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Diagnosis and Treatment of Alcoholic Hepatitis: A Systematic Review

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Abstract

Alcoholic hepatitis occurs in about one third of individuals reporting long term heavy alcohol use. It is associated with high short-term mortality, economic burden, and hospital resources utilization. We performed this systematic review to a) describe clinical characteristics and genomics associated with the risk of alcoholic hepatitis; b) discuss role and limitations of liver biopsy and prognostic scoring systems; c) summarize evidence regarding the currently available therapies including liver transplantation; and d) outline emerging therapies with areas of unmet need. Literature search was performed for studies published in English language (January 1971 through - March 2016). Following search engines were used: Pubmed, Elsevier Embase, PsychINFO, and Cochrane Library. For the treatment section, only randomized controlled studies were included for this review. A total of 138 studies (59 randomized, 22 systematic reviews or meta-analyses, 7 surveys or guidelines, 7 population based, and 43 prospective cohort) were cited. There are over 325,000 annual admissions with alcoholic hepatitis contributing to about 0.8% of all hospitalizations in the US. Liver biopsy may be required in about 25–30% cases for uncertain clinical diagnosis. Corticosteroids with or without N-acetylcysteine remains the only available therapy for severe episode. Data are emerging on the role of liver transplantation as salvage therapy for select patients. Abstinence remains the most important factor impacting long-term prognosis. Results from the ongoing clinical trials within the National institute on Alcohol Abuse and Alcoholism funded consortia are awaited for more effective and safer therapies. Alcoholic hepatitis is a potentially lethal condition with a significant short-term mortality. A high index of suspicion is required. There remains an unmet need for non-invasive biomarkers for diagnosis, and predicting prognosis and response to therapy.

Keywords

Alcoholism; Alcoholic liver disease; Recidivism; Pathophysiology; Corticosteroids

INTRODUCTION

Approximately 65% of the US population consumes alcohol regularly with 8–10% reporting heavy alcohol use (an average of ≥ 14 drinks per week in males and ≥ 7 drinks per week in females). (Delker E, 2015) A third of individuals with chronic and active heavy alcohol use develop alcoholic hepatitis (AH), a clinical syndrome presenting with jaundice or hyperbilirubinemia and often features of the systemic inflammatory response syndrome. (Altamirano et al., 2014, Michelena et al., 2015) Genetic polymorphisms, female gender, ethnicity, obesity, concomitant hepatitis C infection and binge drinking modify the AH risk among individuals with heavy alcohol use. (Singal, 2013, Singal et al., 2012b, Salameh et al., 2015) As of 2010, there were 326, 403 annual admissions in the US with a discharge diagnosis of AH. This contributes to 0.83% of all hospitalizations within the US and is associated with high mortality, morbidity, economic burden, and use of hospital resources. (Jinjuvadia et al., 2015)

A high index of suspicion is required for early diagnosis of AH among patients with decompensated alcoholic liver disease. Liver biopsy may be needed in about 25–30% of patients with uncertain clinical diagnosis. (Hardy et al., 2013, O'Shea et al., 2010b) Data are emerging on the role of liver biopsy to predict outcomes and prognosis. (Duvoux et al., 2004, Liangpunsakul and Kleiner, 2014) Several scoring systems based on patient demographics and routine laboratory values have been developed to determine disease severity and overall prognosis. (Singal and Shah, 2011, Maddrey et al., 1978, Dunn et al., 2005, Forrest et al., 2005, Forrest et al., 2010, Louvet et al., 2007, Louvet et al., 2015) In clinical practice, modified discriminant function and model for end-stage disease (MELD) scores are used to determine disease severity and identify patients needing treatment.

Patients with a severe episode of AH frequently manifest with features of acute-on-chronic liver failure with potential 40–50% mortality at 1 month from presentation. (Singal et al., 2014b, Lucey et al., 2009, Mathurin et al., 2011b) Hepatic failure, GI bleeding and hepatorenal syndrome are the most common causes of early death in patients without treatment. (Hmoud et al., 2015, Yu et al., 2010) Superimposed infectious complications from bacterial and fungal organisms are common in AH and often contribute to multi-organ failure in these patients. (Hmoud et al., 2015, Yu et al., 2010, Gustot et al., 2014, Michelena et al., 2015) Abstinence from alcohol use is the most important determinant among survivors of the initial episode, as the recurrent AH episode is invariably more severe and lethal. (Thursz et al., 2015, Potts et al., 2013b, Potts et al., 2013a)

