

WJH 6th Anniversary Special Issues (2): Hepatocellular carcinoma

Severe alcoholic hepatitis-current concepts, diagnosis and treatment options

Won Kim, Dong Joon Kim

Won Kim, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul 156-707, South Korea

Dong Joon Kim, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon 200-704, South Korea

Author contributions: Kim W collected data, reviewed literatures, and wrote the manuscript; Kim DJ designed this review, appraised critically and revised the manuscript.

Correspondence to: Dong Joon Kim, MD, PhD, Professor, Department of Internal Medicine, Hallym University College of Medicine, #153 Gyo-dong, Chuncheon-si, Gangwon-do, Chuncheon 200-704, South Korea. djkim@hallym.ac.kr

Telephone: +82-33-2405646 Fax: +82-33-2418064

Received: August 22, 2014 Revised: September 2, 2014

Accepted: September 16, 2014

Published online: October 27, 2014

Abstract

Alcoholic hepatitis (AH) is an acute hepatic manifestation occurring from heavy alcohol ingestion. Alcoholic steatohepatitis (ASH) is histologically characterized by steatosis, inflammation, and fibrosis in the liver. Despite the wide range of severity at presentation, those with severe ASH (Maddrey's discriminant function ≥ 32) typically present with fever, jaundice, and abdominal tenderness. Alcohol abstinence is the cornerstone of therapy for AH and, in the milder forms, is sufficient for clinical recovery. Severe ASH may progress to multi-organ failure including acute kidney injury and infection. Thus, infection and renal failure have a major impact on survival and should be closely monitored in patients with severe ASH. Patients with severe ASH have a reported short-term mortality of up to 40%-50%. Severe ASH at risk of early death should be identified by one of the available prognostic scoring systems before considering specific therapies. Corticosteroids are the mainstay of treatment for severe ASH. When corticosteroids are contraindicated, pentoxifylline may be alternatively used. Responsiveness to steroids should be assessed at day 7 and stopping rules based on Lille score should

come into action. Strategically, future studies for patients with severe ASH should focus on suppressing inflammation based on cytokine profiles, balancing hepatocellular death and regeneration, limiting activation of the innate immune response, and maintaining gut mucosal integrity.

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Key words: Alcoholic steatohepatitis; Infection; Renal failure; Corticosteroids; Pentoxifylline

Core tip: We should further explore novel molecular targets to restore altered gut mucosal integrity, suppress inflammation based on cytokine profiles, promote hepatic regeneration, and limit innate immune responses in severe alcoholic steatohepatitis.

Kim W, Kim DJ. Severe alcoholic hepatitis-current concepts, diagnosis and treatment options. *World J Hepatol* 2014; 6(10): 688-695 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v6/i10/688.htm> DOI: <http://dx.doi.org/10.4254/wjh.v6.i10.688>

INTRODUCTION

Alcoholic liver disease (ALD) is one of the main causes of end-stage liver disease worldwide^[1]. ALD has a broad disease spectrum, encompassing simple steatosis, steatohepatitis, and cirrhosis. In particular, the short-term mortality in patients with severe alcoholic steatohepatitis (ASH) has been extremely high up to 40%-50%^[2,3]. Although several therapeutic measures are now available to improve survival in those with severe alcoholic hepatitis (AH), overall prognoses remain gloomy.

Recently, severe AH with a significant morbidity and mortality ranks among the most costly diseases during hospitalization in the United States^[4]. Thus, the early

detection of high-risk patients and prompt intervention may assist in the alleviation of healthcare cost associated with severe AH. Accordingly, the accurate prognostic stratification is crucial for individualized therapeutic decisions in patients with AH. Several prognostic scoring systems, to date, have been developed and validated for use in those with AH^[5-10].

The clinical syndrome of jaundice and liver function abnormalities in alcohol abusers is generally called AH, which has often been referred to as “acute alcoholic hepatitis” historically. However, despite the sudden onset of the clinical presentation, this term seems to fade into the mists of history now that AH is usually associated with extensive fibrosis or cirrhosis and often follows a protracted natural course.

