENESIS

The pathogenesis of alcoholic hepatitis is multifactorial. Current evidence suggests that the damage is the end result of the complex interplay between ethanol metabolism, inflammation and innate immunity[4]. Such metabolic pathways generate reactive oxygen species that are potent inducers of lipid peroxidation, which in turn causes hepatocyte death by necrosis or apoptosis. High levels of endotoxemia also have been documented among patients who have AH, probably because of increased intestinal permeability[4]. Endotoxin (lipopolysaccharide) binds to lipopolysaccharide-binding protein, and the complex then attaches to the CD14 molecule on Kupffer's cells that triggers pathways to cause Kupffer' s cell activation[5]. A variety of cytokines are released because of the heightened Th1 response, in particular interferon-gamma and tumor necrosis factor-alpha (TNF-α)[6]. Chemotactic factors such as interleukin-8 cause migration of polymorphonuclear leukocytes to hepatic lobules[7]. These changes induce the systemic inflammatory response syndrome characterized by malaise, fever, and peripheral neutrophil leukocytosis. TNF-α mediates its effects by binding to two cell surface molecules, TNF-R1 and TNF-R2[8]. TNF-R1 is the main inducer of hepatocytotoxicity through necrosis or apoptosis. Ethanol metabolism generates acetaldehyde, and malondialdehyde is one of the end products of lipid peroxidation[9]. Both compounds bind to cellular proteins to form stable adducts. The variable immune response to these neoantigens may contribute to the individual susceptibility to AH. It is likely that both nonimmunologic (oxidative stress, cytokine injury) and immunologic factors play important roles in the pathogenesis of AH[10]. A variety of treatment options in AH share a common treatment goal of blocking the myriad of innate immunologic responses[4,11,12].

CLINICAL PRESENTATION

AH patients generally present with fever, jaundice, hepatomegaly, ascites and/or hepatic encephalopathy. The cardinal sign of AH is the rapid onset of jaundice. Physical examination usually reveals a malnourished patient with fever, low blood pressure and tachycardia. Jaundice and ascites are universal and a significant number of patients have hepatic encephalopathy[13]. If palpable, the liver is usually enlarged and tender. A minority have an audible bruit in the right upper quadrant, believed to be due to increased blood flow in the hepatic artery[14]. Laboratory studies characteristically reveal serum levels of aspartate aminotransferase (AST) that are more than twice the upper limit of the normal range, although rarely above 300 IU per milliliter, whereas serum levels of alanine aminotransferase (ALT) are lower. The ratio of the aspartate aminotransferase level to the alanine aminotransferase level is usually greater than 2, although this finding is neither specific nor sensitive[15]. Elevation in the gamma glutamyltransferase level is more sensitive (70%) but less specific (65%-80%) than elevation of AST or ALT for excessive alcohol consumption[16]. Other biochemical and hematologic parameters often seen during AH include hypokalemia, hypomagnesemia, hyperuricemia, hypertriglyceridemia, and hyperferritinemia[17]. A low zinc level, hypoalbuminemia, and low blood urea nitrogen may indicate malnutrition[18]. An elevated mean corpuscular erythrocyte volume is found frequently in those ingesting more than 50 g alcohol per day[19]. Leukocytosis and thrombocytopenia are commonly seen. The white blood cell count is often elevated, although it may be even higher with leukemoid reactions. Thrombocytopenia may be transitory or persistent in those who have concomitant cirrhosis. Liver biopsy normally shows ballooning degeneration, focal hepatocyte necrosis, and neutrophilic infiltration[4,20].

PREDICTORS OF MORTALITY

Several clinical scoring systems, the Child-Turcotte-Pugh score (CTP)[21], the Maddrey discriminant function[22], the Lille Model[23], the model for end stage liver disease (MELD) scores[24], and the Glasgow alcoholic hepatitis score[25], have been derived to predict the clinical outcomes of patients with AH. The assessment of the disease severity becomes an important and practical issue for clinicians involved in the management of patients with AH. Many scoring systems have been developed for use in clinical practice.

CTP is traditionally used for cirrhotic patients with mortality rates of about 10% to 15%, 25% to 30%, and 70% to 80% at 1 year for stages A, B, and C, respectively. Although it is not a traditional scoring system for AH patients, the CTP score was useful in predicting mortality at 3 to 6 mo[26-28]. Presently, the CTP score is not widely used for assessing severity of AH.