With the recently reported STOPAH (Steroids Or Pentoxifylline for Alcoholic Hepatitis) study, the efficacy of corticosteroids, the only intervention with traditionally accepted benefit, has become hotly debated. (Thursz et al., 2015) Abstinence from alcohol and nutritional supplementation are critical in the management of these patients. (Thursz et al., 2015, Singal and Charlton, 2012, O'Shea et al., 2010b) Recognizing the lack of clinical

research and available effective therapies to treat AH,(Shah, 2010) National Institute of Alcoholism and Alcohol Abuse few years ago funded several consortia in the US to conduct clinical trials for development of newer effective and safer therapies for this disease. Data are emerging on the benefits of liver transplantation as a therapeutic option for select severe AH patients who do not respond to available pharmacological interventions.(Mathurin et al., 2011a, Singal et al., 2012a, Hasanin et al., 2015) However, the utilization of this option remains controversial.(Hasanin et al., 2015)

In this systematic review, we provide an evidenced based synthesis of the published literature to describe clinical characteristics and genomics associated with AH, diagnosis of AH and the role of liver biopsy, treatment options for AH with emerging pharmacological therapeutic targets and the utility of liver transplantation in the management of patients with AH.

METHODS

Data Sources and Searches

Studies were identified by systematic searches conducted by a medical librarian (LV) in the following electronic databases: PubMed (earliest index date through 03 /2016], Elsevier Embase [1973-through 03/2016], ProQuest PsychINFO (up to 03/2016), and the Cochrane Library (through 03/2016.) A combination of keyword variants, synonyms and database subject headings was used for the concepts of alcoholic hepatitis, therapy, and various pharmacological and non-pharmacological treatments. These were then combined to form the final searches. For the complete PubMed search strategy and MeSH words, please see *details* in the supplement section. Clinical Trials.gov [<https://clinicaltrials.gov/>] was searched for ongoing clinical trials on alcoholic hepatitis. Additionally, the reference lists of selected articles and key systematic reviews were scanned.

Study Selection

Two investigators (SK and AKS) independently reviewed the studies identified on initial search to select studies for this systematic review. Studies were limited to English language, and only publications including human subjects were included. Medline records were excluded in the Embase search strategy. Any discrepancy was resolved by discussion and consensus.

Data Extraction and Quality Assessment

One independent investigator reviewed the selected studies (KS on diagnosis and liver transplantation sections and AKS on pathophysiology with clinical features and treatment sections) for data synthesis. Only randomized controlled studies were included for treatment section. For the other sections, prospective cohort and population based studies were included. Retrospective studies were not included. Abstracts were included for critical data and if the full papers on that issue were unavailable. Any discrepancy was resolved by discussion and consensus.

Data Synthesis and Analysis

Studies published in the last five years and seminal landmark studies were focused to develop the current status in each section.

RESULTS

Potentially relevant 196 articles on AH were reviewed (49 on clinical and genomics, 15 on diagnosis, 121 on treatment, and 11 on liver transplantation) to select 144 articles for writing this manuscript (Supplemental Figure 1). Of these, 138 references (59 randomized, 22 systematic reviews or meta-analyses, 7 surveys or guidelines, 7 population based, and 43 prospective cohort) were cited.

Pathophysiology of Alcoholic Hepatitis

Alcohol has been used for centuries, but it was recognized as a direct hepatotoxin only in the 1960s.(Rubin and Lieber, 1973). AH is a complex disease with interaction of A) gut and liver axis: small bowel bacterial overgrowth, dysbiosis and altered gut microbiome with more pathogenic bacteria, increased gut permeability, translocation of bacterial lipopolysaccharide into the liver via portal vein, stimulation of toll like receptors-4 on hepatic macrophages and kupffer cells and B) initiation of an inflammatory cascade mediated by tumor necrosis factor- α (Figure 1).(Keshavarzian et al., 2009, Mutlu et al., 2012, McClain and Cohen, 1989) Patatin-like phospholipase protein (PNPLA3) polymorphisms, Caucasian race, and female gender may increase susceptibility to AH. (Singal, 2013, Salameh et al., 2015) Individual susceptibility to alcohol induced damage may also be driven by differences in the composition and metabolites of intestinal microbiota. (Llopis et al., 2015) The cytokine load consists of pro-inflammatory cytokines of the interleukin-1 family mediating inflammasome formation and anti-inflammatory cytokines of interleukin-10 family. Cytokines (especially interleukin-8) and chemokines recruit neutrophils to the liver, a characteristic histological finding in AH patients (Supplemental Figure 2). Neutrophils recruited to the liver increase hepatocyte growth factor and help in tissue repair and recovery from AH.(Taieb et al., 2002) Innate immunity dysfunction among patients with progressive disease leads to complete immune paralysis with onset of multi-organ failure, infections, and death. Hepatic macrophages also cross talk with hepatic stellate cells activating collagen tissue formation and altering hepatic hemodynamics with resultant portal hypertension. Oxidative stress occurs from multiple sources including acetaldehyde from metabolism of alcohol, inflammatory cytokines and neutrophils, apoptotic cells, and alcohol-induced nitrosative stress.(Singal et al., 2011a)