ASH is a pathologic disease entity, defined as the coexistence of steatosis, hepatocellular ballooning, neutrophilic infiltration, and perisinusoidal fibrosis^[11]. ASH is not exclusively accompanied by AH but can be superimposed on any different stages of ALD comprising steatosis, steatohepatitis, fibrosis, and cirrhosis^[12,13]. However, it is not much well-known which patients with ASH will progress to clinically evident AH. In addition, the true incidence and prevalence of ASH or AH among alcohol abusers remain unclear due to the uncertainties behind a clinical diagnosis of AH and the limited number of studies with liver biopsy to ascertain a histologic diagnosis of ASH.

Recently, the updated practice guidelines for management of ALD have been released from the European Association for the Study of the Liver^[14] as well as the American Association for the Study of Liver Diseases^[15]. Herein, we attempt to address some issues regarding different types of alcohol-induced liver failure, new prognostic scoring systems, general therapeutic measures, and potential specific therapies in patients with severe ASH from a clinical perspective.

DIAGNOSIS

Different types of alcohol-induced liver failure

Traditionally, there are two different types of liver failure, which have different prognoses and call for different therapeutic approaches. One is acute liver failure (ALF), which occurs suddenly in patients without previous any liver disease. The other is chronic liver failure (CLF) due to chronic hepatic decompensation (CHD), which is found in those with end-stage liver cirrhosis as a result of slow progression of underlying liver disease. Since the advent of albumin dialysis, a new subtype of CLF, that is, acute-on-chronic liver failure (ACLF) has been widely recognized and highlighted in the field of clinical practice^[16-18]. This new entity is characterized by an acute and rapid deterioration within several weeks on the top of underlying compensated liver disease, mostly cirrhosis, leading to deep jaundice, renal impairment, hepatic encephalopathy, and multi-organ failure in the early stage^[19]. Indeed, among the patients hospitalized for alcoholic cirrhosis, ACLF showed a 3-mo mortality rate of 60% *vs*

that of 20% in case of CHD, illustrating the severity of this new clinical syndrome^[20]. Currently, an excessive pro-inflammatory response to bacterial components such as gut microbiota and lipopolysaccharide (LPS) seems to play an important role in ACLF, linking the gut, liver, and portal to systemic circulation^[21].

In the same manner, alcohol can also instigate two different types of liver injury including ACLF and CHD. The most critically ill patients with alcohol-induced liver failure are some people suffering from severe ASH, mostly superimposed on alcoholic cirrhosis, and secondly those with decompensated cirrhosis. Precipitating events such as variceal hemorrhage, infection, and hepatitis B viral reactivation are usually crucial for the onset of ACLF, given that the rapid and aggressive control of these triggers can allow a complete reversal of ACLF. In this regard, an early use of transjugular intrahepatic portosystemic shunt effectively prevented the development of ACLF in patients with high-risk varices^[22]. Similarly, early suppression of hepatitis B viremia by tenofovir prevented those with spontaneous reactivation of hepatitis B presenting as ACLF from progressing to multi-organ failure^[23]. CHD is the most frequent subtype of alcohol-induced liver failure and is characterized by the complications of portal hypertension and mild to moderate jaundice in the early stage. The 1-year mortality rate was 29% in case of the appearance of ascites; however, it was 64% if hepatic encephalopathy occurred as a complication of portal hypertension in patients with alcoholic cirrhosis^[24]. ACLF is the less frequent subtype of alcohol-induced liver failure but accounts for more than 40% of emergency hospitalization due to alcoholic cirrhosis in tertiary referral hospitals^[20]. ACLF can be induced by several precipitating events in patients with alcoholic cirrhosis; however, one of the most common triggers is severe ASH, which occurs in roughly 25% of the patients with ACLF^[20].

Prognostic scoring systems

The best way to reverse alcohol-induced ACLF is to detect and control severe ASH as early as possible, which is less likely to recover spontaneously. In this regard, a variety of prognostic scores have been developed primarily to select patients with severe ASH at high risk of early (1, 2, or 3 mo) death^[5-8,10]. There are several disease-specific prognostic models (MDF: Maddrey's Discriminant Function; GAHS: Glasgow Alcoholic Hepatitis Score; ABIC: Age-Bilirubin-INR-Creatinine Score; Lille model; MAGIC: Model for Alcoholic hepatitis to Grade the severity In an Asian patient Cohort) and a non-disease-specific model (MELD: Model for End-Stage Liver Disease) (Table 1)^[5-8,10].

