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Review Article

Recent updates on alcoholic hepatitis

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ABSTRACT

Alcoholic hepatitis (AH) is a unique clinical syndrome that affects patients with chronic and active harmful alcohol consumption, and is associated with a high mortality of up to 40% at 1 month from presentation. It is important to assess disease severity and prognosis at time of presentation to identify patients at risk for high mortality and potential candidates for specific therapies. The cornerstone therapy for AH is enteral nutrition and abstinence. Steroids remain the only pharmacological option for severe AH however, adverse effects and lack of long-term benefit limit their routine use. Early liver transplantation is a potential salvage therapy for select severe AH patients. This review article comprehensively covers recent advances on the clinical unmet needs in the field including newer therapies and therapeutic targets, role of liver transplantation, and emerging biomarkers throughout the disease process from diagnosis, assessing prognosis and disease severity, and predicting responsiveness to medical therapies for severe AH.

1. Introduction

Alcoholic hepatitis (AH) is a distinct clinical syndrome among patients with chronic and active alcohol consumption and is associated with very high morbidity and a short-term mortality of as high as 30–40% over a period of 1 month [1–3]. Clinically, AH presents with acute on chronic liver failure with jaundice, and is often associated with features of systemic inflammatory response syndrome (SIRS) [2,4,5]. Clinical diagnosis of AH is based on rapid development or worsening of jaundice with a total serum bilirubin greater than 3 mg/dl, AST and ALT elevated but usually <400 IU/L with AST/ALT ratio of >1.5, documented heavy alcohol use until 8 weeks prior to presentation, and exclusion of other causes of chronic liver disease [6,7]. Diagnosis may be confounded in about 20–30% of patients especially when the alcohol use history is unreliable or in the presence of concomitant markers suggestive of other liver diseases. These patients will require a liver biopsy for definitive diagnosis of AH [8,9]. A multidisciplinary team approach is required to manage these highly complex and sick patients [2]. It is essential to estimate the disease severity as patients with severe disease have high mortality and select patients can be approached for specific therapeutic options. There are many scoring systems available to gauge disease severity, and most frequently used in routine clinical practice are Maddrey's discriminant function (mDF) and Model for end stage liver disease (MELD) scores [10–12]. Progressive liver failure, gastrointestinal bleeding, and multi organ failure especially hepatorenal syndrome are common causes of mortality in these patients. Further, superimposed bacterial and fungal infections follow these patients like a shadow, in turn worsening the disease pathology and mortality [4,13,14]. Treatment with steroids remains the only pharmacological option for patients with severe AH to provide short-term mortality benefit without any long-term benefit. Since the STOPAH (Steroids Or Pentoxifylline in Alcoholic Hepatitis) study report few years ago, even this option has become controversial in terms of short-term mortality benefit [1,2,9,15]. Over the last decade, liver transplantation (LT) has emerged with increasing enthusiasm as definite therapeutic option for select severe AH patients [6,16,17]. Last decade has also witnessed emerging data on non-invasive biomarkers for clinical diagnosis of AH, predicting prognosis, and response to treatment. Abstinence is key and recidivism with recurrent AH carries higher mortality risk [1,15,18].

The aim of this review article is to outline the recent advances in management and treatment of AH, role of LT, and synthesizing data on emerging biomarkers.

