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Research Article

Severe Alcoholic Hepatitis-optimizing Medical Management: Whether we need a Liver Transplant

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Abstract

Severe alcoholic hepatitis is an ethical and clinical conundrum, wherein a liver transplant is often recommended. The adequacy of medical treatment versus the risk of recidivism after transplant is often debated. Complete recovery in 26 of 27 patients with severe alcoholic hepatitis was observed, and hence the data was retrospectively analysed.

Methods: 27 patients, with severe alcoholic hepatitis, with Maddrey's discriminant function between 59.7 to 165.2 (mean 107.53), from June 2017 to May 2022, were followed up for between 11 months to 6 years. INR ranged from 1.99 to 3.7 (mean 2.709), and bilirubin was between 7.6 to 37.01, (mean 20.859). 8 patients had pre-existing liver cirrhosis. All patients received probiotics, nutritional support, physical rehabilitation, saturated fat (clarified butter/ desi ghee) supplementation, and anti-oxidant support.

At 90 days, total bilirubin improved to between 1.0 to 6.8 (mean 2.625). ALT (Alanine Transaminase/ SGPT) ranged from 65 to 550 (mean ALT – 197); and AST (Aspartate Transaminase / SGOT) ranged from 58 to 810 (mean AST – 271.51). Both the AST and ALT were near normal after 90 days. One patient died due to bacterial pneumonia and sepsis; the remaining 26 patients made a complete recovery. All patients including those with diagnosed liver cirrhosis, had complete resolution of their ascites, and near-normal liver function. At the last outpatient visit, none had ascites, edema, or encephalopathy, and had normal albumin levels and INR values.

Conclusion: Probiotics, nutrition, a saturated fat diet, and exercise; all have shown benefits in patients with severe alcoholic hepatitis when tested individually. Concomitant use of all the above has not been reported in the treatment of alcoholic hepatitis. The role of nutrition alone versus the contribution of nutritional deficiencies and the role of gut-derived endotoxemia need to be studied in detail. How to identify patients who need a transplant, if it is needed at all, remains a challenge.

More Information

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Keywords: Severe alcoholic hepatitis; Liver transplant; Probiotics; Nutrition; Reversible liver failure; Saturated fat diet

Abbreviations: AH: Alcoholic Hepatitis; SAH: Severe Alcoholic Hepatitis; MDF: Maddrey's Discriminant Function; AHHS: Alcoholic Hepatitis Histology Score; AASLD: American Academy for Study of Liver Diseases; TNF: Tumor Necrosis Factor; G-CSF: Granulocyte Colony Stimulating Factor; FMT: Fecal Microbiota Transplant; NAFLD: Non Alcoholic Fatty Liver Disease; NASH: Non Alcoholic Steatohepatitis; MELD: Model for End Stage Liver Disease; INR: International Normalized Ratio; ECOG: Eastern Co-operative Oncology Group; AST (SGOT): Aspartate Transaminase (Serum Glutamate Oxaloacetate Transaminase); ALT (SGPT): Alanine Transaminase (Serum Glutamate Pyruvate Transaminase); MHE: Minimal Hepatic Encephalopathy.

Introduction

Alcohol is one of the leading causes of liver disease worldwide, and the spectrum of alcoholic liver disease extends from fatty liver to mild hepatitis, to liver fibrosis, and to advanced liver cirrhosis. With treatment of hepatitis B + C, and early interventions in Non-Alcoholic Fatty Liver Disease (NAFLD) and non-alcoholic steatohepatitis (NASH), alcoholic liver disease is set to become a more common cause of liver disease.

Indian Council for Research on International Economic Relations (ICRIER) study estimated that the alcohol market in India alone is about 52.5 billion USD and is growing at a rate of 6.8%. Alcohol consumption in India alone amounted to about five billion litres in 2020 and was estimated to reach about 6.21 billion litres by 2024 [1]. Gupta, et al. found that alcohol-related liver disease in India occurs at a much younger age and affects the productive population [2].

Aims and objectives

Some patients suffering from severe alcoholic hepatitis made a remarkable recovery with medical management alone; despite having been referred for a liver transplant. None of these patients were given steroids, but it was noticed that a pattern of treatment seemed to work. The aim of this project was to analyse the patient data that was prospectively

collected and to review the available knowledge to identify probable therapeutic options and to share our experience.