MDF is still one of the most commonly used prognostic models to predict survival outcomes in patients with ASH with 32 of a cutoff value^[10,25]. Severe ASH (MDF ≥ 32) mostly progress to the systemic inflammatory response syndrome (SIRS) and multi-organ failure, which are often seen in other types of ACLF. MAGIC is a recently developed, new model to predict liver-related death in Asian patients hospitalized for AH^[8]. The unique

Table 1 Components of clinical scoring systems to assess prognosis in alcoholic hepatitis

	Bilirubin	PT/INR	Cr/BUN	WBC	Age	Albumin	Potassium	Change in bilirubin from day 0 to day 7
MDF ^[10]	+	+	-	-	-	-	-	-
MELD ^[6]	+	+	+	-	-	-	-	-
GAHS ^[7]	+	+	+	+	+	-	-	-
ABIC ^[5]	+	+	+	-	+	+	-	-
Lille ^[9]	+	+	+	-	+	+	-	+
MAGIC ^[8]	+	+	+	-	-	-	+	+

PT/INR: Prothrombin time/international normalized ratio; Cr/BUN: Creatinine/blood urea nitrogen; WBC: White blood cell; MDF: Maddrey's discriminant function; MELD: Model for end-stage liver disease; GAHS: Glasgow alcoholic hepatitis score; ABIC: Age, serum bilirubin, INR, and serum creatinine; MAGIC: Model for alcoholic hepatitis to grade severity in an Asian patient cohort.

findings of this model are as follows: (1) the MAGIC is the first prognostic model derived from an Asian population with AH; (2) it mainly focused on the prediction of natural outcomes of untreated patients with AH; (3) it firstly brought the prognostic role of hyperkalemia in AH to light, and most importantly; and (4) the spontaneous evolution in bilirubin levels is incorporated into this new model, emphasizing the importance of early amelioration of liver function in relation to the improvement of survival. However, this model should be further validated in other ethnic populations with severe ASH.

Corticosteroids seem to improve survival outcomes in patients with severe ASH without specific contraindications such as gastrointestinal bleeding, hepatorenal syndrome (HRS), uncontrolled infection, hepatitis B virus infection, and pancreatitis^[14,15]. A recent meta-analysis of individual patient data from 5 randomized controlled trials demonstrated that a 28-d survival rate was higher in corticosteroid-treated patients than in placebo-treated ones (80% *vs* 66%)^[26]. MDF, GAHS, and MELD at baseline assist in defining severe ASH and guiding when to initiate steroid treatment. On the other hand, early change in bilirubin level, *in vitro* resistance to steroid, and the Lille score at day 7 allow us to decide on the responsiveness to corticosteroids and whether to stop corticosteroids during steroid treatment^[9,27-29].

Recently, an alcoholic hepatitis histologic score (AHHS) has been suggested to predict survival outcomes accurately in patients with biopsy-proven, ASH^[30]. The AHHS is calculated by grading the extent of fibrosis, the degree of neutrophilic infiltration, bilirubinostasis patterns, and megamitochondria^[30]. In particular, the pattern of bilirubinostasis was closely associated with the development of bacterial infections during hospitalization^[30,31].

TREATMENT

General therapeutic measures

Alcohol abstinence is the linchpin of therapy for AH, since abstinence failure increases mortality rates among those with AH^[32]. However, anti-craving drugs such as disulfiram, naltrexone, and acamprosate are not routinely recommended to patients with severe AH due to the risk of potential hepatotoxicity. Although an anti-craving medication is not promptly given to patients hospitalized for severe AH, an abstinence treatment should be consid-

ered to reduce the recurrence of alcohol use disorders after recovery of liver function. Baclofen could effectively suppress a craving for alcohol and keep an abstinence from alcohol in patients with alcoholic cirrhosis without incurring hepatotoxicity; however, additional research is needed to prove an anti-craving efficacy in those with severe AH^[33].

Patients with AH often suffer from serious malnutrition resulting from promiscuous eating habits, alcohol-related diarrhea, decreased small bowel absorption capacity, anorexia, and an excessive catabolic state, which is directly related to increased mortality^[34]. Accordingly, most of them require nutritional support including the adequate calorie and protein supply as well as vitamin B and mineral repletion along with dextrose water infusion. In addition, when oral feeding is not well tolerated in patients with AH, they often need fat-soluble vitamin supplementation and enteral nutrition. However, there was no significant difference of a 1-mo mortality rate in a previous study comparing enteral nutrition and corticosteroids in patients with severe AH^[35]. Nonetheless, further studies are warranted to evaluate the impact of the combination treatment on survival, because early death was more frequent in the enteral nutrition group and late mortality was higher in the steroid-treated group.