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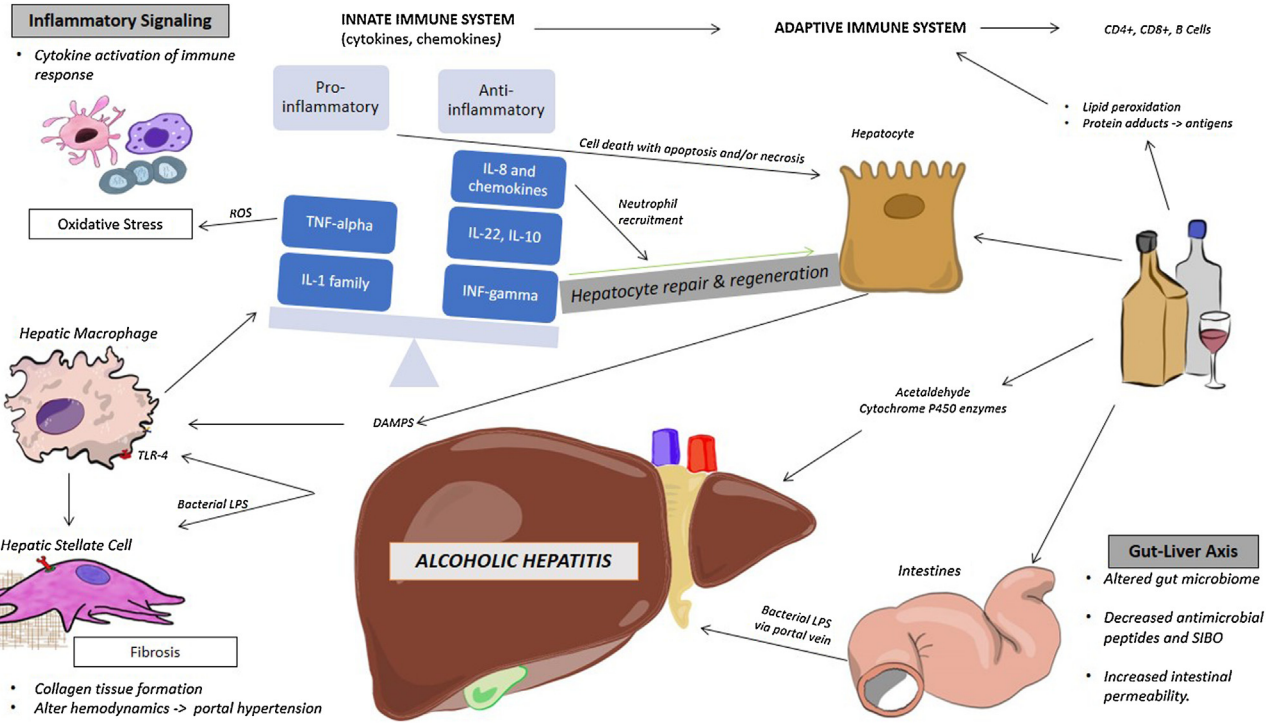

Fig. 1. Pathophysiology of alcoholic hepatitis (AH).
Pathophysiology of alcoholic hepatitis (AH) is due to harmful effects of alcohol via a) toxic by-products namely acetate and acetaldehyde and b) changes in the gut microbiome with small intestinal bacterial overgrowth (SIBO) as a result of decreased antimicrobial peptides from Paneth cell damage and increased intestinal permeability. Inflammatory signaling sets in as a result of lipopolysaccharide (LPS) to translocate into the portal vein with activation of toll like-4 receptors (TLR-4) receptors on hepatic macrophages. This is perpetuated by the damage associated molecular patterns (DAMPs) from apoptosis and necrosis or cell death of hepatocytes. Anti-inflammatory responses driven by cytokines including interferon tumor necrosis factor (TNF) alpha, interferon (IFN), interleukin (IL)-8 with recruitment of neutrophils, and IL-10 family of cytokines drive hepatic regeneration. Oxidative stress with mitochondrial damage and dysfunction develops mediated by the reactive oxygen species (ROS) as a result of direct effects of alcohol on the innate and adaptive immune system, as well as mediated by cell death pathways. All these pathways activated in the hepatic tissue cross talk with the hepatic stellate cells and activated stellate cells lay down collagen with altered hepatic hemodynamics resulting in portal hypertension.

2. Clinical presentation

Patients with AH present with acute or rapid onset of jaundice, acute on chronic liver failure and history of heavy chronic alcohol ingestion up until 8 weeks prior to symptom onset [1,6]. Patients usually report nausea, vomiting, malaise and loss of appetite [1,5,19]. As these patients often are drinking until the day of presentation, features of alcohol withdrawal may be present [6,20]. Malnutrition and sarcopenia can be seen in these patients to varying degrees [1,6,20]. Physical examination findings may often overlap with findings seen in cirrhosis as about 80% of these patients may have underlying cirrhosis or its complications such as ascites, signs of portal hypertension, temporal wasting, sarcopenia, palmar erythema [1,21]. Patients with severe AH may present with features of systemic inflammatory response syndrome (SIRS) in about 40–50% of patients, characterized by the presence of 2 or more of the following: heart rate >100 /min, temperature >38 °C, respiratory rate >20 breaths/min, white cell count >12k or <4k. Although SIRS can occur in the absence of infection (sterile SIRS), underlying infection should be ruled out in these patients [4,22].

