Review

Chronic Hepatitis

Alcoholic hepatitis: an update for best practice

PJ Parekh, R Shams, MJ Ryan, DA Johnson*

Abstract

Introduction

Alcoholic hepatitis, with its significant associated morbidity and mortality, remains a plague affecting the United States. Several advancements have been made in the field of alcohol-associated liver disease, yet the pathophysiology behind alcoholic hepatitis remains uncertain. The major barrier in attempting to better understand the pathophysiology and ultimately reduce the associated morbidity and mortality lies in the limited available data. This article reviews the proposed pathophysiology of alcoholic hepatitis, its prognostic indicators, mechanism for use of corticosteroids and pentoxifylline, hepatorenal syndrome, the importance of nutritional status and future considerations in therapy.

Conclusion

It is evident that further research is necessary to better understand the pathogenesis of alcoholic hepatitis and identify therapeutic targets to ultimately reduce the significant associated morbidity and mortality.

Introduction

Alcoholic hepatitis (AH) refers to a clinical syndrome of liver failure, which typically occurs after decades of alcohol abuse (mean intake of ~100 g/day)[1]. It is associated with a 1-month mortality rate of up to 40% and thus accounts for significant health care costs in the United States[1]. In 2007, 56,809 patients were

* Corresponding author
Email: dajevms@aol.com

Eastern Virginia Medical School, Norfolk, VA, United States

hospitalised for AH with an average hospital cost of $37,769[2]. Put in perspective, that is twice the cost of an average hospitalisation for a myocardial infarction and approximately four times the cost for an acute pancreatitis hospitalisation.

The current mainstay treatment in the setting of severe AH is corticosteroids or pentoxifylline, as recommended by the American Association for the Study of Liver Diseases (AASLD)[3]. New data for the treatment of severe AH is constantly emerging from further investigation into the roles of corticosteroid and pentoxifylline as mono and combination therapy, as well as novel cytokine-specific targeted agents, yet its associated morbidity and mortality remain significant. This article reviews the current theories behind the pathophysiology of AH, each of its prognostic indicators, the pharmacology and limitations behind the use of corticosteroid and pentoxifylline therapy, the relevant data supporting the use of current therapy, hepatorenal syndrome (HRS), the importance of nutritional status and the future direction in the treatment of AH.

Discussion

Pathophysiology

The pathophysiology of AH is not well understood; however, the current literature supports a two-part insult. The first revolves around the oxidative stress as a by-product in the metabolism of alcohol and the second around the translocation of endotoxin from the intestinal lumen into the portal circulation[4].

Alcohol is metabolized to produce acetate by way of oxidation to acetaldehyde, which occurs within the hepatocytes. This generates an excess of reducing equivalents, notably nicotinamide adenine dinucleotide (NAD) and its reduced form NADH[5]. The resulting changes in the reduction–oxidation potential inhibit fatty acid oxidation and the tricarboxylic acid cycle. It is also thought to stimulate lipogenesis. In addition, alcohol inhibits peroxisome-proliferator-activated receptor alpha (PPAR-α) and adenosine monophosphate (AMP) kinase and stimulates sterol regulatory element-binding protein 1. This results in lipid metabolism, and the ultimate outcome is the accumulation of fat molecules in hepatic tissue and subsequent metabolic remodelling of the liver[6].

The second insult stems from the translocation of endotoxin into portal circulation. Endotoxin, synonymous with lipopolysaccharide, is a major component of the outer wall of Gram-negative bacteria. In a normal host, gut permeability restricts the translocation of endotoxin. In the setting of chronic alcohol ingestion, however, the gut permeability becomes altered allowing for translocation of endotoxin into portal circulation[7]. Upon entry, endotoxin activates Kupffer cells by binding to CD14, toll-like receptor 4 (TLR4) and MD2[5]. This cascade of events results in the release of reactive oxygen species (ROS) and cytokines by the Kupffer cells. The cytokines and ROS produced cause mitochondrial injury, activation of apoptosis, stimulation of lipid synthesis[8] and a pro-inflammatory state[9], namely via cytochrome P-450[8] and tumour necrosis factor α (TNF-α)[9]. TNF-α activity, which is mediated via TNF receptor 1 (TNF-R1), appears to be restricted to the mitochondria[5]. Chronic alcohol ingestion depletes mitochondrial glutathione further

OA Hepatology
Open Access

Review

exacerbating TNF-α activity[10]. The net result is expression of the Fas ligand and release of cytochrome *c* leading to increased hepatocyte susceptibility to activated natural killer T cells and apoptosis of the cell[11]. Figure 1 depicts endotoxin-activating Kupffer cells resulting in the release of ROS and cytokines and its downstream effect on hepatocytes.

Prognostic indicators
Five major scoring models are used to risk stratify patients with AH. The first is Maddrey's discriminant function (DF), which was developed in 1978 and modified in 1993[12]. The formula used to calculate DF is [4.6 × (patient's prothrombin time – control prothrombin time (in seconds)] + serum total bilirubin (in mg/dL). A calculated

value greater than 32 is associated with a 1-month mortality rate between 35% and 45%, and becomes the reason to initiate corticosteroid or pentoxifylline therapy[13]. Monsanto et al. recently performed a retrospective study of 45 patients with severe AH and assessed short-term mortality at 30 and 90 days. They found DF to be the only independent predictor of mortality using a multivariate analysis. Receiver operating characteristic curves for DF revealed an excellent ability to predict 30- and 90-day mortality rates compared to the Model of End Stage Liver Disease (MELD), concluding DF to be a more accurate prognostic indicator as compared to MELD in predicting short-term mortality in the setting of AH[14].