In patients with severe AH, renal impairment is a frequently accompanied symptom during hospitalization and also represents an important predictor of infection and survival. The most common cause of acute renal dysfunction is HRS. To prevent HRS, nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs, aminoglycoside, diuretics, and contrast dye should be avoided and volume expanders including albumin and fresh frozen plasma might be administered. Bacterial infection is frequent but difficult to diagnose, since SIRS criteria are often associated with sterile inflammation in ASH. Infection is commonly seen in around 25% of patients with severe ASH at admission and another quarter finally become infected while receiving corticosteroids during admission^[36]. Thus, infection and renal failure in ASH have a major impact on survival and should be screened, prevented, or treated at all time-points. Empirical use of antibiotics, although widely instituted, is not routinely warranted. Recent data demonstrated that corticosteroids are not contraindicated for the treatment of ASH after a complete control of infection^[36]. Infection developed

during steroid treatment, however, was not the result of immunosuppression by corticosteroids but that of non-response to corticosteroids suggesting severe liver impairment^[36]. Such being the case, empirical antibiotic treatment may be more beneficial to steroid responders rather than non-responders by improving survival only in the former.

Specific therapies

Corticosteroids: Apart from general therapeutic measures, specific therapies are indicated for patients with severe AH (MDF ≥ 32) who are at high risk of early death according to clinical prognostic scores^[26]. The impact of corticosteroid treatment on survival in those with severe AH has been under debate for the last three decades because of heterogeneity of the study design among different studies and selection bias from ambiguous diagnostic criteria lacking histologic confirmation. Moreover, the mechanisms underlying corticosteroid treatment for AH remain largely unknown. A recent study has carefully examined the effects of prednisolone on liver injury and regeneration in several experimental models regarding alcoholic liver injury^[37]. In general, corticosteroids suppress inflammatory and immune-mediated hepatic destruction, but their marked, anti-anabolic effect may suppress regeneration and slow healing by inhibiting expression of genes (*i.e.*, *pSTAT3*) regulating the proliferation and repair of hepatocytes^[37]. This study may give some new insights on prednisolone treatment for AH. In a recent meta-analysis, patients allocated to corticosteroid treatment (40 mg/d for 28 d) had a higher 28-d survival rate than those allocated to non-corticosteroid treatment^[26]. Corticosteroids have now become a first-line therapy for biopsy-proven, severe ASH. Steroids may be sometimes deleterious in conditions other than ASH, which represent 10%-30% of patients with a clinical diagnosis of AH, dominated by infection-related decompensation. Moreover, the treatment of non-severe forms of AH by corticosteroids is not recommended. Thus, the effect of corticosteroids on survival seems to be restricted to biopsy-proven, severe ASH. Approximately, 60% of patients with advanced forms of ASH might benefit from corticosteroid treatment. Thus, early recognition of non-responders to corticosteroids (40% of the patients) is essential to define stopping rules and minimize the unnecessary exposure to corticosteroids^[9]. A Lille score ≥ 0.56 at 7 d upon corticosteroids is defined as non-response to steroids. In non-responders, a 28-d survival rate was no more than 50% despite the continued treatment of corticosteroids^[26].

Pentoxifylline: Pentoxifylline shows an antioxidant effect and weakly inhibits tumor necrosis factor- α (TNF- α) synthesis. In patients with severe ASH receiving pentoxifylline, a 6-mo survival rate was higher than in those treated with placebo^[38]. The survival benefit was attributable to a lower incidence of HRS. However, this beneficial effect was challenged by two recent meta-analyses demonstrating that pentoxifylline decreased the risk