The discriminant function index (DFI) was initially described by Maddrey *et al*[22] in a placebo-controlled study to assess the benefit of corticosteroid therapy in 55 patients with AH. Using the formula: 4.6 × prothrombin time (PT) in seconds + serum bilirubin (mg/dL), patients with a DFI above 93 and treated with placebo had a 28 d survival of 25%, whereas those with a score

Table 1 Clinical scoring system to evaluate the severity of alcoholic hepatitis

Clinical scoring system	Formula
Modified discriminant function[29]	[4.6 × (PT test - control)] + serum bilirubin (mg/dL)
MELD[34]	3.78 × $\log_e$[serum bilirubin (mg/dL)] + 11.2 × $\log_e$[INR] + 9.57 × $\log_e$[serum creatinine (mg/dL)] + 6.43
Lille score[23]	Scoring system derived from age, serum albumin (day 0), serum bilirubin (days 0 and 7), creatinine (day 0) and PT (day 0)[23]
Glasgow alcoholic hepatitis score[25]	Scoring system derived from age, WBC, BUN, PT and bilirubin[25]

WBC: White blood cell; BUN: Blood Urea Nitrogen; PT: Prothrombin time; MELD: Model for end stage liver disease; INR: International normalized ratio.

of 93 or lower had 100% survival. This score was then modified (modified discriminant function or mDF) using prolongation of PT in seconds (over control) instead of absolute value of PT[29]. Patients without treatment and mDF score of 32 or higher and/or the presence of encephalopathy had a 28 d survival of about 65%. One study confirmed this observation with untreated patients having 28 d survival of 68% among patients with mDF $\geqslant$ 32[30]. The current practice guideline recommends that AH patients with mDF score of $\geqslant$ 32 should be considered for corticosteroid therapy[31]. The advantages of the mDF are its simplicity of calculation and validation in many clinical trials. However, non-standardization of the PT testing with laboratory to laboratory variation depending on the type of thromboplastin used by the laboratory is a limitation[32].

About 40% of patients with severe AH failed to respond to treatment with steroids. In a prospective study on 320 biopsy-proven severe AH, non-responders to steroids could be identified based on early change in bilirubin level and other five variables. This led to the development of Lille score[23]. Survival at 6 mo was lower for patients with a Lille score of 0.45 or higher compared with patients with Lille score of less than 0.45 (25% *vs* 85%, $P < 0001$). The corticosteroid was discontinued for patients with a Lille score of 0.45 or greater at 1 week. The Lille score maintains accuracy in predicting the survival when used across a range. In a retrospective study on 641 biopsy-proven AH, a linear correlation with survival was seen among groups with Lille score of less than 0.16, 0.16 to 0.56, or greater than 0.56 with survival rates of 87%, 70%, and 21%, respectively at 6 mo[33]. The drawback of this scoring system is that it does not guide initiation of steroid treatment because it cannot be calculated at the time of admission.

The MELD score was initially developed to predict survival in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunting. It has since been revised and validated to predict survival for patients with cirrhosis and is the basis for organ donor allocation in liver transplantation[24,26,34]. Laboratory values used to calculate the MELD score are the international normalized ratio, creatinine, and bilirubin. Two recent studies showed that MELD score is useful for predicting 3 mo mortality of patients with severe AH not treated with corticosteroids[27,35]. Its accuracy was comparable to that of DF in predicting 3 mo mortality of patients with severe AH[35]. Using the optimal cutoff point (21 for MELD and 37 for DF), MELD had a sensitivity of 75% and a specificity of 75% and DF a sensitivity of 88% and a specificity of 65%. Another study confirmed that DF and MELD had similar accuracy in predicting survival of patients with AH[27].

The Glasgow Alcoholic Hepatitis Score (GAHS) was developed in an effort to overcome the low specificity of the Maddrey DF and lack of an optimal predictive cutoff point for the MELD score. It was derived from a retrospective analysis of patients with ALD, with logistic regression used to identify variables associated with mortality[25]. GAHS is a scoring system based on age, serum bilirubin, blood urea nitrogen, PT, and the peripheral white cell count. GAHS $\geqslant$ 9 is a predictor of mortality and is more accurate than DF in predicting both 28- and 84 d mortality but is equivalent to MELD in predicting 28 d mortality[25].

An ideal prognostic scoring system should be simple, accurate, validated and should be able to guide treatment initiation and response. However, we still do not have a single scoring system that passes all these criteria. At present, the mDF score continues to be used for initiating treatment and the Lille score for guiding treatment response. Table 1 showed the scoring system to assess the severity of AH.