In 2005, the Glasgow alcoholic hepatitis score (GAHS) was derived from a population of 241 treatment naïve patients from Glasgow and later validated in a separate cohort of 195 treatment naïve patients from throughout the United Kingdom. Forrest et al. found the GAHS to be more accurate in predicting mortality outcomes at 28 and 84 days post-admission when compared to DF. Patients with a GAHS <9 are unlikely to benefit from treatment with corticosteroids irrespective of DF >32. Patients with a GAHS ≥9 have an extremely poor prognosis if left untreated. The 28- and 84-day survival rates for patients with a GAHS ≥9 were 52% and 38%, respectively, if left untreated. Treatment with corticosteroids increased the 28-day survival rate to 78% and the 84-day survival rate to 59% ($p = 0.02$)[15]. Table 1 depicts the formula used to calculate the GAHS.

In 2008, Dominguez et al. derived a scoring system termed ABIC (Age, serum Bilirubin, INR and serum Creatinine) from a multivariate analysis of 103 patients with biopsy-proven AH. The ABIC scoring system is calculated as (age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8). A calculated value of <6.71, 6.71–9.0 and >9.0 correlates to a low risk (100% survival rate), intermediate risk (70% survival rate) and high risk (25% survival rate) of mortality at 90 days, respectively. The same intervals can be used stratify patients according to their 1-year mortality risk as well[16]. In 2010, Forrest et al. performed a retrospective analysis of 181 patients from the GAHS validation group (separate from the population from which GAHS was derived) comparing the GAHS and ABIC scoring models. The GAHS and ABIC scores were calculated for each patient on the day of admission and 1-week post-admission. Table 2 depicts the results of the comparative analysis performed by Forrest et al. showing similar outcomes
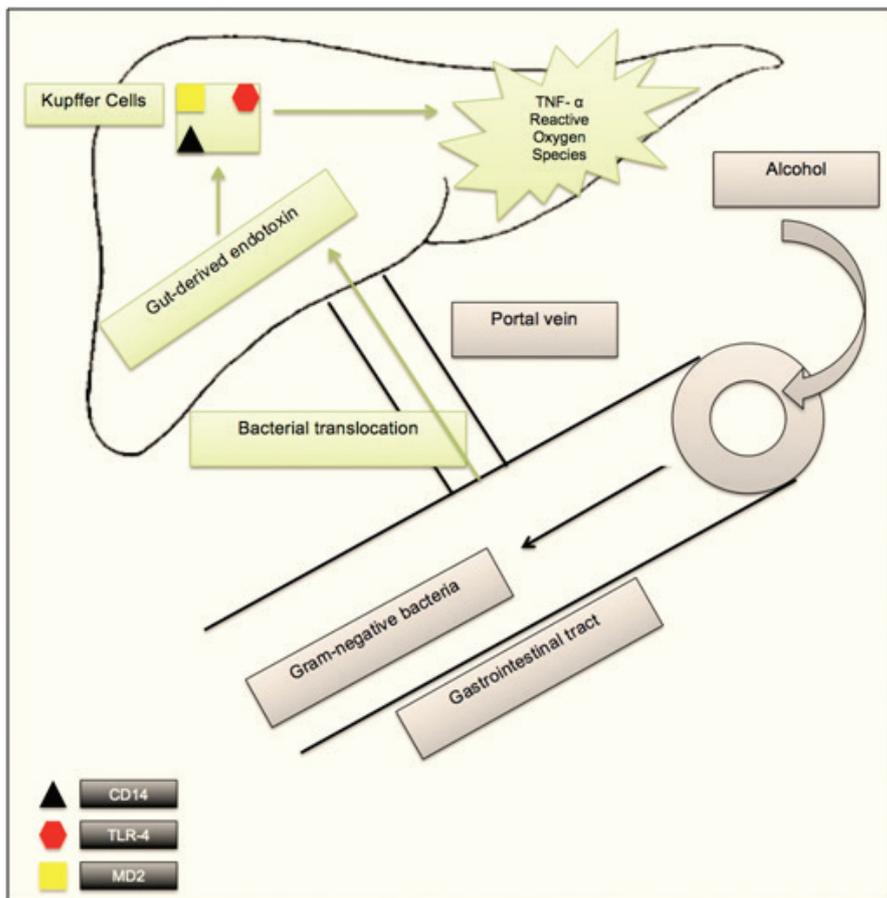

Figure 1: Activation of Kupffer cells by endotoxin.

OA Hepatology
Open Access

between the GAHS and ABIC scoring models. Table 3 depicts the area under the curve (AUC) analysis for both scoring models on the day of admission and at 1-week post-admission. These authors found both the GAHS and the ABIC to be statistically superior to DF and concluded both scoring systems to be highly predictive if calculated on admission. The authors also noted the accuracy of ABIC to deteriorate slightly at 1-week post-admission whereas GAHS slightly improves. In addition, the GAHS system differentiates patients that are likely to benefit from corticosteroid therapy from those who are unlikely to benefit, whereas the ABIC model cannot[17].