Materials and methods

27 patients, 26 males and I female, with liver failure secondary to alcohol were seen between June 2017 to May 2022. All patients had a history of recent heavy alcohol consumption. All patients had already been seen at other non-transplant centres and had been diagnosed with severe alcoholic hepatitis and liver failure. All patients had been advised to undergo liver transplantation. All these 27 patients had not received any other form of therapy in terms of alternative medicine (Ayurveda/ Homeopathy/ Unani). There were 8 other similar patients who had been taking Ayurvedic or Homeopathic medication and were excluded from this study. All patients were followed up for between 11 months to 78 months.

Written informed consent was taken from all patients for the use and reproduction of their clinical data. All patients were treated at the respective hospitals and primary medical centres. Approval from each Institutional board was sought, which was however bypassed and deemed unnecessary because there was no new treatment was being used and there was no deviation from optimal medical management. Blood tests were done at admission, and also on day 7, day 30, and day 90. Standard liver function tests were done, along with serum albumin levels, INR, serum ammonia levels, and serum creatinine levels. All patients underwent imaging including CT (computerized tomography) of the abdomen and upper GI (gastro-intestinal) endoscopy. This study was a retrospective analysis of prospectively collected data. MDF (Maddrey's discriminant function, Lille model scores, and MELD scores were calculated for all (Table 1). Glasgow alcoholic hepatitis score was not included, because data was not available for all patients.

All patients received the following medication:

1. Esomeprazole 20mg daily per orally.
2. Multivitamin B-complex syrup 10 ml daily.
3. Tablet Alcomax (®Delvin formulations Ltd) OR Tablet Alcofix (®Alniche pharmaceuticals) twice a day.
4. Low-salt protein supplements were used to complete calorie intake where required.
5. Patients with cirrhosis and esophageal varices were given Carvedilol 3.125mg twice a day.
6. Probiotics – Tab VSL#3 (®Sun Pharmaceutical Ltd) OR Tab Visbiome (®Zydus Cadila Ltd) once a day.
7. Liquid Lactulose to ensure soft easy-to-pass stool, when required.
8. Tablet Carvedilol 3.125 mg twice a day if esophageal varices.
9. Saturated fat in the form of Clarified Butter (Ghee) 10 gm twice a day.

All the above medication was prescribed for a period of 6 weeks to 8 weeks initially and continued on individual assessments thereafter. Fresh frozen plasma was transfused to maintain INR less than 3, and all patients with INR more than 1.6 received intravenous vitamin K for 5 days.

All patients were discharged from hospital when they were able to comply with dietary and exercise instructions. The blood tests were monitored weekly for a month, bi-weekly for the next 3 months, and monthly thereafter till normalcy. All data was collected and reported as findings or incidences. There was no comparative analysis and hence statistical analysis was not required.

Results

There were 26 males and 1 female. All patients had severe alcoholic hepatitis with MDF (Maddrey's discriminant function [3]) ranging from 59.7 to 165.2 (mean 107.53) **(Table 2).** The oldest patient was 61y old and the youngest 21y old, mean age of 40.037. All patients were diagnosed with clinically severe alcoholic hepatitis with coagulopathy, MDF > 32, and INR > 2. INR ranged from 1.99 to 3.7 (mean 2.709), and serum bilirubin at the time of admission was between 7.6 to 37.01, (mean 20.859), which gradually improved over a time of 12 to 16 weeks.

Table 1: Prognostic scoring models for alcoholic hepatitis.

Prognostic Score	Decision Rule	Pros	Cons
Maddrey's Discriminant Function (DF).	Score = 32 indicating severe AH requiring the use of corticosteroids.	Well-established, with consistent use across studies. Historically predicted 28-day mortality of 35% without steroid treatment.	Uses the absolute value of prothrombin time instead of radiometric INR.
Glasgow Alcoholic Hepatitis Score (GAHS).	Score = 9 indicating severe AH requiring the use of corticosteroids.	Improved accuracy at predicting 28-day mortality. Compared to DF.	Less accurate than the MELD + Lille combined score.
Age, serum bilirubin, INR, and serum creatinine (ABIC) score.	Score = 6.71 indicating an intermediate or higher risk of death, requiring the use of corticosteroids.	Improved accuracy at predicting 28-day mortality compared to DF.	Less accurate than the MELD + Lille combined score.
Model for End-Stage Liver Disease (MELD).	Score > 21 as an independent predictor of mortality.	Improved accuracy at predicting 28-day mortality compared to DF.	Initially derived based on a small single-center study.
Lille model.	Score > 0.45 at day 7 indicating non-response to corticosteroids and suggested discontinuation of treatment.	Dynamic model utilizing active changes in clinical status. Improved discriminatory power compared to static models.	Utilized only for patients receiving corticosteroids.