2.1. Pathophysiology of AH (Fig. 1)

AH is the result of direct and indirect effects of ethanol and involves a complex interplay and involvement of various pathways. In the gut, alcohol damages Paneth cells that are responsible for the production of antimicrobial peptides, thus leading to small intestinal bacterial overgrowth (SIBO) [1]. This allows pathogenic bacteria to grow and allows translocation of bacterial lipopolysaccharide into the portal vein to the liver. In the liver, LPS stimulates toll like receptors (TLR-4) on macrophages leading to activation of the inflammatory cascade [23,24].

The inflammatory cascade is also upregulated by acetaldehyde and acetate, the metabolic by products of ethanol metabolism by hepatocytes and cytochrome p450 enzymes. The inflammatory signaling involves both pro and anti-inflammatory pathways, which drive apoptosis, cell necrosis, liver fibro genesis, and hepatic regeneration, which ultimately determine the fate of the disease pathology, with resolution of disease or progressive liver failure and mortality [22,25].

For example, TNF-alpha is upregulated in AH and leads to increased levels of reactive oxygen species (ROS) in hepatocyte mitochondria causing cell death and severe mitochondrial depletion of glutathione, an important antioxidant. Other pro-inflammatory cytokines include the interleukin-1 (IL-I) family. Conversely, the anti-inflammatory factors are activated by Kupffer cells and include IL-8 and chemokines, which are responsible for neutrophil recruitment, and IL-10, IL-22 and INF-gamma, all of which are responsible for hepatocyte regeneration [1,26]. Furthermore, the innate immune system activates the adaptive immune system: CD4+, CD8 + T cells and B cells. In addition, long term alcohol use leads to lipid peroxidation, increased levels of malondialdehyde and 4-hydroxynonenal that form protein adducts that serve as antigens to activate the adaptive immune system. This pathway is poorly understood and more research is needed to understand the adaptive immune system activation as it relates to AH [26].

AH can lead to liver fibrosis by activation of hepatic stellate cells. These cells are activated by hepatic macrophages, Kupffer cells or by bacterial LPS. Once activated, hepatic stellate cells initiate collagen

Table 1
Emerging biomarkers in the management of alcoholic hepatitis.

Serum biomarkers	
CCL 20	Driver of inflammation and fibrosis and increased levels assists with diagnosis
Exosomes, miRNA-192 and miRNA-30a	Significantly increased in AH
M30 and M65	Low M30:M65 ratio is seen in AH
PNPLA3 gene polymorphisms	Associated with severe AH in AALD patients
M1 macrophages; M1/M2 ratio	Macrophages transform to M1 phenotype in AH; High M1/M2 ratio is present in AH
Malondialdehyde	Associated with poorer prognosis
Malondialdehyde-acetaldehyde adducts	Elevated levels helpful to predict mortality at day 1 and day 7
M30/M65 ratio	Lower ratio seen in those with poorer prognosis
Osteopontin	Increased levels associated with severity of AH
Interleukin-6	May help risk stratify severe AAH with highest risk of mortality
Deoxycholate and glycodeoxycholate	Low levels associated with increased mortality at 6 months
Urinary biomarkers	
Acetyl-L-carnities Octanoylcarnitine Decanoylcarnitive Alpha-ketoglutaric acid	Urinary levels increased in steroid nonresponsive
Breath biomarkers	
Trimethylamine (TMA) and pentane	Breath levels used to diagnosed AH.

tissue formation and alter hepatic hemodynamics by decreasing endothelial nitric oxide synthase (eNOS) leading to portal hypertension. In addition, acetaldehyde directly upregulates expression of collagen in stellate cells [1,26]. Natural killer (NK) cells are designed to combat hepatic fibro genesis by activating TRAIL and INF-gamma (anti-inflammatory cytokines) however, ethanol leads to decreased effects of NK cells, allowing the pro-inflammatory state to take over [26].

3. Diagnosis

3.1. Clinical and biochemical

Clinical criteria for diagnosis of AH include rapid development or worsening of jaundice, serum bilirubin greater than 3 mg/dl, AST and ALT elevated but usually <400 IU/L with AST/ALT ratio of >1.5, documented heavy alcohol use until 8 weeks prior to presentation, and exclusion of other causes of chronic liver disease. A detailed history to quantify alcohol consumption and time of last alcohol intake often requires corroboration of information from family members or close friends [6,7]. Complete infectious work up is needed to exclude associated infection or sepsis—including ascitic fluid examination, ultrasound for excluding biliary source, blood and urine cultures, and chest x ray examination [1,3,6,19]. MELD and mDF scores are calculated to determine the disease severity and to aid in identifying candidates for pharmacological therapy [6].