The MELD scoring system was initially developed to predict the 90-day mortality of patients who had undergone placement of a trans-jugular intrahepatic portosystemic shunt (TIPS)[18]. The MELD score is now used to determine prognosis and prioritize recipients on the liver transplant recipient list in place of the Child-Pugh score. The MELD score is calculated as 3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43. It should be noted that any value less than 1 should be rounded off to 1 in order to prevent the occurrence of a score below 0, and if a patient has been dialysed twice in the past 7 days, the serum creatinine used should be 4.0[19]. A calculated score of >40, 30–39, 20–29, 10–19 and <9 corresponds to a 90-day mortality of 71.3%, 52.6%, 19.6%, 6.0% and

1.9%, respectively[20]. In 2008, Kim et al. found hyponatremia to be an independent prognostic indicator of mortality rates amongst patients on the transplant waiting list. As a result a modified scoring system, called MELD-Na, incorporating hyponatremia was derived[21]. In 2010, Hsu et al. compared the predictive accuracy of the MELD and MELD-Na scoring models in 182 patients with decompensated hepatitis. The authors found the MELD-Na model to be a more accurate scoring model compared to the traditional MELD scoring system[22].

In 2007, Louvet et al. derived a scoring system named the Lille Model as a means to differentiate between patients responding to corticosteroid therapy and those who do not, and as a prognostic indicator. The Lille Model is calculated as $3.19 - 0.101 \times (age [years]) + 0.147 \times (albumin\ day\ 0\ [g/L]) + 0.0165 \times (bilirubin\ day\ 1\ [\mu mol/L] - bilirubin\ day\ 7\ [\mu mol/L]) - (0.206 \times renal\ insufficiency) - 0.0065 \times (bilirubin\ day\ 0\ [\mu mol/L]) - 0.0096 \times INR$. Survival probability at 6 months is defined by the 0.45 cut-off, with a score of <0.45 corresponding to survival rate of 85% and a score of >0.45 to a rate of 25%[23]. The Lille Model can also be used to classify responders to corticosteroid therapy. Mathurin et al. found that those with a Lille score of <0.16, 0.16–0.56 and >0.56 were classified as complete responders, partial responders and null responders, which correlated to a 28-day survival of 91.1 ± 2.7%, 79.4 ± 3.8% and 53.3 ± 5.1%, respectively[24]. Based on the data, patients with a calculated Lille score of ≥0.45 at day 7 of therapy are not likely to benefit and, therefore, discontinuation of treatment is warranted. It should be noted, however, that use of the Lille Model is not recommended in the most recent AASLD guidelines due to insufficient data at the time of publication. Table 4 provides a summary of the prognostic indicators discussed.

Table 1	Glasgow alcohol hepatitis score[15]		
Score	**1**	**2**	**3**
Age	<50	>50	
WBC (10^9/l)	<15	>15	
Urea (mmol/l)	<5	>5	
PT ratio or INR	<1.5	1.5–2.0	>2.0
Bilirubin (µmol/l)	<125	125–250	>250

Table 2	Comparison of survival rates calculated on the day of admission[17]				
	GAHS <9 (n = 91)	**GAHS ≥9 (n = 90)**	**ABIC <6.71 (n = 45)**	**ABIC 6.71–8.99 (n = 89)**	**ABIC ≥9 (n = 47)**
28-Day mortality	11.0%	47.8%	11.1%	20.2%	63.8%
84-Day mortality	17.6%	57.8%	17.8%	31.5%	68.1%

Table 3	C-statistics for AUC analysis calculated on the day of admission and 1-week post-admission[17]			
	GAHS Day 1	**GAHS Day 7**	**ABIC Day 1**	**ABIC Day 7**
28-Day outcome	0.82 (0.75, 0.87)	0.87 (0.80, 0.92)	0.80 (0.73, 0.87)	0.80 (0.72, 0.86)
84-Day outcome	0.82 (0.74, 0.88)	0.85 (0.77, 0.90)	0.79 (0.71, 0.86)	0.77 (0.69, 0.84)

OA Hepatology
Open Access

Table 4 Summary of prognostic indicators used in AH		
Scoring system	**Formula**	**Interpretation**
Maddrey's DF	[4.6 × (patient's prothrombin time − control prothrombin time (in seconds)] + serum total bilirubin (in mg/dL)	>32 = 1-month mortality rate of 35%–45%. Initiate corticosteroid or pentoxyfylline therapy
GAHS	See Table 1	<9 = are unlikely to benefit from treatment with corticosteroids irrespective of a Maddrey's DF ≥9 = 29-day survival of 52% if untreated (78% if treated with corticosteroids) and an 84-day survival of 38% if untreated (59% if treated with corticosteroids)
ABIC	(age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8)	<6.71 = low 90-day mortality risk (100% survival rate) 6.71–9.0 = intermediate 90-day mortality risk (70% survival rate) >9.0 = high 90-day mortality risk (25% survival rate)
MELD	3.78[Ln serum bilirubin (mg/dL)] + 11.2[Ln INR] + 9.57[Ln serum creatinine (mg/dL)] + 6.43	>40 = 71.3% 90-day mortality 30–39 = 52.6% 90-day mortality 20–29 = 19.6% 90-day mortality 10–19 = 6.0% 90-day mortality <9 = 1.9% 90-day mortality
MELD-Na	MELD − NA − [0.025 × MELD × (140 − NA)] + 1	Similar to MELD
Lille Model	3.19−0.101 × (age [years]) + 0.147 × (albumin day 0 [g/L]) + 0.0165 × (bilirubin day 1 [μmol/L] − bilirubin day 7 [μmol/L]) − (0.206 × presence of kidney failure y/n) − 0.0065 × (bilirubin day 0 [μmol/L]) − 0.0096 × INR	<0.45 = 6-month survival rate of 85% >0.45 = 6-month survival rate of 25% <0.16 = complete responders. 28-day survival rate of 91.1 ± 2.7% 0.16–0.56 = partial responders. 28-day survival rate of 79.4 ± 3.8% >0.56 null responders. 28-day survival rate of 53.3 ± 5.1% ≥0.45 at day 7 of treatment = consider discontinuation of corticosteroid therapy