8 patients had pre-existing liver cirrhosis with 6 patients having mildly shrunken liver and 2 patients having hepatomegaly. All the remaining patients had hepatomegaly. 25 out of 27 patients had ascites, which was usually mild. All the patients with cirrhosis had at least moderate ascites. No patient was abstinent before the onset of jaundice and there was significant alcohol intake till the time of presentation to the hospital. Most patients had a good performance status, ECOG (Eastern Cooperative Oncology Group) [4] status 1 to ECOG 2, only 3 patients had ECOG status 3, and none ECOG status 4. No patient had significant encephalopathy, though all patients had a significantly elevated serum ammonia level (49 to 181 (mean 102.407)) (normal level – 16-60mcg/dL). Only 1 patient presented with upper gastrointestinal bleeding, which proved to be due to variceal bleeding secondary to chronic EHPVO (extra-hepatic portal vein obstruction). All patients with diagnosed liver cirrhosis had grade 2 to grade 3 varices, the other patients had no clinically significant varices or mildly prominent veins. The patient with EHPVO had grade 3 to grade 4 varices with portal biliopathy. 21 patients had no features of encephalopathy, whereas 6 patients had MHE (minimal hepatic encephalopathy or grade 1 encephalopathy.

All patients were advised regarding the risk of severe alcoholic hepatitis and the need to be listed for liver transplantation. 6 patients declined the option of a liver transplant due to a lack of resources; 21 patients were wait-listed for deceased donor liver transplant. A written informed consent for medical treatment was taken and data was collected prospectively.

All patients were subject to the same treatment protocol. Antibiotics were not administered unless there was evidence of infection clinically. Only one patient, with a lower respiratory infection, received antibiotics, who eventually succumbed to sepsis and multi-organ failure.

All patients were given nutritional support to ensure a calorie intake of 40 Kcal/ Kg/day with 1g/kg body weight protein per day. Enteral tube feeding was introduced where indicated and was required in 19 patients. Sodium restriction was advised and multivitamins were introduced. Physiotherapy support was introduced and an exercise regimen was established.

At 90 days since the first time of admission, total bilirubin had improved to between 1.0 to 6.8 (mean 2.625). At the time of presentation, the ALT (Alanine Transaminase/ SGPT) ranged from 65 to 550 (mean ALT – 197); and AST (Aspartate Transaminase / SGOT) ranged from 58 to 810 (mean AST – 271.51). Both the AST and ALT were near normal after 90 days. The patient with EHPVO first underwent biliary stenting with a covered self-expanding stent, followed by portosystemic shunt surgery; and remains symptom-free at 2 years after surgery.

One patient died due to bacterial pneumonia and ARDS (Acute Respiratory Distress Syndrome), the remaining 26 patients made a complete recovery. All patients including those with diagnosed liver cirrhosis, had complete resolution of their ascites, near normal bilirubin levels. At the last outpatient clinic visit, (between 11 months to 7 y after alcoholic hepatitis) none had any signs of decompensation, no ascites, no edema, no encephalopathy, normal albumin levels, and normal INR values (< 1.2).

Review of literature

What is alcoholic hepatitis: Alcoholic Hepatitis (AH) is a condition in which acute liver inflammation occurs due to heavy alcohol intake (mean intake, approximately 100 g/day) [5-7]. Conventionally, the severity of alcoholic hepatitis is defined by Maddrey's discriminant function (MDF), which is calculated as:

MDF = 4.6 × (patient's prothrombin time-control) + patient's serum bilirubin (mg/dL).

MDF > 32 carries a poor prognosis, with mortality of 20 to 30% within 1 month after presentation and 30 to 40% within 6 months of presentation [8].

Ethyl alcohol is broken down to acetaldehyde, which is highly toxic to hepatocytes by glutathione depletion, lipid peroxidation, and mitochondrial damage [9]. Some liver injury models in animals show that, after systemic activation, neutrophils migrate into the liver parenchyma and kill sensitized liver cells, likely aggravating liver injury [10]. Alcohol and its metabolite acetate up-regulate histone acetylation, contributing to the up-regulation of several proinflammatory cytokines that could promote injury and hepatitis [11]. Also, there is activation of the adaptive immunity and inhibition of liver regeneration in alcoholic hepatitis [12].

The histopathological examination will show neutrophilic lobular inflammation, degenerative changes in hepatocytes (ballooning and Mallory-Denk bodies (Mallory Hyaline)), steatosis, and pericellular fibrosis [13].