Clinical presentation of Alcoholic Hepatitis

The clinical presentation of AH is characterized by acute onset; chronic alcohol use until at least 3–4 weeks prior to presentation; jaundice or hyperbilirubinemia; acute-on- chronic liver failure; and frequent occurrence of systemic inflammatory response syndrome. Clinical jaundice is present in about 37–60%, elevated bilirubin is always present. Anorexia, nausea, vomiting, and malaise are commonly reported. (Singal et al., 2014b, Lucey et al., 2009, Mendenhall, 1981, Lischner et al., 1971, Altamirano et al., 2014, Gustot et al., 2014, Michelena et al., 2015) Other common manifestations include fever (23–56%), abdominal

pain in about 20%, and malnutrition in 60–90% ((Mendenhall, 1981, Lischner et al., 1971) About 80–90% of AH patients have underlying cirrhosis and may present with complications of liver disease including ascites, variceal hemorrhage, hepatic encephalopathy, and hepatorenal syndrome. Features of alcohol withdrawal may be present. (Lischner et al., 1971, Mendenhall, 1981) Mechanisms of the susceptibility to AH in the presence of chronic alcohol related liver injury remains unclear. Physical examination reveals icterus often accompanied by tender hepatomegaly, ascites, edema, portal hypertension, and features of malnutrition.(Mendenhall, 1981, Mendenhall et al., 1995a) Laboratory evaluation shows hyperbilirubinemia (usually above 5 mg/dL), elevated aminotransferases (rarely above 300–400 IU/l), and coagulopathy.(Lucey et al., 2009, Singal et al., 2014b) Leukocytosis is often present. Other lab abnormalities may be present from organ failure, due to either superimposed infections or from progressive liver failure.(Hmoud et al., 2015, Michelena et al., 2015)

Diagnosis of Alcoholic Hepatitis

Diagnosis of AH should always be considered in a patient with chronic alcohol use presenting with liver disease. As the clinical profile of AH may mimic sepsis or cholangitis, detailed work up including chest X-ray, blood cultures, ascitic fluid examination, urinalysis and culture, and abdominal imaging should be obtained. (Lucey et al., 2009, Singal et al., 2014b) Decompensation of alcoholic liver disease from causes other than AH and other liver diseases should also be considered. Atypical features for AH include jaundice for over 3 months, transaminases over 400 IU/l, and last alcohol use more than 4 weeks prior to presentation. White blood cell count and platelet count may help to determine the clinical diagnosis of AH.(Hardy et al., 2013) However, 25–30% of AH patients may require liver biopsy for accurate diagnosis especially when the clinical diagnosis remains uncertain. (O'Shea et al., 2010b, Petts et al., 2015)

Histological findings in a typical AH patient (Supplemental Figure 2) include lobular inflammation with neutrophilic infiltration, ballooning degeneration with apoptosis or necrosis of hepatocytes, and Mallory bodies. More severe cases demonstrate intrahepatic cholestasis, ductular stasis of bile or bilirubinostasis, and perivenular fibrosis.(Spahr et al., 2001, Altamirano et al., 2014, Michelena et al., 2015) The majority of patients demonstrate varying degrees of fibrosis and steatosis. Transjugular liver biopsy is recommended as coagulopathy and/or ascites are frequently present in these patients. The transjugular route also provides information on the wedge hepatic venous gradient and portal pressure, which correlates with outcome and patient survival.(Rincon et al., 2007) Histological findings with grade of steatosis, neutrophilic infiltration, mega mitochondria, and bilirubinostasis may also predict outcome of AH patients and response to corticosteroids.(Duvoux et al., 2004, Shasthry et al., 2014, Mathurin et al., 1996, Altamirano et al., 2014) Furthermore, liver biopsy provides guidance on selection of patients for recruitment into clinical trials.(Petts et al., 2015, Hardy et al., 2013) Emerging modalities for diagnosis include doppler ultrasound examination of the liver for measurements on hepatic blood flow, (Han et al., 2002, Abhilash et al., 2015), mitochondrial bioenergetics measurements in peripheral blood cells, and assessment of markers of liver progenitor cell proliferation. (Singal et al., 2014a, Sancho-Bru et al., 2012)