In July 2013, Lafferty et al. performed a prospective analysis evaluating the use of GAHS, DF, MELD and ABIC in the management of AH. The GAHS, DF, MELD and ABIC scores were calculated on admission and serially over the first week of hospital management in 182 patients with AH. Patients with a GAHS ≥9 were considered for treatment with corticosteroids or pentoxifylline. The authors found no difference in outcome between favourable scores as per the recommended cut-off points. Patients with a GAHS <9 had similar outcomes despite a favourable or unfavourable DF, MELD or ABIC score. Patients with a GAHS ≥9 had a better 90-day outcome when compared to those with a GAHS <9 at 58% and 30%, respectively ($p = 0.01$). Patients who had a fall in bilirubin of ≥25% after a week of treatment with corticosteroids were noted to have an improved survival compared to those who did not at 82% versus 44%, respectively ($p = 0.0005$). The authors concluded that a GAHS ≥9 identified patients who may benefit from treatment and that response to treatment can be assessed using the Lille score or by a 25% reduction in serum bilirubin[25].

Corticosteroids
The use of corticosteroids remains the mainstay in the treatment of severe AH. Corticosteroids travel into the cell due to their lipophilic nature and can ultimately penetrate the nucleus resulting in positive up-regulation of anti-inflammatory gene expression. The direct stimulatory properties of corticosteroids work in conjunction

with its properties to indirectly inhibit pro-inflammatory gene expression, notably NF-κB and activator protein 1 (AP-1), which has been shown in recent studies[26]. The net result is a reduction of inflammatory cytokines, most importantly TNF-α.

Over the past four decades, there have been numerous studies investigating and validating the benefit of corticosteroid use in AH. In 2002, Mathurin et al. analysed individual data collected from the three principal investigators (Mendenhall, Carithers and Ramond). They found corticosteroids to have a significantly higher survival rate (84.6 ± 3.4%) as compared to placebo (65.1 ± 4.8%) (p = 0.001). The authors concluded improvement in short-term survival of patients with severe AH with the use of corticosteroids[27]. In 2011, Mathurin et al. performed a meta-analysis of the five most recent randomised trials comparing corticosteroids to placebo in the setting of severe AH. The authors found a significant improvement in 28-day survival rates in patients with severe AH treated with corticosteroids, particularly in those classified as responders by the Lille Model[24]. The most recent Cochrane analysis concluded that there is insufficient evidence for the use of corticosteroids in effective treatment of AH. However, the same meta-analysis concluded corticosteroids to have a survival benefit in patients with severe AH as defined by a DF ≥32. The potential bias is due to heterogeneity in the data[28].

It is prudent to evaluate patients with AH for any contraindication to corticosteroids prior to initiating therapy. Contraindications to corticosteroid therapy include active gastrointestinal bleeding, renal failure, acute pancreatitis, active tuberculosis, uncontrolled diabetes and psychosis[29]. The presence of an infection was previously considered to be an absolute contraindication to corticosteroid

therapy; however, recent data has shown otherwise. Louvet et al. performed a prospective analysis of 246 patients with severe AH to evaluate the incidence of infection before and after corticosteroid therapy and whether or not infection contraindicates the use of corticosteroid therapy. The data showed that steroids can safely be started and have the potential to improve outcomes in these patients, if their underlying infection is adequately treated[30]. Screening for underlying infections is warranted; however, it should not preclude a patient with AH from receiving corticosteroid therapy.

Pentoxifylline

Pentoxifylline is a methylxanthine considered to be an alternative for the treatment of AH in patients with contraindications to corticosteroids or non-steroid responders. It is a competitive, non-selective phosphodiesterase inhibitor that increases intracellular cyclic adenosine monophosphate (cAMP). The downstream effects of this include activation of protein kinase A, inhibition of TNF-α, stimulation of interleukin-10 (IL-10) and leukotriene synthesis, which ultimately results in decreased inflammation[31]. Its anti-inflammatory properties, namely inhibition of TNF-α and stimulation of IL-10, are what many believe to be the underlying mechanism in treating severe AH.

In 2000, Akriviadis et al. performed a double-blinded placebo-controlled study in which 101 patients with severe AH were randomised to pentoxifylline (400 mg three times daily) or placebo (cyanocobalamin). Twelve of the 49 patients in the pentoxifylline-treated group died during the course of the trial; of these six deaths were a result of HRS. Comparatively, 24 of the 52 control patients died during the course of the trial, of which 22 deaths were a result of HRS, leading the authors to conclude that pentoxifylline decreases

short-term mortality and the risk of HRS in patients with severe AH[13]. In 2012, Sidhu et al. performed a prospective, randomised trial where 50 patients with several AH (DF >32) were randomised to pentoxifylline (400 mg three times daily) or placebo for 4 weeks. The results from this trial were comparable to the results obtained by Akriviadis et al. The authors found a 20% mortality rate at 4 weeks in the pentoxifylline-treated group versus 40% in the placebo group. In addition, there was a significant reduction in urea, creatinine and serum TNF-α in the pentoxifylline-treated group. This led the authors to conclude that pentoxifylline decreases short-term mortality and improves renal and hepatic functions in patients with severe AH[32].