TREATMENT

General treatment of alcoholic hepatitis includes treatment of ascites by salt restriction and the use of diuretics, and treatment of hepatic encephalopathy by lactulose and gut-cleansing antibiotics. Infection should be treated with appropriate antibiotics, chosen according to the sensitivity of the organism isolated[36]. A daily protein intake of 1.5 g/kg of body weight is recommended. Administration of B-complex vitamins is required to prevent Wernicke encephalopathy[37]. Benzodiazepine should be used for acute alcoholic withdrawal syndrome with caution due to potential encephalopathy precipitated. Careful and frequent monitoring with a validated withdrawal-symptom scale such as the Clinical Institute Withdrawal Assessment for Alcohol should be considered[38]. Pharmacological therapies for AH are discussed below.

Corticosteroids

Corticosteroids suppress the immune system activated by enhanced generation of neo-antigens, such as malondi-

aldehyde and acetaldehyde protein adducts, cytochrome P4502E1 and 3A4, and liver membrane antigen[39]. It also inhibits the production of TNF-α[40]. At least 12 randomized, controlled clinical trials have assessed the effectiveness of corticosteroids in patients with alcoholic hepatitis. Several studies found no benefit[41-47], while others reported improved survival[22,29,48-50]. Subsequent meta-analyses also produced conflicting results. Two questioned their efficacy[40,51], while three suggested a useful role of corticosteroids[30,52,53]. Current practice guideline recommends glucocorticoid treatment in patients with severe alcoholic hepatitis (mDF > 32) with hepatic encephalopathy[31]. Steroid treatment is contraindicated in those with infection, GI bleeding, acute pancreatitis, or renal failure[54].

A meta-analysis of individual data used Lille model to evaluate patient with severe alcoholic hepatitis response to corticosteroid treatment. This study confirmed the need for adapting corticosteroid therapy to response to treatment. A subgroup analysis was performed according to the percentile distribution of the Lille score. Patients were classified as complete responders (Lille score < 0.16; 35th percentile), partial responders (Lille score 0.16-0.56; 35th-70th percentile) and null responders (Lille > 0.56; 70th percentile). This approach identified three patterns of responses, complete, partial and null, with significant differences in survival benefit: 91% *vs* 79% *vs* 53%, $P <$ 0.0001. Corticosteroids showed a significant effect on 28 d survival in complete (hazard ratio 0.18) and in partial responders (hazard ratio 0.38), but not in null responders. Lille model allows clinicians to better stratify the response to treatment and improve prediction of survival[52].

Anti-TNF therapy

Pentoxifylline, a phosphodiesterase inhibitor, has been shown to decrease the transcription of the TNF-α promoter[55,56]. There are several trials studied the efficacy of pentoxifylline in alcoholic hepatitis, mostly severe alcoholic hepatitis. The results are controversial. At least two trials showed benefit, improving short-term survival in patients with severe alcoholic hepatitis[57,58]. One study using pentoxifylline in subjects with severe alcoholic hepatitis showed the improvement in mortality which was secondary to a concomitant decrease in the incidence of hepatorenal syndrome[57].

Another recent randomized control trial compared effectiveness of corticosteroids and pentoxifylline in patients with severe alcoholic hepatitis. This study showed that pentoxifylline is superior to prednisolone for treatment of severe alcoholic hepatitis with a significantly lower MELD score at the end of 28 d of therapy[59]. However, in another randomized controlled trial to study the combination of corticosteroids and pentoxifylline compared with corticosteroids alone, there is no survival advantage at 6 mo in adding pentoxifylline to steroids in patients with severe alcoholic hepatitis compared with corticosteroid alone[60].

A cohort study evaluated the effect of early switch to pentoxifylline in patients with severe alcoholic hepatitis in non-responders to corticosteroid. The study included 121 patients who were treated initially with 40 mg oral prednisolone daily. Twenty nine patients who failed to show a decrease in bilirubin levels within 7 d were switched to oral pentoxifylline (400 mg twice a day) and compared to 58 matched non-responders treated with corticosteroids only. In the pentoxifylline group, 69% of patients died within 2 mo, and 27.6% had some form of renal insufficiency. This outcome was not statistically different from that of 58 matched historical controls with severe alcoholic hepatitis who were maintained on oral prednisolone despite failure to respond within the first week of therapy (65% mortality, 20% with renal insufficiency). Non-responders to corticosteroid do not obtain any benefit from an early switch to pentoxifylline[61].