of fatal HRS but did not improve survival significantly, although it remains inconclusive^[39,40]. Recently, a Korean multicenter study group has made a head-to-head comparison between pentoxifylline and prednisolone^[41]. The results demonstrated that the efficacy of pentoxifylline was not statistically equivalent to that of prednisolone in terms of 6-mo survival, supporting prednisolone as a preferred treatment option for severe AH. However, in patients with severe AH and contraindications to corticosteroids, pentoxifylline still can be considered as an alternative therapeutic option^[14,15]. In a recent prospective trial including 270 patients with severe ASH, the combination of pentoxifylline and prednisolone did not bring any significant survival benefit over prednisolone alone^[42]. However, a limitation of this study was that they failed to include a treatment arm receiving only pentoxifylline^[43]. To overcome this limitation, a large randomized trial with a sufficient sample size is ongoing in the United Kingdom comparing pentoxifylline with corticosteroids or a combination of both in patients with severe AH^[44]. Finally, in patients with severe ASH and non-response to corticosteroids based on the Lille model, an early switch to pentoxifylline did not improve the survival outcome^[45]. Collectively, pentoxifylline has no additional beneficial effect in combination with corticosteroids in patients with severe ASH and also pentoxifylline alone is ineffectual in non-responders to steroids.

N-acetyl cysteine: Recently, the combination treatment with N-acetyl cysteine (NAC), an antioxidant and prednisolone significantly reduced a 1-mo mortality rate compared with prednisolone alone by preventing HRS and infection, although the difference was no longer statistically significant at 3 and 6 mo^[46]. However, given the trend toward improved survival in those treated with NAC, additional studies are required to determine the optimal dosing schedule and treatment duration of NAC.

Anti-TNF agents: Since strong evidence supported a central role for TNF- α in several experimental models of ALD, a randomized controlled study in patients with severe ASH tested infliximab in combination with corticosteroids^[47]. In fact, the treatment aimed at blocking TNF- α , compared to placebo, was associated with a higher probability of severe infection and mortality^[47,48]. Presumably, prolonged or excessive TNF blockade may cause profound immunosuppression and negatively impact liver regeneration^[49-51].

Liver transplantation: AH is not considered as a usual indication for liver transplantation (LT). This is related both to the fact that most patients with AH will recover for at least 6 mo after abstinence, and to the "6-mo abstinence rule"^[52]. The 6 months' abstinence rule, although socially acceptable and associated with low harmful alcohol relapse, can be replaced with other elements predictive of abstinence such as social and familial support and absence of psychiatric, addictive disorders^[52]. The Lille model now allows the early identification of non-re-

Table 2 Summary of potential molecular targets and novel targeted therapies for alcoholic hepatitis

Key element of the pathogenesis	Treatment	Effect	Clinical trial
FXR dysregulation	OCA ^[67]	FXR agonist	Moderately severe AH (placebo <i>vs</i> OCA)
Altered gut integrity	Zinc ^[68]	Restoration of gut integrity	Severe AH
	LGG ^[69]	Probiotic effect	Mild to moderate AH (placebo <i>vs</i> LGG)
	Rifaximin ^[70]	Intestinal decontamination	Severe AH (steroid <i>vs</i> steroid + rifaximin)
Innate immune activation	Imm 12-E ^[71]	Anti-LPS antibody	Severe AH (steroid <i>vs</i> steroid + low/high dose Imm 12-E)
	Anakinra ^[57,58,72]	IL-1RA	Severe AH (steroid <i>vs</i> anakinra + pentoxifylline + zinc)
	Rilonacept ^[57,58]	IL-1 inhibitor	Severe AH with response to steroid at day 7 (steroid <i>vs</i> steroid + rilonacept)
	Mycophenolate mofetil	IMPDH inhibitor	Severe AH without response to steroid at day 7 (standard of care <i>vs</i> steroid + mycophenolate)
Sterile necrosis and apoptosis	Emricasan ^[54]	Pancaspase inhibitor	Severe AH with steroid contraindications (placebo <i>vs</i> emricasan)
Impaired regeneration	G-CSF ^[63,64]	HPC mobilization	Severe AH without response to steroid at day 7 (placebo <i>vs</i> G-CSF)
	IL-22 ^[59,73,74]	Hepatoprotective effect	Only preclinical studies

FXR: Farnesoid X receptor; OCA: Obeticholic acid; AH: Alcoholic hepatitis; LGG: Lactobacillus GG; LPS: Lipopolysaccharide; IL-1RA: Interleukin-1 receptor antagonist; IL-1: Interleukin-1; IMPDH: Inosine-5'-monophosphate dehydrogenase; G-CSF: Granulocyte-colony stimulating factor; HPC: Hepatic progenitor cell; IL-22: Interleukin-22.

sponders to steroids, only 25% of whom being alive at 6 mo. Recently, an early LT concept was suggested to those with a first episode of severe ASH not responding to steroids^[53]. Explicit improvement of survival was observed in patients who received early LT compared to historical controls without response to steroids^[53]. Obviously, early LT in ASH may be relevant only in highly selected patients with a first episode of severe ASH, a favorable addiction profile, and not responding to medical therapy.