Assessment of disease severity—Once the diagnosis of AH is determined, it is crucial to assess the disease severity. Several scoring systems have been developed to assess disease severity and for predicting mortality at 28 days and at 3 months from presentation. (Maddrey et al., 1978, Dunn et al., 2005, Srikureja et al., 2005, Dominguez et al., 2008, Forrest et al., 2005) However, every scoring system has some limitations (Supplementary Table). In routine clinical practice, mDF and MELD scores are used to assess disease severity and guide treatment initiation. (O'Shea et al., 2010b) Lille score, with early change of bilirubin at one week after starting corticosteroids is used to help guide clinicians whether these drugs should be continued beyond one week or not. (Louvet et al., 2007) Neutrophilia, increased hepatic neutrophilic infiltration, portal blood flow changes with hepatic venous pressure gradient, ductular bilirubinostasis, and degree of steatosis on biopsy have been shown to correlate with outcome and response to corticosteroids. (Mathurin et al., 1996, Michelena et al., 2015, Rincon et al., 2007, Duvoux et al., 2004) Although, most scoring systems are comparable on accuracy, dynamic model with MELD score at baseline and Lille score at one week of corticosteroid therapy performs better than either score alone in predicting disease severity and outcome. (Louvet et al., 2015) Data are emerging on mitochondrial bioenergetics measurements in peripheral blood cells at the time of initial presentation as a predictor of corticosteroid response. If confirmed and validated, this non-invasive biomarker may potentially personalize therapy in AH patients and selectively treat those who are likely to respond to corticosteroids, and open up the potential for mitochondrial based therapies. (Singal et al., 2014a)

Treatment

Various therapeutic options are outlined in Table 1.

Corticosteroids—Since the first RCT in 1971, (Porter et al., 1971) a total of 13 placebo-controlled studies have been published with differences in type and dose of corticosteroid, inclusion or exclusion criteria, biopsy confirmation for AH diagnosis, and follow up duration. (Helman et al., 1971, Campa et al., 1973, Blitzer et al., 1977, Shumaker et al., 1978, Maddrey et al., 1978, Lesesne et al., 1978, Depew et al., 1980, Theodossi et al., 1982, Mendenhall et al., 1984a, Bories et al., 1987, Carithers et al., 1989, Ramond et al., 1992) Of these, corticosteroids showed survival benefit in only five studies. (Helman et al., 1971, Maddrey et al., 1978, Lesesne et al., 1978, Carithers et al., 1989, Ramond et al., 1992) Pooled data on the mortality benefit of corticosteroids from meta-analyses of these 13 RCTs is also conflicting with benefit in two, (Imperiale et al., 1999) and no benefit in the other. (Christensen and Gluud, 1995) Cochrane meta-analysis of 15 RCTs, including two more studies, one comparing corticosteroids to enteral nutrition, (Cabre et al., 2000) and another one to an antioxidant cocktail, (Phillips et al., 2006) confirmed that corticosteroids are beneficial for patients with severe AH. (Rambaldi et al., 2008) Two meta-analyses using the individual patient data on severe AH from 3 largest studies in one and from 5 studies in the other, (Mendenhall et al., 1984a, Carithers et al., 1989, Ramond et al., 1992, Cabre et al., 2000, Phillips et al., 2006) showed a 40–50% survival benefit with corticosteroid treatment. (Mathurin et al., 2011b, Mathurin et al., 2002) Based on these data, the American Association for Study of Liver Diseases and the American College of Gastroenterology

recommend use of oral prednisolone 40 mg per day or equivalent intravenous dose in patients having severe AH.(O'Shea et al., 2010b, O'Shea et al., 2010a)

Corticosteroids are anti-inflammatory and reduce cytokine load. (Richardet JP, 1993, Spahr et al., 2001) However, response is observed in only 40–50% patients, whose lymphocytes are sensitive to inhibition of proliferation with corticosteroids.(Kendrick et al., 2010) Further, corticosteroids have potential side effects of such as infections, hyperglycemia, electrolyte disturbance, and weight gain. Of these, infection, especially fungal infections, is most relevant in AH patients.(Louvet et al., 2009, Hmoud et al., 2015, Michelena et al., 2015),(Gustot et al., 2014) Response to corticosteroids is assessed at 1 week of therapy using Lille score (a continuous score between 0 and 1), with a score of 0.45 or below classified as response and above 0.45 as non-responses to corticosteroids.(Louvet et al., 2007, Mathurin et al., 2003) This means that over half of severe AH patients, who are potential non-responders to corticosteroids, will be treated with these potentially toxic drugs. These limitations reduce the routine use of corticosteroids for severe AH in spite of the clinical indication.(Singal et al., 2013, Ahn J, 2009) (Lucey et al., 2009) About 20% of patients presenting with AH have concomitant hepatitis C, which increases the mortality risk because of synergistic interaction between hepatitis C and alcohol in causing hepatocellular damage.(Singal et al., 2011b) With the advent of direct acting antiretroviral for hepatitis C, studies are needed among AH patients with concomitant hepatitis C to examine efficacy of treating hepatitis C on the outcome from AH.