Several studies have directly compared pentoxifylline to corticosteroids. In 2009, De et al. performed a randomised, double-blind controlled study where 68 patients with severe AH (DF >32) were randomised to pentoxifylline (400 mg three times a day) or prednisolone (40 mg daily). After 3 months, the mortality risk was significantly higher in the prednisolone-treated group than in the pentoxifylline-treated group, 35.29% versus 14.71% (p = 0.04), respectively. Six patients in the prednisolone-treated group developed HRS compared to 0 in the pentoxifylline-treated group. Lastly, pentoxifylline was associated with a lower MELD score at the end of 28 days compared to prednisolone, 15.53 ± 3.63 versus 17.78 ± 4.56 (p = 0.04), respectively. This led the authors to conclude pentoxifylline to be superior to prednisolone for the treatment of severe AH[33]. In 2013, Parker et al. performed a meta-analysis of 10 trials including 884 patients and found that pentoxifylline was superior to placebo in the prevention of fatal hepatorenal syndrome and as a result may be a viable alternative to corticosteroids

OA Hepatology
Open Access

when they are contraindicated or in non-responders. The data, however, was controversial in delineating superiority of either pentoxifylline or corticosteroids[34].

Hepatorenal syndrome

HRS is a sequelae of AH that carries a dismal prognosis, particularly type 1 (defined as an increase in serum creatinine up to at least 2.5 mg/dL within 2 weeks). The pathophysiology in the development of HRS revolves around splanchnic vasodilation with decreased systemic vascular resistance. This results in blood pooling within the splanchnic vascular bed, a reduction in effective circulating volume and subsequently an activation of the renin–angiotensin–aldosterone system. This leads to sodium and water retention as well as potent vasoconstriction. AH may lead to further peripheral vasodilation and intrarenal vasoconstriction, thus exacerbating this vicious cycle and precipitating renal failure. The presence of type 1 HRS has been shown to be an independent prognostic indicator in these patients irrespective of the MELD score[35].

Albumin along with vasoconstrictors (octreotide, midodrine and noradrenaline) is considered the first-line agent for type 1 HRS. Albumin serves to volume expand plasma, whereas the vasoconstrictors regulate the vasculature tone within the splanchnic bed. The combination results in an increase in effective circulating volume[35]. Pentoxifylline has been shown to decrease the instance of HRS amongst patients with HRS[13,33,34]; however, larger powered studies validating this data are not yet available.

Nutritional status

The nutritional status of patients suffering from AH is of utmost importance. The lack of key proteins and amino acids is thought to decrease the liver's ability to neutralize the damaging effects of free radicals. Thus, in theory, improved nutrition could balance these adverse effects, enhance regeneration and improve outcomes[36]. Unfortunately, however, the data indicates that good nutrition may improve liver function tests and decrease hepatic fat accumulation, but does not change mortality rates[37,38]. This indicates that optimal nutritional status in conjunction with other medical treatment may be effective in reducing the complications associated with AH, namely infections.

Vitamin deficiencies are common amongst those who consume significant amounts of alcohol, even in the absence of AH. Most notably, vitamin A, B_1 and B_6, D and folic acid are common and may in fact compound the detrimental effects of alcohol, that is, the development of Wernicke's encephalopathy with vitamin B_1 deficiency[36]. As a result, patients suffering from AH are routinely treated with a multivitamin and folic acid.

There has been a recent paradigm shift in screening patients with AH for vitamin D deficiency, given their predisposition towards the development of osteoporosis and fractures, reduced muscle strength and malignancy. In 2011, Malham et al. performed a retrospective analysis of 89 patients with alcoholic cirrhosis and found 85% to have serum vitamin D levels below 50 nmol/L and 55% had levels below 25 nmol/L. The authors found that serum vitamin D levels were inversely proportional to liver disease severity and concluded that vitamin D deficiency relates to liver dysfunction rather than aetiology[39].

Alternative considerations in therapy

As previously outlined, TNF-α plays a pivotal role in alcohol-induced necroinflammation and thus, targeted therapy offers theoretical advantage. Infliximab and etanercept are two potent anti-TNF-α monoclonal antibodies that have been used in recent studies. Despite the promise of these treatments, however, the studies have shown no additional benefit but rather the potential for decrement. In 2004, Naveau et al. performed a double-blind randomised controlled trial where 36 patients were randomised to receive prednisolone (40 mg daily) or prednisolone (40 mg daily) and infliximab (10 mg/kg) at weeks 0, 2 and 4. After 28 days, seven patients from the combination group died as compared to only two patients from the group receiving sole prednisolone therapy. This was thought to be secondary to the increased rate of infection in the infliximab group. The authors concluded that the addition of infliximab may be harmful in patients with severe AH[40]. In 2008, Boetticher et al. performed a double-blind randomised controlled trial where 48 patients with moderate to severe AH (MELD ≥15) were randomised to six subcutaneous injections of etanercept or placebo for 3 weeks with a primary end point being mortality at months 1 and 6. The 1-month mortality rate between the two groups was similar; however, the 6-month mortality rate was significantly higher in the etanercept group than in the placebo group (57.7% vs. 22.7%, respectively), which was attributed to a higher rate of infection. The authors concluded that etanercept was associated with a significantly higher mortality rate after 6 months and is not a viable alternative for the treatment of patients with AH[41].