About 20–30% of patients require liver biopsy for definitive diagnosis of AH when the clinical diagnosis is uncertain [7,27]. The criteria for diagnosis of AH have been formulated by the NIAAA Alcoholic Hepatitis Consortia. Clinical criteria required for making a diagnosis of AH (probable AH) include history of heavy and chronic alcohol intake until at least 4–6 weeks prior to presentation, AST > ALT with ratio >1.5:1 and absolute numbers not over 400 IU/L, and absence of other causes of liver diseases such as autoimmune disease and drug induced liver injury. When the diagnosis is confounded by absence of any of these criteria the patient is diagnosed as possible AH, which would require a liver biopsy for confirmation of AH diagnosis of definite AH [7].

Trans jugular approach is preferred for obtaining the liver tissue as coexistent coagulopathy is often present [6]. Further, this approach allows measurement of portal pressure and estimates short term prognosis, as the degree of portal hypertension and hyper dynamic circulation are more severe in patients with acute AH [28]. Diagnostic findings of AH on liver biopsy include macro vesicular steatosis, lobular inflammation with neutrophils ballooning degeneration with hepatocyte necrosis, bilirubin plugs with canalicular and ductular cholestasis, and chicken wire fibrosis with fibrotic tissue deposition in the pericellular and/or perivenular spaces [3,5,29]. Liver biopsy also provides estimation of disease severity with calculation of AH histologic score which factors degree of fibrosis, severity and location of bilirubin stasis, degree of neutrophilic infiltration, and mega mitochondria on electron microscopic examination. Of these neutrophilic infiltration and mega mitochondria are associated with better prognosis, while the other two variables are associated with poorer prognosis [5,30]. The degree of fibrosis, degree of neutrophil infiltration, type of bilirubin stasis and presence of mega mitochondria were independently associated with 90-day mortality and can identify non responders to steroids [5,30].

Liver biopsy is an invasive procedure, and hence non-invasive biomarkers are needed for diagnosis of AH among patients with decompensated ALD (Table 1). A pro-inflammatory cytokine, CCL20 a driver of inflammation and fibrosis mediates lipopolysaccharide induced liver injury and is a potential driver of inflammation and fibrosis in AH. Thus, CCL20 may assist with diagnosis as levels are increased in patients with alcoholic hepatitis [31]. MicroRNAs (miRNAs), or non-coding RNAs, associated with extracellular vesicles (EVs)/exosomes are also associated with AH [32]. For example, the total number of EVsmiRNA-192 and miRNA-30a are increased in patients with AH [32]. Patatin-like phospholipase domain protein 3 (PNPLA3) gene polymorphisms are isoleucine-to-methionine substitutions at position 148 that predispose to risk of advanced spectrum of ALD including AH among individuals consuming harmful amounts of alcohol [33,34].

M1 Kupffer class of macrophages are elevated in AH and M2 Kupffer cells regulate the amount of M1 class suggesting a potential role of M1 to M2 cells ratio in diagnosis of AH [35].

Patients with liver disease have higher levels of certain volatile substances in the breath samples compared to healthy controls [36]. In this study, breath levels of trimethylamine and pentane were 90% sensitive and 80% specific in diagnosing AH [36]. Other compounds elevated in AH include 2-propranolol, acetaldehyde, acetone and ethanol. However, these breath samples have been unsuccessful at predicting severity of AH [37]. Mitochondrial dysfunction and oxidative stress is an important component in the pathogenesis of AH. Mitochondrial oxygen consumption rate or

bioenergetics of mitochondria in purified monocytes isolated from peripheral blood sample can stratify decompensated ALD patients to those with and without AH [38,39]. Most biomarkers are limited by lack of validated data in large multicenter studies, unavailability in routine practice, cost (Table 1).

3.2. Predictors and scoring systems to estimate disease severity

Of the clinical variables, underlying cirrhosis, hepatic encephalopathy, and hepatorenal syndrome suggest poor outcome among AH patients as well as those with cirrhosis of other etiologies. For example, in one retrospective study on 366 patients with severe AH, superimposed hepatorenal syndrome in 24 (6.6%) patients predicted worse survival at 1 month from presentation compared to remaining patients without hepatorenal syndrome (17 vs. 68%, $P < 0.001$) [40]. Several scoring systems have been developed to predict disease severity and prognosis of AH patients at the time of presentation. These include Child-Pugh Turcotte (CPT), modified discriminant function (mDF), model for end-stage liver disease (MELD), Glasgow alcoholic hepatitis, and ABIC scores [10]. Although none of these scores is an ideal perfect scoring system [10], mDF and MELD scores are most often used in clinical practice as these are simple, objective, internationally validated, and can help selecting candidates for medical therapy with corticosteroids. In a given patient with AH, mDF score $\geq$32 or MELD score of >20 or presence of hepatic encephalopathy suggests a severe episode and indicates consideration of corticosteroid therapy [6].