Pentoxifylline—With the use of corticosteroids remaining controversial, pentoxifylline 400 mg three times daily by mouth in the seminal randomized placebo controlled study reduced short term mortality in severe AH patients.(Akriviadis et al., 2000) However, many other studies using pentoxifylline have reported conflicting data with mortality benefit in one, (Paladugu H, 2006) and no benefit reported in three other studies. (McHutchinson JG, 1991, Sidhu et al., 2012, Lebrec et al., 2010) In a meta-analysis, the pooled data from six studies did not show evidence for survival benefit in using pentoxifylline in severe AH. (Whitfield et al., 2009) Pentoxifylline was also not beneficial when used as a salvage therapy for non-responders to corticosteroids,(Louvet et al., 2008) and as an adjuvant to corticosteroids.(Mathurin et al., 2013, De et al., 2014, Sidhu et al., 2012) Two randomized studies comparing corticosteroids and pentoxifylline showed benefit with pentoxifylline in one,(De et al., 2009) while the other non-inferiority trial showed that pentoxifylline is not equivalent to corticosteroids.(Park et al., 2014) To define the status of corticosteroids and pentoxifylline in the treatment of AH, a multicenter randomized controlled study from UK (STOPAH) planned to enroll 1200 patients (300 each treated with pentoxifylline, prednisolone, both, or placebo).(Forrest et al., 2013) Results from this study (which was terminated early), on 1103 randomized patients showed that prednisolone tended to improve survival ($P=0.06$) and there was no survival benefit with the use of pentoxifylline. None of the drugs improved medium and long term survival at 3 months and at 1 year.(Thursz et al., 2015) This study was limited by excluding sicker patients from enrollment with low overall 28 day mortality of 19%, as well as enrollment based on clinical diagnosis with potential misclassification of decompensated alcoholic cirrhosis as AH.(Thursz et al., 2015) A recent network meta-analysis of 22 randomized studies, including the STOPAH study, showed

moderate quality evidence for benefit of corticosteroids alone and in combination with pentoxifylline or with N-acetylcysteine, and low quality evidence for benefit of pentoxifylline alone.(Singh et al., 2015) In the background of unavailability of effective drugs for severe AH patients, prednisolone alone or in combination with N-acetylcysteine should be considered for severe AH (Figure 2). Pentoxifylline in all the studies including the STOPAH study showed a beneficial effect in protecting renal function and preventing hepatorenal syndrome. Given the excellent safety profile of pentoxifylline, its role for select AH patients with renal failure remains a testable hypothesis.

Other Therapies

Abstinence: Abstinence is the most important factor driving the long-term outcome in AH patients.(Thursz et al., 2015, Potts et al., 2013a) Apart from behavioral therapy, pharmacological options should be considered for patients at risk for recidivism after discharge from the hospital in a patient recovering from AH.(Singal et al., 2014b, Lucey et al., 2009) Of all the available drugs to maintain abstinence, baclofen, gamma amino butyric acid agonist, examined in an open label study in severe AH patients, has shown good efficacy and safety profile.(Yamini et al., 2014) Other drugs including acamprosate and naltrexone, and metadoxine, although effective and safe in alcoholics, have not been studied in patients with AH. (Addolorato et al., 2013, Higuera-de la Tijera et al., 2015)

Nutritional supplementation: Protein-calorie malnutrition occurs frequently in AH patients and negatively impacts their outcome.(Mendenhall et al., 1995b, Mendenhall et al., 1984b, Mendenhall et al., 1995a) Nutritional supplementation should be considered for every AH patient irrespective of disease severity (Figure 2). Enteral supplementation is preferred whenever possible as it is safer, maintains gut integrity, and reduces infection risk. Five RCTs have shown improvement in nutritional status, liver function, and reduced risk for infections with enteral supplementation, however there was no survival benefit.(Calvey et al., 1985, Cabre et al., 2000, Mendenhall et al., 1985, Mendenhall et al., 1993, Moreno et al., 2010) A recent RCT showed that enteral nutrition is difficult to achieve in these patients and also confirmed lack of survival benefit of nutritional supplementation as adjuvant to corticosteroids.(Moreno et al., 2016a) Parenteral nutrition may be considered when enteral feeding is difficult in patients having ileus, bowel obstruction, or protracted nausea or vomiting. After documentation of survival benefit with parenteral nutrition in AH patients in one study,(Nasrallah and Galambos, 1980) six further studies failed to show this survival benefit.(Diehl et al., 1985, Naveau et al., 1986, Achord, 1987, Simon and Galambos, 1988, Mezey et al., 1991, Bonkovsky et al., 1991) Meta-analyses from pooled data on randomized studies have shown benefits of nutritional supplementation in improving liver function with reduction in encephalopathy and infections. Survival benefit was seen among select patients having markedly reduced oral intake.(Fialla et al., 2015, Salameh H, 2013) This observation has also been made in other studies examining the correlation of caloric intake with the survival outcome in AH patients. ((Mendenhall et al., 1995a, Moreno et al., 2016b) Hence, AH patients should have daily calorie counts to identify individuals who could benefit from nutritional supplementation.