Clinical presentation

Sudden worsening of, or new onset of jaundice; unresolving fever; encephalopathy; and sometimes gastro-intestinal bleeding; may be the initial presenting symptom in some patients [14]. Diagnosis is usually clinical, in patients presenting with acute jaundice, fever, malaise, weight loss, and malnutrition. Liver function tests usually show elevation of aspartate aminotransferase (AST/ SGOT) to values 1.5x to 2x times that of alanine aminotransferase (ALT/ SGPT). The AST ranges usually > 50 to 300 IU/mL[5]. Inaccuracy in the diagnosis of alcoholic hepatitis without a liver biopsy happens about 4% to 46% of the time [15,16] ; but, Dhanda, et al. said that a liver biopsy is not required for diagnosing

alcoholic hepatitis unless there was doubt in the diagnosis [15]. The AHHS or the alcoholic hepatitis histologic score was developed by a multi-national effort, however, it has limited applicability, as it required within 48 hours of admission, and to be read correctly by an experienced pathologist [17].

Various prognostic scores exist, attempting to predict the prognosis of clinical alcoholic hepatitis. Madrey's Discriminant Function (MDF, Lille Model, ABIC (age, bilirubin, INR, and creatinine); Glasgow (GAHS score), and MELD (Model for End Stage Liver Disease are the most widely recognized scores for the clinical severity of Alcoholic Hepatitis (SAH). Of these MDF and Lille Models are the most commonly used scores.

Treatment

The first step in the management of patients with alcoholic hepatitis is ensuring adequate airway, breathing, and circulation. Specific treatment starts with alcohol abstinence and the correction of malnutrition, as many patients have underlying protein-calorie malnutrition [18]. It may be difficult to achieve adequate enteral, and nasogastric tube feeding may be considered, however supporting data is little, and the risk of aspiration exists [19]. However, nutrition seems to be important, as shown by a randomised prospective Spanish study in 1990. In a multi-center randomised study, enteral nutrition (2000kcal/d) was compared to prednisolone for 28 days, and similar rates of survival were observed [20]. In addition, enteral nutrition may reduce the risk of bacterial translocation and gut-derived infections.

Literature seems to suggest that consistent enteral nutrition in patients with alcoholic hepatitis and alcoholic liver disease may reduce mortality at 6 months [18].

Drugs

Until 2016 only steroids and pentoxifylline were listed in guidelines for the treatment of alcoholic hepatitis. Now, Severe Alcoholic Hepatitis (SAH) is often managed with corticosteroids [21]. The 2019 AASLD guidelines recommend the use of steroids in patients with MDF > 32 or MELD score > 20 [22]. Now the AASLD guidelines recommend nutritional support and steroids as the only treatments with known benefits. Literature shows that intake lower than 21.5 kcal/kg/day results in increased rates of infection and mortality at 6 months (65.8% versus 33.1%; $p < 0.0001$) [23]. The AASLD guidelines, however, recommend that therapeutic doses of zinc should be considered in moderate and severe alcoholic hepatitis, as it contributes to the integrity of the gut mucosal barrier.

Steroids have shown an improvement in survival in treated patients [24-26]; however, data is not uniform. One meta-analysis, as early as 1995, using different statistical weighting of the varying trials, was unable to show any difference [27]. A significant meta-analysis of combined individual data of 5 randomized, controlled trials, involving 418 patients confirmed the efficacy of glucocorticoids. 221 patients receiving steroids had higher 28-day survival rates than the placebo arm (80% *vs.* 66%) [28]. A meta-analysis involving 2111 patients, by Louvet, et al. in 2018, showed cortico-steroids to be beneficial. Corticosteroids reduced the risk of death within 28 days of treatment, but not at 6 months [29].

Most clinical trials use prednisolone as against prednisone, and thus clinical data is available for prednisolone. Besides, there is also a pharmacologic concern over the diminished hepatic metabolism of prednisone (the prodrug) to prednisolone in a dysfunctional liver.

Pentoxifylline is a weak Tumor Necrosis Factor (TNF) antagonist. Because TNF alpha has been thought to play an important role in the pathogenesis, pentoxifylline gained support in the treatment [30]. The evidence came from a randomized control trial in 2000 [30], which showed better hospital survival, probably through renal protection [31]. However, evidence started dwindling, and in 2009, a Cochrane meta-analysis, in alcoholic hepatitis with MDF greater than 32, showed that pentoxifylline showed no evidence of benefit [32]. In 2009, Krishna De, et al. in a randomized, double-blind trial, found pentoxifylline to be superior to prednisone in the treatment of alcoholic hepatitis [33]. In 2014, the Korean Study Group for alcohol-related problems found that the 1-month survival rate of patients receiving pentoxifylline was 75.8% (15 deaths) compared with 88.1% (7 deaths) in those, taking prednisolone ($p = 0.08$). At 6 months there was no difference between the two groups [34].