Other biomarkers studied to estimate disease severity and prognosis of AH patients are serum malondialdehyde (MDA), a byproduct of lipid peroxidation which forms adducts with acetaldehyde with high immunogenicity resulting in secretion of chemokines and cytokines [41,42] (Table 1).

Cytokeratin-18 inclusions or Mallory bodies on liver histology [43], released after hepatocyte death and taken up by EVs with higher ratio of uncleaved or M65 to cleaved or M30 levels [44,45]. Osteopontin, a matrix protein and immune modulator [46,47]; serum lipidomic profile with evidence of enhanced triglyceride lipolysis with impaired beta oxidation of fatty acids [48]; elevated serum IL-6 levels [49]; serum levels of CCL-20 [31,39]; and changes in gut microbiome with elevated 16 s bacterial and endotoxin levels and lower levels of bacteroides [50].

4. Management of alcoholic hepatitis

4.1. General treatment

The cornerstone of treatment for AH is abstinence from alcohol consumption, and most important determinant of long-term outcome [15,18,51]. Pharmacological therapy in addition to behavioral therapy is a key to prevent relapse [3,19]. An open label retrospective study showed significant benefit with baclofen in patients with AH with improvement in serum transaminases, bilirubin, PT/INR and MELD score. Baclofen works on Gamma Amino Butyric acid receptors, and controls cravings with minimal side effects [52]. Nutritional supplementation should be offered to patients with AH irrespective of the disease severity, especially for patients with markedly reduced caloric intake below 1000–1200 calories per day, as severe protein calorie malnutrition negatively impacts patient outcomes [53]. Enteral nutrition is preferred as it maintains integrity of the gut preventing translocation of gut microbiota [1]. Patients with AH are at higher risk of developing infections, and complete infectious work up including work up for underlying spontaneous bacterial peritonitis is recommended [4,13,14].

4.2. Specific pharmacological treatment

Corticosteroids are the first line option for patients with severe AH provided there are no contraindications for their use, which may be present in about 50% patients such as infections, uncontrolled diabetes, gastrointestinal bleeding, renal failure [4,54,55] (Fig. 2). They suppress cellular (Th1) immunity and thereby reduce the cytokine signaling pathways and inflammation in the liver [56]. The STOPAH study which is to the date the largest multicenter randomized controlled study showed lack of survival benefit of both corticosteroids and pentoxifylline over placebo in patients with severe AH [15]. Meta-analyses including the STOPAH study have shown short-term survival benefit of steroids at one month only without any survival benefit beyond one month. Therefore, societies like ACG and AASLD recommend the use of 40 mg prednisone per day for 28 days in severe AH patients eligible to receive these drugs [6,27].

Pentoxyfylline inhibits tumor necrosis factor (TNF) has also been studied extensively in the treatment of severe AH. Though initial studies showed mortality benefit in patients with AH with DF > 32 [57], later studies failed to show any improvement. However, most of these studies have shown the benefit of pentoxifylline in preventing the development of hepatorenal syndrome [58]. Although, the societies recommend no role of this drug in the treatment of severe AH [6,59], at the ground level this drug continues to be used as an alternative therapy given its excellent safety profile.

Other drugs including glutathione, anti-TNF agents etanercept and infliximab, androgenic steroids, propylthiouracil, and vital therapy have not shown any clinical benefit and are not used for the treatment of AH patients [60–63].

Although, oxidative stress is an important component in the pathology of AH, in general the antioxidants like SAMe, vitamin E, and silymarin have failed in the treatment of ALD and AH [64]. However, two antioxidants N-acetylcysteine and metadoxine deserve special mention. In one multicenter European study on 174 severe AH patients, use of *N*-acetylcysteine as an adjunct to corticosteroids decreased the onset of hepatorenal syndrome and of infections, however failed to provide survival benefit [65]. Metadoxine as adjunct to corticosteroids or to pentoxifylline was shown to improve medium term survival at 3 months in severe AH patients. However, it is unclear whether this benefit was truly an antioxidant effect or benefit of metadoxine on alcohol abstinence [66].