Antioxidants: Oxidative stress from multiple sources is a major component in the pathogenesis of AH (Figure 1). Intra-venous N-acetylcysteine as an adjuvant to prednisolone was beneficial in improving 28 day survival as compared to prednisolone alone. The benefit of N-acetylcysteine was due to a reduction in deaths from infections and from hepatorenal syndrome.(Nguyen-Khac et al., 2011) In another study, intravenous N-acetylcysteine failed when used as an adjuvant to enteral nutrition.(Moreno et al., 2010) Other drugs including vitamin E, antioxidant cocktail, and metadoxine have shown some benefit in AH patients, however, further studies are needed to validate and confirm the beneficial effects of these agents.(Mezey et al., 2004, Phillips et al., 2006, Stewart et al., 2007, Higuera-de la Tijera et al., 2015)

Miscellaneous therapies: Tumor necrosis factor- α (TNF) is one of the major players in the pathogenesis of AH (Figure 1).(McClain and Cohen, 1989) However, randomized studies with anti-TNF agents including infliximab and etanercept were negative, with actually more deaths occurring in the treated arm.(Naveau et al., 2004, Boetticher et al., 2008) Other therapies using amlodipine,(Bird et al., 1998) insulin and glucagon infusion; (Bird et al., 1991, Trinchet et al., 1992) androgenic steroids;(Rambaldi and Gluud, 2006) and propylthiouracil(Halle et al., 1982) have not been shown to be useful in the treatment of AH. Albumin dialysis using molecular absorbent system in a randomized study improved liver function, portal hypertension, and liver disease complications without benefit on overall patient survival.(Banares et al., 2013) This modality may be used in select cases as a bridging therapy, before they are considered for liver transplantation or when labeling further medical treatment as futile. Neutrophils in the liver are a good source of hepatocyte growth factor with degree of neutrophilic infiltration in the liver directly correlating with improved survival.(Taieb et al., 2002, Michelena et al., 2015, Altamirano et al., 2014) Based on this concept, use of granulocyte colony stimulating factor in an RCT showed encouraging data with improved patient survival.(Singh et al., 2014) However, there remains risk for superimposed infections in this sick population with the use of these drugs. Larger, better designed studies from the Western hemisphere are needed as basis for documenting the efficacy and safety of this approach for treatment of severe AH.

Emerging Therapies: Recognizing the lack of effective safe therapies for AH and scarcity of clinical research in this field, National Institute of Alcohol Abuse and Alcoholism took the major initiative a few years ago with the funding of major consortia to conduct clinical trials as basis for development of effective and safe drugs for the treatment of severe AH (Table 2). Results from all these ongoing trials are awaited and would potentially help in improving outcome of patients with severe.

Liver Transplantation

An established treatment option for patients with alcoholic cirrhosis, liver transplantation remains controversial for AH patients. This is due to the requirement of the criterion of at least six months of abstinence before being considered for transplant, which cannot be met by a patient with severe AH.(Singal et al., 2012a, Mathurin et al., 2011a) The six month abstinence criterion was introduced to allow for spontaneous recovery of liver function from the acute effects of alcohol use.(Lucey et al., 1997) Data on six months of abstinence as a

predictor of recidivism remain controversial. In fact, stronger predictors are younger age, psychosomatic status and social support.(McCallum and Masterton, 2006) In a systematic review of 22 studies examining predictors of recidivism, six months abstinence prior to LT emerged as predictor of recidivism in only 2 of 11 studies. In contrast, lack of social support, psychological comorbidities, younger age, and polysubstance abuse predicted recidivism accurately in 14 of 18 studies examining these variables.(McCallum and Masterton, 2006) In a prospective study, use of liver transplantation in severe AH patients, who did not respond to corticosteroids and had excellent psychosocial support, provided survival benefit compared to AH patients who did not receive liver transplant.(Mathurin et al., 2011a) Furthermore, most of this benefit was derived in the first six months suggesting that severe AH patients not responding to available medical therapies cannot afford to wait for six months for liver transplantation.(Mathurin et al., 2011a) In this study, rigorous psychosocial evaluation was performed as basis for selecting patients for transplantation. Treating medical team, liver transplant surgeons, social work team, and anesthesiology team all agreed upon excellent psychosocial support before wheeling in the patient for liver transplantation. Similar outcomes were also reported in a recently reported series on nine severe AH patients who did not respond to corticosteroids and received early LT. Compared to 85 severe AH patients not responding to corticosteroids and ineligible for early LT, patients receiving salvage LT had better six months survival (89 vs. 11%, $P<0.001$). (Im et al., 2016) Benefit of liver transplantation was also shown in a population-based study using the United Network of Organ Sharing database in the US. The study showed that the outcomes of AH patients are similar to transplant recipients for alcoholic cirrhosis.(Singal et al., 2012a) Other studies have also shown that the presence of histological findings of AH in the explant liver does not impact the post-transplant outcome.(Wells et al., 2007, Tome et al., 2002) In spite of the benefit of liver transplantation in select AH patients, the transplant community continues to face challenge in using this treatment option. In a recently performed survey of liver transplant centers in the US, only 12 of 45 centers reported performing liver transplantation for AH patients with documented non-response to corticosteroids.(Hasanin et al., 2015) Recidivism after liver transplantation for AH in all these four studies was similar to recidivism after transplantation for alcoholic cirrhosis.(Mathurin et al., 2011a, Singal et al., 2012a, Hasanin et al., 2015, Im et al., 2016) Common barriers to liver transplantation in AH include socio-cultural factors, public opinion that alcohol is in itself a self- inflicted disease, and shortage of donor organs.(Hasanin et al., 2015) However, if used for select severe AH patients, this approach would not consume more than 1–3% of the liver donor pool.(Hasanin et al., 2015, Mathurin et al., 2011a, Im et al., 2016) Liver transplantation should be considered for select AH patients as salvage therapy as this condition affects young and middle-aged individuals (Figure 2).