Sidhu, et al. showed pentoxifylline improved renal and hepatic function and improved short-term survival [35]. However, 2 trials in France failed to show a benefit of pentoxifylline, in patients who had failed prednisolone; or in combination with prednisolone compared to prednisolone alone [28,29]. Then came the landmark STOPAH trial (Steroids or Pentoxifylline for alcoholic hepatitis); which enrolled 1092 patients across 65 hospitals in the UK. The conclusion was only prednisolone improved 28-day survival rates and that neither prednisolone nor pentoxifylline alone nor in combination improved longer-term survival at 90 days and 1 year. Pentoxifylline was no better than placebo in reducing mortality [36]. Thus, it was evident that the treatment of alcoholic hepatitis had not progressed much for almost 4 decades, leaving a dire need for new therapies.

Other agents

i. N-acetylcysteine with steroids: A multi-center randomized control study from France found that N acetylcysteine with steroids was better than steroids alone, and improved short-term survival [37]. However further evidence supporting the use of N-acetylcysteine is scant [38,39].

ii. **Silymarin:** Silymarin derived from Milk Thistle is a hepato-protectant in intoxication with Amanita Phylloides [40]. The use of silymarin grew after a trial in 1989, which showed a significant survival benefit in cirrhotic patients treated with silymarin [41]. In 1998, in another trial of 200 patients with alcoholic liver disease, silymarin had no effect on survival. A Cochrane review of 13 studies involving 915 patients found that Milk Thistle (Silymarin) does not influence the course of alcoholic and/or hepatitis B/C liver injury [43].

iii. Propylthiouracil, Colchicine, S-Adenosyl-L-methionine (SAMe), and Polyenyl-phosphatidylcholine – All the above mentioned have been tried in the treatment of alcoholic hepatitis, but evidence is lacking; and data shows that all propylthiouracil, SAMe, and polyenyl-phosphatidylcholine were not superior to placebo in clinical trials [44-47].

iv. Granulocyte-colony stimulating factor: Singh, et al. [48], in 2014, in a randomized study of 46 patients, were able to show that, G-CSF, at a dose of 5 μg/kg subcutaneously every 12 h for 5 consecutive days resulted in significant improvement in CTP, MELD, and MDF at 1, 2, and 3 months; and resulted in improved survival. However, Nahas, et al. in 2023, found no difference in 30-day, 90-day, and 1-year mortality rates [49]. Subsequent reviews of evidence concluded that current evidence is highly heterogeneous, and G-CSF cannot be recommended for all patients with alcoholic hepatitis [50,51]. G-CSF will need to be investigated further to assess its usefulness.

v. **Canakinumab:** Canakinumab is a human monoclonal antibody targeting IL-1 beta and subsequently IL-6 signalling [52], was investigated in 48 patients in a multicenter randomized controlled trial. In patients with biopsy-proven alcoholic hepatitis, MDF > 32 and MELD < 27; there was improvement in ALT levels and in histology; however, there was no significant improvement in the MELD scores or in the Lille model scores [53].

vi. **Anakinra:** The DEFEAT alcoholic hepatitis trial found that Anakinra in combination with zinc supplementation and pentoxifylline, improved the mortality at 180 days [54]. Anakinra is an IL-1 receptor antagonist, blocking IL-1 alpha and IL-1 beta.

vii. Anti-TNF alpha agents, infliximab [55], and etanercept [56], both initially showed promise in smaller studies, but subsequently were found to result in unacceptably high infection and mortality rates.

viii. Selonsertib [57] and emicrasan [58], both did not show any benefit; or had safety issues related to toxicity and side effects.

ix. **Fecal Microbiota transplant (FMT):** In an open labelled trial from South India, comparing steroids, pentoxifylline, nutritional therapy, and FMT, it was seen that FMT improved survival at 1 and 3 months; and also reduced the infection complications, inflammatory markers, and oxidative stress [59]. The same group found a higher 6-month survival in patients undergoing FMT as against pentoxifylline, in addition to decreased incidences of clinically significant ascites (56.0% *vs.* 25.5%, $p = 0.011$), hepatic encephalopathy (40.0% *vs.* 10.6%, $p = 0.003$), and critical infections (52.0% *vs.* 14.9%, $p < 0.001$) [60]. They also found that the incidence of ascites, hepatic encephalopathy, infections, and major hospitalizations was significantly lower in patients receiving FMT. Alcohol relapse rate was also lower, and the time to relapse was higher, the 3-year survival was higher in patients receiving FMT [61]. FMT improved survival at 28 and 90 days significantly and led to improvements in the clinical severity scores in patients with severe alcoholic hepatitis presenting as ACLF (acute on chronic liver failure) [62].

x. **Probiotics:** Gut dysbiosis can lead to compromise of the intestinal mucosal barrier, with resultant leakage of pro-inflammatory substances, which reach the liver through the portal circulation, resultant LPS exposure, and hepatocyte injury [63]. The resultant hepatocyte stellate cell activation, oxidative stress, and fibrosis can lead to progressive liver damage and dysfunction.