4.2.1. Predictors of response to medical treatment

Lille score, calculated at day 7 after starting the corticosteroid therapy is used to determine treatment response. Developed on well characterized biopsy proven severe AH patients, it is a linear score between 0 and 1, and a score of >0.45 determines non-response to corticosteroids, and it is recommended to discontinue further corticosteroid therapy in these patients (Fig. 2) [67]. Although, this is a fairly accurate score, lack of validation data in cohorts from other countries and centers and need for administering corticosteroids for seven days before response can be assessed are limitations of this score [10,68]. Lille score calculated at day 4 of corticosteroids treatment has also shown to be accurate as day-7 score, however, the societies recommend to give steroids for 7 days before determining the responsiveness to corticosteroids [69]. Recently, dynamic score including baseline MELD score at presentation and Lille score at day 7 has been shown to be better than either score alone in estimating disease severity and prognosis. For example, a patient with baseline MELD score of 21 and non-response to corticosteroids (Lille score of >0.45) has two folds increased mortality compared to another patient with MELD score of 21 who responds to corticosteroids (24 vs. 12%, $P < .001$) [70].

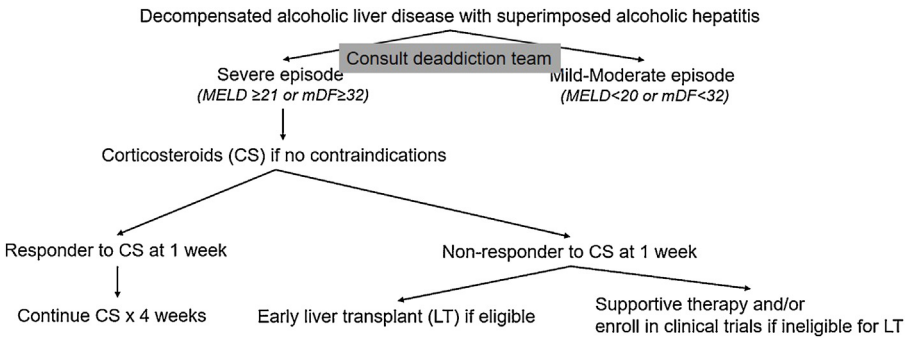

Fig. 2. Algorithm on the management of alcoholic hepatitis. MELD: model for end stage liver disease; mDF: modified discriminant function.

Non-response to corticosteroids is observed in 40–60% of patients and its mechanisms are not well understood. Immune activation by disease pathology has been speculated to be one likely mechanism. For example, in one in-vitro study, response to corticosteroids therapy was associated with baseline inherent ability of corticosteroids to suppress lymphocyte proliferation, as measured by phytohemaglutination assay performed on lymphocytes isolated from peripheral blood sample, obtained from patients with severe AH (Table 1) [71]. Given complexity of these measurements and lack of further validation of these data, this is not available for clinical application in routine practice. In another study, bioenergetics of peripheral monocytes at baseline was useful to predict responsiveness to corticosteroids [39].

Urinary biomarkers like acetyl-L-carnitine (12-fold), octanoylcarnitine (4-fold), decanoylcarnitine (4-fold), alpha-ketoglutaric acid, acetyl-L-carnitine and 3-hydroxysebasic acid have been shown to predict responsiveness to corticosteroids and discriminate non-survivors from survivors (Table 1) [37]. Hepatic venous pressure gradient can also predict response to medical therapy, and in one study value >22 mmHg was associated with 6.7 folds increased odds of mortality [28].