N-acetylcysteine (NAC) augments glutathione reserves and binds directly to toxic metabolites, thus protecting hepatocytes from necrosis[42]. In 2011, Nguyen-Khac et al. performed a double-blind randomised controlled trial where 174 patients were randomised to receive only prednisolone (40 mg daily) therapy or in addition to NAC on day 1 (at a dose of 150, 50 and 100 mg/kg over a period of 30 min, 4 h and 16 h,

Table 5 Summary of recent studies for the treatment of alcoholic hepatitis

Study	Year	Sample size	Study design drug schedule	Duration	Outcome
Akriviadis E et al.[13]	2000	101	Pentoxifylline (PTX) 400 mg po TID vs. placebo	6 months	Improvement in short-term survival in the PTX group likely secondary to significant decrease in the risk of developing HRS.
Mathurin P et al.[27]	2002	215	Prednisolone 40 mg po QD vs. placebo	28 days	85% improvement in short-term survival of patients with severe alcoholic hepatitis as compared to 62% in the placebo group.
Sphar L et al.[48]	2002	20	Prednisolone 40 mg po QD + infliximab (1 infusion 5 mg/kg) vs. Prednisolone 40 mg po QD + placebo	30 days	100% two-month survival in the prednisolone–placebo group as compared to 82% survival in the prednisolone–infliximab group.
Naveau S et al.[40]	2004	36	Prednisolone 40 mg po QD × 1 month + 3 infusions of infliximab 10 mg/kg at day 0, 14, 28 vs. Prednisolone 40 mg po QD × 1 month + placebo	30 days	82% two-month survival of prednisolone–placebo group as compared to 61% survival in the prednisolone–infliximab group. Study terminated early as a result of increased mortality in patients receiving combination therapy.
Sidhu SS et al.[32]	2006	50	PTX 400 mg po TID vs. placebo	28 days	Mortality rates significantly lower in the PTX-treated group as compared to placebo (20% vs. 40%, respectively). Also noted was a reduction in serum urea, creatinine, tumour necrosis factor and calculated DF in the PTX-treated group.
Paladugu H et al.[49]	2006	30	PTX 400 mg po TID vs. placebo	28 days	Reduced mortality rate and reduction in the development of HRS in the PTX-treated group.
Lebrec et al.[50]	2007	335	PTX 400 mg po TID vs. placebo	6 months	No reduction in short-term mortality in patients with advanced cirrhosis treated with PTV; however, there is a reduction in the risk of complications.
Boetticher et al.[41]	2008	48	Etanercept (6 SQ injections) vs. placebo	3 weeks	Significantly higher mortality rate in patients receiving etanercept therapy.
De BK et al.[33]	2009	68	PTX 400 mg po TID vs. prednisolone 40 mg po QD	12 months	Reduced mortality rate in the PTX-treated group as compared to the prednisolone treated group (14.71% vs. 35.29%, respectively).
Sidhu SS et al.[51]	2011	70	Prednisolone 40 mg po QD + PTX 400 mg po TID vs. prednisolone 40 mg po QD	6 months	Combination therapy was not associated with an additional survival benefit compared to corticosteroid therapy alone.
Mathurin P et al.[52]	2011	270	Prednisolone 40 mg po QD + PTX 400 md po TID vs. prednisolone 40 mg po QD	28 days	No difference in 28-day or 6-month survival rates.
Garcia JG et al.[53]	2012	60	PTX 400 mg po TID vs. prednisolone 40 mg po QD	28 days	No difference in 28-day mortality between the two groups.
Mathurin P et al.[54]	2013	270	Prednisolone 40 mg po QD + PTX 400 mg po TID vs. prednisolone 40 mg po QD + placebo	6 months	4-week treatment with PTX and prednisolone did not result in improved 6-month survival compared to prednisolone alone. The study may have been underpowered to detect a significant difference in the incidence of HRS, which was seen less frequently in the group receiving PTX.

Review

respectively) and on days 2 through 5 (100 mg/kg/day). The authors found the mortality rates to be significantly lower at 1 month in the prednisolone plus NAC group than in patients who received only prednisolone therapy (8% vs. 24%, respectively) ($p = 0.006$). At 3 and 6 months, the mortality rate was not significantly different amongst the two groups, which was the study's primary outcome. Interestingly enough, however, the group receiving combination therapy was noted as having a lower rate of infection and a lower mortality rate secondary to HRS, which could prepare grounds for further studies with NAC in the future[43].

IL-10 is an anti-inflammatory cytokine that activates signal transducer and activator of transcription 3 (STAT3). Once activated, STAT3 has a pivotal role in blunting the inflammatory response by macrophages and Kupffer cells[44]. There have been only a few pilot studies evaluating the use of recombinant human IL-10 (rhuIL-10) in combination with corticosteroids. One such study showed that rhuIL-10 did not decrease IL-8 or TNF-α production, possibly because despite the up-regulation of IL-10 in severe AH, the levels evaluated were not sufficient enough to reduce TNF-α levels[45]. The findings suggest that IL-10 may be a potential for alternative treatment; however, further investigation is necessary.

Similarly, IL-1β is a pro-inflammatory cytokine that is up-regulated in AH. Several mouse models have demonstrated that IL-1β signalling is required for the development of alcohol-induced liver steatosis, inflammation and injury. In vivo studies with IL-1 receptor antagonists blocked the signalling cascade, resulting in a marked reduction of alcohol-induced liver inflammation, steatosis and injury[46]. Unfortunately, there is limited data as to whether or not these findings translate to in vitro, and further investigation is necessary. Table 5 summarises the most recent studies regarding corticosteroids, pentoxifylline, combination therapy and novel approaches.

Liver transplantation: a potential cure?

The role of early liver transplantation in patients with AH remains controversial. Current practice guidelines dictate that patients are required to abstain from alcohol for 6 months in order to be considered for liver transplantation. However, the survival rate in patients with severe AH who fail to respond to medical therapy (i.e. corticosteroids) is approximately 25%, as outlined by Louvet et al.[23] The ethical considerations of limited organ availability and the likelihood of patients with alcohol dependence to relapse are pitted against the high mortality rate amongst these patients.