Additionally, probiotics, prebiotics, synbiotics, fecal microbial transplantation (FMT), and bioengineered bacteria; all have shown in various studies the improvement in the severity of alcoholic liver disease. Probiotics were tried as early as 2008, and evidence published in 2015, showed that probiotics resulted in reduced endotoxemia and improved liver function [64]. Duan, et al. found that cytolysin-secreting Enterococcus faecalis (E. faecalis) contributed significantly to the mortality of severe alcoholic hepatitis patients through hepatocellular injury [65]. Scheunert was the first researcher in 1920 to argue that "dysbiosis" of gut microbiota was associated with diseases in horses [66]. Now, 100 years later we recognize the role of gut microbiota in many human diseases. Chronic alcohol abuse leads to overgrowth of aerobic and anaerobic bacteria in the jejunum [67]. The usefulness of probiotics in alcoholic liver disease has been shown in many mouse models and few human clinical trials [68-71]. 4 weeks of rifaximin also significantly reduced endotoxin, IL-6, and TNF-alpha and improved renal function and systemic hemodynamics in alcoholic liver disease [72]. However, this needs to be validated by bacterial studies.

Newer probiotics are genetically engineered to further enhance their beneficial effects, which enhance the selection of health-promoting genes, causing improved, better host-

bacteria interaction, immunomodulation, antimicrobial activity, or pathogen control [73]. Genetically modified *Lactobacillus reuteri*-secreting mouse IL-22 was given in a mouse model of alcohol-induced liver disease. IL-22 restricted to the intestinal environment stimulated the expression of antimicrobial molecules, reducing the translocation of bacteria and reducing ethanol-alcohol-induced liver injury, steatosis, and inflammation [74]. Faecal virome and phageome differences have been described in alcohol-associated liver disease, NAFLD, and cirrhosis. Virome diversity was increased in patients with alcohol-associated liver disease and alcohol-associated hepatitis, compared with non-alcoholic controls [75]. In a double-blind, multi-centre RCT in 2022, 89 patients were randomized to receive probiotics or placebo, and probiotics improved the Child-Pugh scores ($p < 0.001$) also, the probiotics group showed a decline in the levels of alanine aminotransferase and gamma-glutamyl transpeptidase [76]. Neuman, et al. in a review in 2020, observed that gut microbiota are key elements in immune responses, inducing proinflammatory T helper 17 cells and regulatory T cells in the intestine, and alcohol consumption changes the intestinal microbiota [77]. Many researchers have shown that alcohol, especially binges increases lipo-polysaccharide (LPS) levels in the systemic circulation, and LPS activates inflammatory pathways releasing proinflammatory cytokines by Kupffer and other hepatic cells, inducing liver and systemic inflammation, or alcoholic hepatitis [78].

xi. **DUR-928:** Probably the most promising therapy in alcoholic hepatitis, also called Larsucosterol, regulates multiple pathways in liver injury and inflammation. In the pilot study, Lille model scores were less than 0.45 in 89% of subjects with improvement in biochemical parameters in most subjects [79].

New targets and treatments

There are many potential targets for intervention in alcoholic hepatitis. However, research is hampered by the lack of suitable animal models.

1. **CXC chemokines:** In alcoholic hepatitis, hepatic expression of CXC chemokines is increased and correlates with survival time and the degree of portal hypertension [80].

2. IL 22 – Interleukin 22 has antioxidant, antiapoptotic, antisteatotic, proliferative, and antimicrobial effects [81].

3. **Complement:** Complement activation is an important pathway that leads to inflammation in alcoholic hepatitis. In fact, many candidates, that inhibit complement activation are undergoing clinical trials for the treatment of other conditions; and may be tried for alcoholic hepatitis [82].

4. **Apoptosis:** Apoptosis plays a significant role in alcoholic hepatitis, so inhibitors of apoptosis may end up being a treatment option [83].

5. **Osteopontin:** Osteopontin is an extra-cellular matrix protein that is increased in alcoholic hepatitis, and levels may correlate with the severity of alcoholic hepatitis. So, it may prove as a target for the treatment of alcoholic hepatitis [84].