Novel therapies

Despite the current specific therapies against AH, the overall prognosis of severe AH remains dismal. Owing to the scarcity of available therapeutic resources, undoubtedly, there is an urgent need for novel and innovative therapies to combat against severe AH. Over the past several decades, we have made great progress in grasping the clinical course of AH but not been capable of successfully identifying therapeutic targets. The failure of most clinical trials in AH results from a poor knowledge of the key disease drivers. Secondly, systemic large-scale studies are required before we can engage into targeted, therapeutic trials. Finally, all animal models used to test targets represent mild ALD but not severe liver disease that characterizes AH.

Thus, to settle the aforementioned issues, we are increasingly encouraged to conduct multi-center collaborative trials that use common protocols, include biomarkers, and address the spectrum of AH. To that end, recently, National Institute on Alcohol Abuse and Alcoholism has decided to support four AH consortia, which will explore translational studies and clinical trials for AH^[54]. Clinical studies will collect and bank genetic or other biologic samples and consents to allow translational studies of basic mechanisms, genetics, epigenetics, and systems biology of AH severity and of treatment response. In parallel with that, several interventional trials are ongoing through multi-institutional consortia to test proof-of-concept for new therapies (Table 2)^[54].

Scientific integration for developing new biomark-

ers and novel therapies for AH mainly focuses on several key elements of the pathogenesis of AH. Firstly, inflammation cascade and innate immune activation are demarcating features of severe AH compared to mild to moderate ALD^[55-58]. The syndrome of AH results from severe inflammation and cytokine dysregulation^[59,60]. Secondly, gut integrity is significantly altered in AH allowing pathogen-associated molecular patterns to enter the liver and systemic circulation and induce innate immune activation^[61,62]. Gut-derived endotoxins and other bacterial products that trigger inflammation are a consequence of increased permeability and altered gut barrier function^[62]. Thirdly, cell survival and death pathways contribute to liver dysfunction and the release of damage-associated molecular patterns that further fuel inflammation including hepatocellular apoptosis, sterile necrosis, and injury^[61]. Finally, hepatocellular regeneration is profoundly impaired in patients with severe ASH with liver failure. In this regard, it is therapeutically important to characterize the mechanisms of the poor hepatocyte regeneration and promote the differentiation of progenitor cells into functional mature hepatocytes^[63-66].

CONCLUSION

There is a pressing need for better definitions to distinguish AH from other clinical syndromes. The definitions need to be related to risk and outcomes, to improve clarity of taxonomy, reduce problems with basic *vs* clinical classification, and aid in treatment decisions. To standardize the nomenclature of AH, we should compare the clinical, analytical, and molecular characteristics of early ASH that is completely asymptomatic with those of classical AH that appears in patients with jaundice and/or decompensation. Alcohol abstinence is the sine qua non of therapy for AH, and, in the milder forms, is prerequisite to clinical recovery. Severe ASH may progress to multi-organ failure and, in particular, renal impairment and infection are the most worrisome complications requiring screening, prevention, and treatment. Clinical

prognostic scores such as MDF and MELD are useful tools to determine whether to initiate steroids and the Lille model at day 7 can be applied to assess responsiveness to steroids as stopping rules. Pentoxifylline can be alternatively used as a first-line therapy in severe ASH patients with contraindications to steroids. However, pentoxifylline provides no additional beneficial effect to patients with severe ASH receiving corticosteroids. Early switch to pentoxifylline either does not significantly improve survival in non-responders to steroids. Convincingly, future studies should include homogenous population and direct to AH patients with intermediate severity and partial or non-responders to steroids. Strategically, we should explore novel therapeutic targets to restore altered gut mucosal integrity, suppress inflammation based on cytokine profiles, promote hepatic regeneration, and limit innate immune responses in severe ASH.

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