The effectiveness of pentoxifylline was reported in a recent systemic review[62]. Five trials, with a total of 336 randomized participants, were included. A total of 105 participants (31%) died. Of the five included trials, four (80%) had a high risk of bias. Meta-analysis using all five trials showed that pentoxifylline reduced mortality compared with control (RR = 0.64; 95%CI: 0.46-0.89). However, this result was not supported by trial sequential analysis, which adjusts for multiple testing on accumulating data. Furthermore, four of the five trials were judged to have a high risk of bias, thus risking an overestimated intervention effect. Meta-analysis showed that pentoxifylline reduced the hepatic-related mortality due to hepatorenal syndrome (RR = 0.40; 95%CI: 0.22-0.71). The current available data may indicate a possible positive intervention effect of pentoxifylline on all-cause mortality and mortality due to hepatorenal syndrome. The results from this Cochrane systemic review are in accordance with recent meta-analysis on the use of pentoxifylline for the treatment of severe alcoholic hepatitis[63]. Currently, pentoxifylline remains an option when corticosteroids are contraindicated, but in many centers, this drug is first-line treatment for severe AH patients[64].

Several studies showed the ineffectiveness of Infliximab in patient with alcoholic hepatitis[65-67]. In a large NIH-sponsored study, another anti-TNF compound, etanercept, did not demonstrate any beneficial effects in patients with alcoholic hepatitis[68].

Enteral nutrition

Patients with alcoholic hepatitis are normally malnourished[54,69-71]. One study showed the similar efficacy between nutritional support and steroid therapy[72].

N-acetylcysteine

Oxidative stress is implicated in the pathogenesis of alcoholic hepatitis[4]. Several studied failed to show the effectiveness of *N*-acetylcysteine in the treatment of alcoholic hepatitis[73-76]. One recent randomized controlled trial compared patients who receive *N*-acetylcysteine in-

travenously or a placebo perfusion along with adequate nutritional support for 14 d. Survival rate at 1 and 6 mo were not significantly different in *N*-acetylcysteine and control group[73]. The other three randomized controlled trials compared survival rate between patients who receive corticosteroid with and without *N*-acetylcysteine. Although combination therapy with corticosteroid plus *N*-acetylcysteine increased 1-mo survival among patients with severe acute alcoholic hepatitis[76], 6 mo survival was not improved[74,76].

Anabolic steroids

A systemic review showed the ineffectiveness of anabolic steroid in subjects with alcoholic hepatitis[77].

Propylthiouracil

Propylthiouracil (PTU) decreases the hypermetabolic state induced by alcohol[78,79], and inhibits oxidative stress[80]. Previous studies showed conflicting results of PTU in the treatment of alcoholic hepatitis[81,82]. In a recent systemic review, PTU failed to show the effect in the treatment of alcoholic liver disease[83,84].

S-adenosyl-L-methionine

Abnormal methionine metabolism occurs in animals fed ethanol and in end-stage cirrhotic patients due to defect in methionine/glutathione metabolism[4,71]. The use of S-adenosyl-L-methionine is not helpful in patients with alcoholic liver disease[85,86].

Liver transplantation

Liver transplantation for patients with alcoholic hepatitis is not recommended according to the current guidelines[87]. The 6 mo abstinence is generally required[88]. A recent study showed the benefit of early liver transplantation to improve the 6 mo survival rate in patients with severe alcoholic hepatitis who are not responding to medical therapy[89]. Twenty six patients (median Lille score, 0.88) were selected and place on liver transplantation list within a median of 13 d after nonresponse to medical therapy. The cumulative 6 mo survival rate was higher among patients who received early transplantation than among those who did not (77% *vs* 23%, $P < 0.001$). This benefit of early transplantation was maintained through 2 years of follow-up (HR, 6.08; $P = 0.004$)[89]. Despite the good outcome from this study, liver transplant as treatment of alcoholic hepatitis remains controversial, and in an era of organ shortage current guidelines do not recommend transplantation as the treatment option.

Treatment for alcoholism

Abstinence is important in order to prevent further liver injury and it appears to benefit patients at every stage of the disease[39,90,91]. Several medications might be used to help with abstinence, such as naltrexone and acamprosate[92,93]. Another randomized, double-blind controlled study has shown baclofen, an alpha-aminobutyric acid B-receptor agonist, can promote short-term abstinence in a group of actively drinking patients with alcoholic cirrhosis[94]. Generally, treatment of alcohol disorders required multi-disciplinary approaches.

CONCLUSION

In summary, alcoholic hepatitis is still a major problem in the United States due to significant morbidity and mortality. Currently, corticosteroids or pentoxifylline are the main pharmacological treatment options; though the outcomes from the therapies are poor. Because of the limitations in the therapeutic options, it is no doubt that there is a critical need for the newer and more effective pharmacological/hepatoprotective agents to treat AH. There are several ongoing studies supported by the National Institute on Alcohol Abuse and Alcoholism through multi-institutional consortia to test several novel compounds for AH[64]. Once completed, it is expected that the results from these trials will lead to the advancement in the therapy for patients with AH.

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