In 2011, Mathurin et al. published data from a prospective study evaluating the benefit of early liver transplantation among patients with severe AH (defined by a Lille score of ≥0.45)[47]. A team comprised of internal medicine physicians, hepatologists, psychiatrists and transplant surgeons evaluated each potential transplant candidate in a multi-disciplinary fashion. A total of 26 patients with severe AH refractory to medical therapy (median Lille score of 0.88) were selected for liver transplant. The mean time from initiating corticosteroid therapy to listing was 13 days and from listing to liver transplantation was 9 days. Six deaths occurred within 6 months after liver transplantation, five of which occurred within 2 weeks as a result of infection. It should be noted that four of the five deaths due to infection were found to be a result of invasive aspergillus. The 6-month survival was significantly higher than survival among non-transplanted patients with an equivalent Lille score (77 ± 8% vs. 23 ± 8% or 30 ± 6% [two control groups], $p < 0.001$). At a 2-year follow-up, 3 of the 25 patients resumed drinking, two relapsing to alcohol dependence (30 g/day and >50 g/day). There was no evidence of liver damage as a result of alcohol use in any patient at the time of follow-up. The authors concluded that early transplantation in patients with severe AH refractory to medical therapy may be of benefit and warrants further study.

The United States has not yet embraced liver transplantation for this patient population. This may be a multi-factorial issue, with some areas of concern including the scarcity of donors, the burden of selecting those suitable for transplantation from the massive patient pool and the likelihood of patients succumbing to alcohol dependence post-transplant. Those in favour of early transplantation argue, there is a perceived bias against patients with AH as compared to those patients with ecstasy-induced liver failure, intentional acetaminophen overdose or the acquisition of viral hepatitis through drug use/high-risk sexual behaviour who can receive liver transplantation. The results by Mathurin et al. are promising and as a result additional trials should be conducted to assess the role of liver transplantation in AH.

Conclusion

AH is a pandemic associated with significant morbidity and mortality often requiring intense medical treatment. Much remains unknown about the pathophysiology behind AH, but that which is known seems to circumvent around the various pro-inflammatory cytokines. The mainstay in therapy to date remains corticosteroids and pentoxifylline, both of which indirectly inhibit TNF-α. It is evident that further research is necessary to understand the pathogenesis of AH and identify therapeutic targets that will ultimately reduce its significant morbidity and mortality.

Review

Conflict of interests

Drs Parekh and Shams: none. Dr Ryan: Consultant—Gilead, Merck, Abbvie, Vertex; Speaker's bureau—Gilead, Janssen, Abbvie, Vertex, Salix, Merck; Research support—Gilead, Janssen, Abbvie, Merck, Boehringer, Achelion, Bristol Byers-Squibb. Dr Johnson: Research support—Gilead, Janssen, Abbvie, Merck, Boehringer, Achelion, Bristol Byers-Squibb.

Abbreviations list

ABIC, Age, serum Bilirubin, INR and serum Creatinine; AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; DF, discriminant function; GAHS, Glasgow alcoholic hepatitis score; HRS, hepatorenal syndrome; IL-12, interleukin-12; MELD, Model of End Stage Liver Disease; NAC, *N*-acetylcysteine; NAD, nicotinamide adenine dinucleotide; PPAR-α, peroxisome-proliferator-activated receptor alpha; ROS, reactive oxygen species; TIPS, transjugular intrahepatic portosystemic shunt; TLR4, toll-like receptor 4; TNF-α, tumour necrosis factor α.

References

1. Singal AK, Kamath PS, Gores GJ, Shah VH. Alcoholic hepatitis: current challenges and future directions. Clin Gastroenterol Hepatol. 2013.
2. Smart L, Gobejishvili L, Crittenden N, Barve S, Mcclain CJ. Alcoholic hepatitis: steroids vs. pentoxifylline. Curr Hepat Rep. 2013 Mar;12(1):59–65.
3. O'shea RS, Dasarathy S, Mccullough AJ. Alcoholic liver disease. Am J Gastroenterol. 2010;105(1):14–32.
4. Morgan TR. Management of alcoholic hepatitis. Gastroenterol Hepatol (N Y). 2007;3(2):97–9.
5. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med. 2009;360(26):2758–69.
6. You M, Crabb DW. Recent advances in alcoholic liver disease II. Minireview: molecular mechanisms of alcoholic fatty liver. Am J Physiol Gastrointest Liver Physiol. 2004;287(1):G1–6.
7. Wiest R, Garcia-tsao G. Bacterial translocation (BT) in cirrhosis. Hepatology. 2005;41(3):422–33.