6. **Bovine colostrum:** In a novel idea, Sidhu, et al. [85], tried to evaluate the efficacy of bovine colostrum in severe alcoholic hepatitis. Bovine colostrum has immunological factors, namely, immunoglobins, lactoferrin, lysozyme, lacto-peroxidase, microRNA, glycoconjugates, B and T lymphocytes, leukocytes, interleukins, and other polypeptide-rich prolines; growth factors and nutrients [86]. Bovine colostrum results in lesser bacteria, lesser LPS (endotoxin), and lesser Candida albicans-derived β-glucans—pathogen-associated molecular particles (PAMPs) entering the portal circulation and reduced activation of the macrophages and Kupffer cells in the liver. This culminates in the markedly reduced production of proinflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha and mitigates the inflammatory responses in alcoholic hepatitis [85].

7. **Clarified butter (Ghee):** Nanji, et al. reported in 2001, that, a diet enriched in saturated fatty acids effectively reverses alcohol-induced necrosis, inflammation, and fibrosis despite continued alcohol consumption [87]. It seems this effect may be mediated through the protective effect of saturated fat on intestinal microbiota, which works by preventing over-colonization by proteobacteria and actinobacteria and maintenance of Bacteroidetes and lactobacilli [88]. A randomized trial is presently underway in New Delhi to study the effect of saturated fat on the Gut-Liver Axis in alcoholic hepatitis, using desi ghee [89]. Alcohol causes intestinal bacterial overgrowth and dysbiosis, intestinal mucosal damage, and enhances intestinal permeability; thereby stimulating proinflammatory cytokines affecting the liver. The use of saturated fat, using clarified butter, aims to prevent ethanol-induced dysbiosis and reduce and revert the inflammatory cascade.

Role of liver transplantation

In 2011, Mathurin, et al. in a landmark breakthrough, were able to show the efficacy and safety of liver transplantation in severe alcoholic hepatitis in carefully selected patients. Only 15% of their patients showed any recidivism, and only one returned to dangerous levels of alcohol intake [90]. However, candidate acceptance into liver transplantation for alcoholic hepatitis is low, but with good success rates.

An RCT comparing early with traditional liver transplant after 6 months of abstinence, failed to demonstrate non-inferior alcohol relapse rates among recipients of early liver transplant [91]. In severe alcoholic hepatitis, patients may not survive long enough to qualify for a transplant, so an early liver transplant could be the only way ahead for non-responders to medical therapy. Many authorities around the world support early liver transplants for select patients, especially in their first episode of severe alcoholic hepatitis, with good social support and the absence of any psychological risk factors [92,93]. There are of course formidable barriers, including shortage of cadaveric organs, insurance approval, the financial burden in view of alcohol abuse, and the risk to the donor in living donor settings.

Discussion

The problems with conducting trials for alcoholic hepatitis are many. Several authorities have recommended the inclusion of patients with uniform criteria in trials evaluating alcoholic hepatitis. The range of morbidity and mortality in patients with a high MELD of more than 32 is broad, and maybe another diagnostic criterion could be employed in the selection of patients for trials of alcoholic hepatitis. Another dilemma is whether a biopsy is required for confirmation of the diagnosis of alcoholic hepatitis. However, the unavailability of trans-jugular biopsy in many hospitals would limit their participation, and thus many patients with severe alcoholic hepatitis may not be included. It may be useful to avoid patients who are very likely to die irrespective of treatment and to exclude them from assessment, as many authors seem to have done. However, patients in the ICU, with severe renal failure, or with very high MDF and MELD scores are important populations to investigate.

Abstinence is key in all alcohol abuse disorders. Nutrition is also a priority. When to initiate liver-specific treatment like corticosteroids has not been established, but generally speaking, a MELD of > 20 has been proposed [94]. Acute kidney injury is always a possibility and one always needs to be mindful of it. Avoiding anti-inflammatories and aminoglycosides; and cautious use of diuretics is prudent.

In our set of patients and the clinical setting, our use of steroids is limited. The clinical presentations of alcoholic hepatitis and sepsis, both result in fever, tachycardia, tachypnoea, and leucocytosis. These shared features with SIRS (systemic inflammatory response); infection, possibility of viral hepatitis present clinical uncertainty over the use of steroids as it may be catastrophic in the presence of infection [18]. A fair number of our patients have some evidence of infection, like a urinary tract infection, respiratory infection, spontaneous bacterial peritonitis, or peripheral limb and intravenous line site infections.