Prognosis of Alcoholic Hepatitis

Untreated severe disease has a potential for mortality as high as 40–50% at one month from presentation. Amount of alcohol consumption, occurrence of acute kidney injury, underlying cirrhosis, systemic inflammatory response syndrome, severity of portal hypertension, development of bacterial or fungal infections, and concomitant hepatitis C infection predict short term mortality.(Altamirano et al., 2012, Maiwall et al., 2015, Rincon et al., 2007, Singal et al., 2012b, Hmoud et al., 2015, Altamirano et al., 2011, Gustot et al., 2014,

Michelena et al., 2015) Serum markers like pro-calcitonin, lipopolysaccharide, liver progenitor cell proliferation, soluble TNF-receptor1, and mitochondrial bioenergetics are emerging non-invasive biomarkers to identify severe AH patients at risk for developing worsening liver failure and bad outcome.(Sancho-Bru et al., 2012, Kumar et al., 2014, Duvoux et al., 2004, Spahr et al., 2004, Singal et al., 2014a, Michelena et al., 2015) There is currently an ongoing observational study examining the role of interleukin 22 serum levels predicting disease severity and outcome of AH patients (<https://clinicaltrials.gov/ct2/show/NCT01918462?term=il-22&rank=2>). Data are also emerging on the role of liver biopsy in predicting outcome and response to therapy.(Duvoux et al., 2004, Altamirano et al., 2014, Michelena et al., 2015) AH is a risk factor for faster progression to advanced fibrosis and cirrhosis.(Mathurin et al., 2007, Pares et al., 1986) Among patients surviving the initial AH episode, patient behavior and maintenance of abstinence determines the medium- and long-term mortality.(Thursz et al., 2015, Potts et al., 2013b, Potts et al., 2013a) Recurrent AH occurs in about two thirds of survivors of the initial episode with an estimated 5 year survival of only about 32%.(Potts et al., 2013a) Recurrent AH and recidivism is more common among women, is more severe than the initial episode, and significantly impacts long-term survival.(Potts et al., 2013b, Potts et al., 2013a) Studies are needed to examine reliable and accurate models predictive of recidivism so as to identify high risk groups for intervention aiming to prevent recidivism and recurrent AH.

CONCLUSIONS

AH is a potentially lethal unique syndrome among patients with chronic heavy alcohol use. A high index of suspicion is required for diagnosis among patients with decompensated alcoholic liver disease. Liver biopsy is recommended for patients with uncertain clinical diagnosis as also recommended by the American Association for Study of Liver Diseases and American College of Gastroenterology. Data are emerging on the beneficial effects of liver transplantation as salvage therapy for select AH patients with non-response to currently available medical therapies. Corticosteroids with and without N-acetylcysteine are considered for severe AH provided there are no contraindications for use of corticosteroids. Liver transplantation should be considered for patients not responding to corticosteroids. In the background of recently reported STOPAH study and emerging data on the beneficial effects of liver transplantation as a salvage therapy for non-responders to pharmacological options,(O'Shea et al., 2010b, O'Shea et al., 2010a) there is a need to update the guidelines on the management of alcoholic liver disease. In spite of recognizing this disease for the last half a century, there are many issues which remain poorly understood with potential for future research (Table 2). Results from the ongoing clinical trials within the National Institute of Alcohol Abuse and Alcoholism funded consortia are awaited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Gut permeability increases from bacterial overgrowth, altered gut microbiome or dysbiosis, and acetaldehyde derived from metabolism of alcohol. Alcohol induced damage to Paneth cells of the gut mucosa decreases antimicrobial peptides, further exacerbating the problem. Bacterial lipopolysaccharides and damage associated protein molecules (DAMP) translocate to the liver via the disrupted gut epithelial tight junctions and the portal vein. Pattern recognition receptors (TLR-4) on the hepatic macrophages and kupffer cells recognize the translocated lipopolysaccharides and DAMP causing the activation of macrophages with release of cytokines including tumor necrosis factor- α . Inflammatory cascade is initiated via the inflammasome complex, which consists of pro interleukin-1 β and caspase-1. Pro-inflammatory cytokines (IL-1 family) and chemokines particularly IL-8 attract neutrophils to the liver. Anti-inflammatory cytokines (IL-10 family including IL-22 and interferon gamma) in combination with recruited neutrophils drive hepatic regeneration. The balance between inflammation and regeneration decides the fate of the pathologic event and outcome of the patient. Oxidative stress occurs via mechanisms indicated by * in the figure, with generation of reactive oxygen species. Activated macrophages also cross talk with hepatic stellate cells