4.3. Liver transplantation

LT has traditionally been not considered an option for patients with AH because of shortage of organs and concern for recidivism [72]. Transplant centers across the world used to consider LT for ALD patients if the candidate has met the abstinence criterion for at least six months. This criterion was introduced to allow the liver disease to get better and not for concern for recidivism [73–75]. In a systematic review on predictors of post-transplant relapse of alcohol use, six months criterion did not emerge as important one for predicting relapse to alcohol consumption after LT. More important recipient variables in this study were younger age, psychosocial status, concomitant polysubstance use, and previous failed rehabilitation attempts [76]. This six months rule was challenged in a prospective multicenter European study, 26 select severe AH patients receiving early LT as salvage therapy had much better survival at six months compared to 26 matched controls with severe AH who were not eligible for early LT (77 vs. 23%, $P < 0.001$) [16]. What is important in this study is that entire survival benefit was observed within the first couple of months after LT, justifying the role of early LT in severe AH if these patients had to be salvaged. Since then multiple single center prospective as well retrospective studies have shown similar data on the benefit of early LT in severe AH [17,77–80]. A recent meta-analysis of all these studies has shown (a) over 16 folds improved survival of patients with severe AH using early LT compared to severe AH patients not receiving LT, (b) 80–90% survival at one year after LT for severe AH which was similar to patients transplanted for alcoholic cirrhosis, and (c) similar rates of relapse to alcohol consumption after LT at 15–20% over 2–3 years comparing AH and alcoholic cirrhosis patients [81]. Based on these encouraging data, societies including ACG and EASL recommend considering LT for select severe AH patients as a salvage therapy (Fig. 2) [6,59]. The criteria for patient selection in most centers are followed based on the criteria used in the European prospective study which were: excellent psychosocial status as agreed upon by the treating team, social worker, surgeons, and anesthesiologists; first episode of hepatic decompensation and of AH, non-response to corticosteroids, and signed document by the recipient for maintaining abstinence after LT and take rehabilitation therapy if directed by the treating team [16] (Table 2). Based on these criteria, only about 2–3% of all AH patients are eligible for this therapy, with no major impact on the donor pool [16,79]. Given that the disease often strikes younger individuals in their prime productive time and this trend in younger individuals is increasing, sharing of donor pool of about 2–3% to these patients seems justifiable. However, there still remain barriers to accepting this modality of treatment for severe AH patients as assessed by public opinions and survey findings of LT centers [79,82]. Most of these barriers surround the issue of awareness and center protocol. Although, most transplant centers interested and considering this treatment option for their severe AH patients have a formal center protocol, there will be a learning curve in terms of patient selection and post-transplant follow up. For example, in the prospective European study six months survival was 77% after LT which is much lower than over 95% expected after transplantation for a patient with cirrhosis [16]. Further, five of the six deaths in that study were due to invasive fungal infections which is frequent complication in these sick patients with severe AH and acute on chronic liver failure [16,83,84]. Furthermore, in a recent study, the proportion of liver transplant for ALD has increased from 24.2% in 2002 to 36.7% in 2016 suggesting a wider acceptance in liver transplant for this population possibly due to the increase in early liver transplant for AH [80].

Table 2
Criteria on selection for early liver transplantation among patients with severe alcoholic hepatitis.

1	Excellent psychosocial status
2	First episode of hepatic decompensation and severe alcoholic hepatitis
3	Non-Response to corticosteroids
4	Signed document by recipient for maintaining abstinence and rehabilitation therapy if indicated

Larger multicenter prospective studies are needed to examine transplant data in AH patients, as basis for developing uniform protocols for patient selection and post-transplant follow up [72].

4.4. New drugs on the horizon

Given the lack of safe and effective therapies for the treatment of patients with ALD and AH, there remains an unmet need for newer

medical therapies. Since the NIAAA initiative and funding multiple consortia for developing newer therapies for AH, many clinical trials are underway [85]. These new therapies and molecules are targeted at different pathways in the AH pathogenesis (Fig. 1). These can be stratified to the following different sections.

4.4.1. Gut liver axis

Gut microbiome maintains intestinal mucosal integrity and epithelial barrier function [86]. A randomized phase-II study using *Lactobacillus rhamnosus* GG is ongoing among patients with moderate AH (MELD score of 11–20), with primary endpoint of change in the MELD score. Another European trial is currently enrolling patients with severe AH to examine the benefit augmentin (amoxicillin plus clavulanic acid) as an adjuvant to corticosteroids, with primary endpoint of 2 months survival (Fig. 1).

Another strategy to modify gut microbiome is fecal microbiota transplantation. In an open label study, this strategy among eight severe AH patients ineligible for corticosteroids showed that fecal microbiota transplantation from healthy relatives improved liver disease, liver disease complications, and patient survival [87].

IgG antibodies found in Bovine colostrum have been studied because of presence of antimicrobials, cytokines, and oligosaccharides [88]. As bacterial LPS plays an important role in initiating inflammatory signaling and AH pathology, purified hyper immune bovine colostrum (IMM-124E) enriched in IgG antibodies against LPS is being studied in a phase-II randomized clinical trial on severe AH patients with MELD score 20–28 as an adjuvant to corticosteroids. With the primary endpoint of reduction in plasma endotoxin (LPS) at 6 months, the trial has been completed and the results are awaited.