Sidhu, et al. also concluded that alcoholic hepatitis in Indian patients is more severe than the Western patients [85]. Alcoholic hepatitis with a MELD score of > 30 or a Maddrey discriminant function of > 60 has a very poor prognosis with very high mortality. Hence liver support approaches or urgent transplantation should be considered. Thus, steroids may not be an option for Indian patients with severe alcoholic hepatitis as the MDF and MELD scores are very high. In their study, the maximum MDF scores were 312.4 in alcoholic hepatitis patients [95].

The lack of universally effective treatments and the lack of predictive biomarkers for treatment response makes the assessment of optimal treatments difficult to judge.

In our patient population, a liver transplant was not an immediate option, either due to a lack of suitable donors or due to domestic issues. Amongst all the 27 patients in this group, antibiotics were not required. One patient had a lower respiratory tract infection, and he was given broad-spectrum antibiotics according to the hospital policies in conjunction with the infectious diseases specialist. Unfortunately, this patient developed septic shock with ARDS and succumbed. One other patient developed a peripheral intravenous site infection with mild cellulitis, which was treated with a short course of flucloxacillin. No other patient required antibiotics usage. One patient had non-cirrhotic portal hypertension with portal biliopathy and alcoholic hepatitis. The variceal bleeding from the portal biliopathy was managed with a covered biliary stent, he underwent medical management of the alcoholic hepatitis followed 3 months later by splenectomy and a proximal splenorenal shunt and has been well ever since. There was only one female patient with acute alcoholic hepatitis with chronic pancreatitis.

From the above it is evident that all patients received the following specific treatment for alcoholic hepatitis:

1. Nutrition and anti-oxidant and micronutrient supplementation.
2. Exercise
3. Probiotics.
4. Saturated fat (ghee/ clarified butter).

All the above treatments have shown to be beneficial in severe alcoholic hepatitis, but never have been studied specifically in combination. It is our thinking that all the possible modes of therapy can be combined since all the above interventions are reasonably safe and all are fairly well tolerated. Exercise has not been specifically mentioned elsewhere, however, physical activity and exercise promote anabolism, tissue repair, and various endogenous healing factors like IGF-1 and growth hormone. Patients with hepatomegaly seem to do better, just like patients who have the ability to take up an exercise regimen early on in the course of the disease. The lack of clinically significant encephalopathy seems to be a positive factor.

Intestinal microbiota, gut-derived endotoxins, and LPS may have an important role to play in the pathogenesis and progression of alcoholic hepatitis. All interventions aimed at gut microbiota, like probiotics, FMT, saturated fat supplementation, and rifaximin; all seem to have a positive influence on the clinical course of severe alcoholic hepatitis.

Conclusion

This set of data obviously has its drawbacks. Ours is only a small set of data with a small number. There is no comparative analysis and this is not a randomized study. There will be some bias in patient selection and treatment. However, the treatment was very standardized and the protocol was followed. Data was recorded accurately and patients with missing data or gaps in data were excluded. There were many other patients who did as well but due to poor follow-up and gaps in data, they could not be included. Patients with other modalities of treatment like alternative therapy including Ayurvedic and Homeopathic treatments were excluded.

However, our data is promising. We need a randomized trial for a complete evaluation. With a RCT more light could be shed on the optimal treatment for alcoholic hepatitis. It seems that patients who are fit to undergo a liver transplant for alcoholic hepatitis do well without a liver transplant too.

Our understanding of alcoholic hepatitis is obviously incomplete. There are of course shortcomings in this study, and a randomized control trial needs to be carried out. However, the difficulties in establishing a randomized trial for severe alcoholic hepatitis are evident. Of all the modalities of treatment studies so far, there does not seem to be any study that has been designed to test a combination of different treatment modalities.

In this subset of patients, there was an obvious selection bias, but seemingly very sick patients were able to survive without a liver transplant. Because of a fear of infections, steroids have not been used as a first line of treatment in this patient population, and had been reserved for non-responders, and yet were never required.

Physical rehabilitation and active physiotherapy were given significant importance, and patients unable to comply may not be suitable candidates for conservative therapy. Infections are obviously a very poor prognostic indicator, and prevention of infection is of paramount importance. Nutrition and correction of nutritional deficiencies is something that needs more evaluation. The role of nutrition alone versus the contribution of nutritional deficiencies and the role of gut-derived endotoxemia need to be studied in detail.

The question that arises, is how to identify patients who need a transplant if it is needed at all.

Declarations

Ethical approval and consent: Hospital ethics committee approval was taken from each hospital.

Consent for publication: Individual patient consent was taken – written and informed.

Availability of supporting data: All clinical data (patient identification removed) can be made available at reasonable request.

Authors' contributions: Single author – responsible for all attributes in the manuscript.

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