with stimulation of fibrogenesis (mainly via tumor growth factor- β). Hepatic stellate cells become activated myofibroblasts and downregulate vascular endothelial nitric oxide synthase (eNOS) activity. This leads to worsening of portal hypertension via fibrosis (fixed component) and decrease in nitric oxide (dynamic component).

Figure 2.

Approach to management of a patient with decompensated alcoholic liver disease.

Table 1

Treatment options for alcoholic hepatitis: current status

A.	Therapies with potential efficacy
1.	Nutrition
	<ul style="list-style-type: none"> - Enteral - Parenteral
2.	Abstinence
	<ul style="list-style-type: none"> - Rehabilitation, behavioral therapy - Baclofen
3.	Specific Drugs
	<ul style="list-style-type: none"> - Corticosteroids - Pentoxifylline - N-acetyl cysteine - Metadoxine
4.	Liver transplantation
B.	Therapies with no efficacy
1.	Anabolic steroids
2.	Propylthiouracil(PTU)
3.	TNF inhibitors
4.	Colchicine
5.	Amlodipine
6.	Insulin and glucagon
7.	Molecular adsorbent recirculating system dialysis
C.	Emerging Therapies
1.	Drugs targeting gut-liver Axis
	<ul style="list-style-type: none"> - Antibiotics, Probiotics(Han et al., 2015) - IgG antibodies to lipopolysaccharide - Melatonin - Zinc - FXR agonist - Micro-RNAs, I 55-I34
2.	Drugs targeting inflammatory cascade
	<ul style="list-style-type: none"> - Emricasan (pan-caspase inhibitor) - Anakinra (Interleukin-I receptor antagonist) - Mycophenolate (MMF)(Basu et al., 2014)
3.	Drugs targeting oxidative stress or metabolism
	<ul style="list-style-type: none"> - Metadoxine*(Higuera-de la Tijera et al., 2015) - Mitoq
4.	Drugs enhancing hepatic regeneration
	<ul style="list-style-type: none"> - Granulocyte colony stimulating factor(Singh et al., 2014) - Erythropoietin - Interleukin-22

Table 2

Areas of unmet need and future research in alcoholic hepatitis (AH)

A.	Epidemiology and Clinical
	<ul style="list-style-type: none"> - Population based studies on prevalence of alcoholic hepatitis in the general population - Mechanistic studies on predisposition to AH in presence of chronic liver injury - Clinical predictors of AH among chronic alcoholics including pattern of drinking - Genome wide association studies for genetic determinants of AH in chronic alcoholics - Prospective studies to determine natural history of AH and response to abstinence
B.	Diagnosis
	<ul style="list-style-type: none"> - Prospective studies on the role of liver biopsy for AH diagnosis - Larger prospective studies on histological scoring systems for prognosticating AH patients - Non-invasive, simple accurate biomarkers for AH diagnosis and predicting severity
C.	Pharmacological therapies
	<ul style="list-style-type: none"> - Better experimental model of AH closely mimicking human AH phenotype - Randomized studies on benefits of pentoxifylline in AH patients with renal failure - Safer and effective targets and pharmacological therapies for AH - Drugs for improving the long-term outcome with improvement in fibrosis as end point - Collaborative studies with addiction service with long term outcome as end point - Reliable and accurate models predictive of recidivism - Randomized studies on efficacy and safety of drugs for maintaining abstinence - Randomized studies to treat hepatitis C with direct acting antiretroviral in AH patients with hepatitis C - Non-invasive simple and accurate biomarkers for predicting treatment response
D.	Liver transplantation
	<ul style="list-style-type: none"> - Larger multicenter prospective data on LT in AH - Uniform protocol for patient selection and immunosuppression regimen after LT