Zinc deficiency often present in ALD and AH worsens increased intestinal permeability [89–92]. A randomized clinical trial has been completed, comparing combo of zinc with pentoxifylline and an IL-1 receptor antagonist (anakinra) vs. corticosteroids in patients with severe AH, with primary endpoint of 6 months survival. The study showed trend towards benefit in the intervention arm and detailed results are described in the next section.

Administration of systemic miRNAs and introducing genes coding for miRNAs is potential therapeutic Arena that is being explored. Levels of miR-155 levels, a marker of liver inflammation increase after chronic alcohol ingestion [93].

Farnesoid X receptor (FXR) is a bile acid receptor, seen in liver and regulates the expression of the gene encoding Bile acid synthesis [94]. Studies in ethanol fed mice have shown suppressed FXR activity and in a murine model of ALD, WAY-362450, an FXR agonist was found to reduce ROSs and also modifying FXR-mediated transcriptional mechanisms has a role in reducing inflammation in alcoholic hepatitis [95,96].

4.4.2. Drugs targeting inflammatory cascade

As IL-1 mediates inflammatory signaling [97], IL-1 receptor antagonist anakinra has been studied for the treatment of AH (Fig. 1). Results of a phase II randomized clinical trial in 103 severe AH patients using anakinra (100 mcg s/c × 14 days) in combination with zinc (220 mg twice daily for 6 months) and pentoxifylline (400 mg three times daily for 28 days) in 53 vs. methylprednisolone 32 mg/d for 28 days in 50 patients showed trend towards six months survival benefit with the combination therapy (70 vs. 56%, P = 0.28). MELD at baseline was the strongest predictor of patient survival [98].

Farnesoid X receptor (FXR), a nuclear receptor in the liver and small intestine controls lipid and bile acid metabolism to provide hepatoprotection via their anti-inflammatory and antifibrotic effects [94,95,99]. A phase II randomized clinical trial has been completed with 10 mg/d of obeticholic acid vs. placebo for 6 weeks in patients with moderate AH (MELD 12–19). The results of this study are awaited.

Caspases are a group of enzymes which mediate inflammation, apoptosis, and necrosis [100]. Based on the efficacy of emricasan, a pan caspase inhibitor in sepsis, randomized placebo-controlled study was started within the NIAAA consortium. However, the study was stopped due to issues with drug bioavailability with high blood levels of the caspase inhibitory compound. Based on some benefit in patients with cirrhosis with MELD score of <20, the drug may be tested for moderate AH patients [101].

Selonsertib (GS-4997), an oral inhibitor of apoptosis signaling kinase-1, has been studied in a phase II study on severe AH patients. Ninety-nine patients were randomized to selonsertib and prednisolone (18 mg + 40 mg) versus placebo plus 40 mg prednisolone. After treatment for 28 days, proportion of patients responding to prednisolone evaluated using Lille score, patient survival at day 7 and at week 8, and infection rates were similar [102]. Other potential therapeutic options in this section include CCR2/5 antagonist cenicriviroc, micro-RNA (miRNAs) or their inhibition [93], and extracorporeal liver assist device (ELAD) [63].

4.4.3. Drugs enhancing hepatic regeneration

Hepatic regenerative capacity after any acute or chronic insult including AH is an important determinant of disease severity, responsiveness to medical treatment, and patient survival [103] IL-22, major cytokine of IL-10 family mediates hepatoprotection and hepatic regeneration [104]. In an observational study, number of immune cells producing IL-22 correlated with survival of severe AH patients. A phase II open label clinical trial has been completed using recombinant fusion protein IL-22 (F652) inpatients with moderate and severe AH with MELD score <28. The drug was found to be safe without any pharmacokinetic issues. Currently, a placebo controlled randomized clinical trial of IL-22 infusion is being planned with the primary end point of 90-day survival in patients with moderate AH and safety assessment for severe AH patients with MELD < 28.

Neutrophilia and number of neutrophils on liver histology is a favorable finding as neutrophils and hepatic progenitor or stem cells are important in mediating regeneration of the liver [5,25,105]. Growth factors like granulocyte colony stimulating factor (G-CSF) have shown to improve the disease severity, complications of liver disease, and patient survival in many randomized placebo controlled studies [106–108]. As these studies are reported from Asia, randomized controlled trials are needed from the Western hemisphere before recommending the use of G-CSF in routine clinical practice for the treatment of severe AH.

Conflict of interest

None declared.

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