8. Mansouri A, Gaou I, De Kerguenec C, Amsellem S, Haouzi D, Berson A. An alcoholic binge causes massive degradation of hepatic mitochondrial DNA in mice. Gastroenterology. 1999;117(1):181–90.
9. http://pubs.niaaa.nih.gov/publications/arh27-4/300-306.htm. [Accessed 6 July 2014].
10. Neuman MG, Shear NH, Bellentani S, Tiribelli C. Role of cytokines in ethanol-induced cytotoxicity in vitro in Hep G2 cells. Gastroenterology. 1998;115(1):157–66.
11. Minagawa M, Deng Q, Liu ZX, Tsukamoto H, Dennert G. Activated natural killer T cells induce liver injury by Fas and tumor necrosis factor-alpha during alcohol consumption. Gastroenterology. 2004;126(5):1387–99.
12. Boyle P, Boffetta P, Lowenfels AB, Burns H, Brawley O, Zatonski W, et al. Alcohol, science, policy and public health. Oxford University Press; 2013. Oxford University Press, USA; 1 edition.
13. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology. 2000;119(6):1637–48.
14. Monsanto P, Almeida N, Lrias C, Pina JE, Sofia C. Evaluation of MELD score and Maddrey discriminant function for mortality prediction in patients with alcoholic hepatitis. Hepatogastroenterology. 2013;60(125):1089–94.
15. Forrest EH, Morris AJ, Stewart S, Phillips M, Oo YH, Fisher NC, et al. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. Gut. 2007;56(12):1743–6.
16. Dominguez M, Rincón D, Abraldes JG, Miguel R, Colmenero J, Bellot P, et al. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. Am J Gastroenterol. 2008;103(11):2747–56.
17. Forrest EH, Fisher NC, Singhal S, Brind A, Haydon G, O'Grady J, et al. Comparison of the Glasgow alcoholic hepatitis score and the ABIC score for the assessment of alcoholic hepatitis. Am J Gastroenterol. 2010;105(3):701–2.
18. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, Ter borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology. 2000; 31(4):864–71.

19. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45(3):797–805.
20. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124(1):91–6.
21. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med. 2008;359(10): 1018–26.
22. Hsu CY, Lin HC, Huang YH, Su CW, Lee FY, Huo TI, et al. Comparison of the model for end-stage liver disease (MELD), MELD-Na and MELDNa for outcome prediction in patients with acute decompensated hepatitis. Dig Liver Dis. 2010;42(2):137–42.
23. Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology. 2007;45(6):1348–54.
24. Mathurin P, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut. 2011;60(2):255–60.
25. Lafferty H, Stanley AJ, Forrest EH. The management of alcoholic hepatitis: a prospective comparison of scoring systems. Aliment Pharmacol Ther. 2013;38(6):603–10.
26. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 2011;335(1):2–13.
27. Mathurin P, Mendenhall CL, Carithers RL, Ramond MJ, Maddrey WC, Garstide P, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol. 2002;36(4):480–7.
28. Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis—a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial

FOR CITATION PURPOSES: *Parekh PJ, Shams R, Ryan MJ, Johnson DA.* Alcoholic hepatitis: an update for best practice. OA Hepatology 2013 Jul 01;1(1):5.

Review

sequential analyses of randomized clinical trials. Aliment Pharmacol Ther. 2008;27(12):1167–78.

29. Singal AK, Walia I, Singal A, Soloway RD. Corticosteroids and pentoxifylline for the treatment of alcoholic hepatitis: current status. World J Hepatol. 2011; 3(8):205–10.

30. Louvet A, Wartel F, Castel H, Dharancy S, Hollebecque A, Canva-Decambre V, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology. 2009;137(2):541–8.

31. Essayan DM. Cyclic nucleotide phosphodiesterases. J Allergy Clin Immunol. 2001;108(5):671–80.

32. Sidhu SS, Goyal O, Singla M, Bhatia KL, Chhina RS, Sood A. Pentoxifylline in severe alcoholic hepatitis: a prospective, randomised trial. J Assoc Physicians India. 2012;60:20–2.

33. De BK, Gangopadhyay S, Dutta D, Baksi SD, Pani A, Ghosh P. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World J Gastroenterol. 2009;15(13):1613–9.

34. Parker R, Armstrong MJ, Corbett C, Rowe IA, Houlihan DD. Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther. 2013;37(9):845–54.

35. Schepke M. Hepatorenal syndrome: current diagnostic and therapeutic concepts. Nephrol Dial Transplant. 2007; 22(Suppl 8):viii2–4.

36. Available at: http://pubs.niaaa.nih.gov/publications/arh294/296-306. NIAAA. [Accessed 13 September 2013].

37. Cabré E, Rodríguez-iglesias P, Caballería J, Quer JC, Sanchez-Lobrana JL, Pares A, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology. 2000;32(1):36–42.

38. Diehl AM, Boitnott JK, Herlong HF, Potter JJ, Van Duyn MA, Candler E, et al. Effect of parenteral amino acid supplementation in alcoholic hepatitis. Hepatology. 1985;5(1):57–63.

39. Malham M, Jørgensen SP, Ott P, , Agnholt J, Vilstrup H, Borre M, et al. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. World J Gastroenterol. 2011;17(7):922–5.

40. Naveau S, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, et al. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. Hepatology. 2004;39(5):1390–7.

41. Boetticher NC, Peine CJ, Kwo P, Abrams GA, Patel T, Agel B, et al. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology. 2008;135(6):1953–60.

42. Lauterburg BH, Corcoran GB, Mitchell JR. Mechanism of action of N-acetylcysteine in the protection against the hepatotoxicity of acetaminophen in rats in vivo. J Clin Invest. 1983;71(4):980–91.

43. Nguyen-Khac E, Thevenot T, Piquet MA, Benferhat S, Goria O, Chatelain D, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1781–9.

44. Wang H, Lafdil F, Kong X, Gao B. Signal transducer and activator of transcription 3 in liver diseases: a novel therapeutic target. Int J Biol Sci. 2011;7 (5):536–50.

45. Naveau S, Balian A, Capron F, Raynard B, Fallik D, Agostini H, et al. Balance between pro and anti-inflammatory cytokines in patients with acute alcoholic hepatitis. Gastroenterol Clin Biol. 2005;29(3):269–74.

46. Petrasek J, Bala S, Csak T, Lippai D, Kodys K, Menashy V, et al. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. J Clin Invest. 2012;122(10):3476–89.

47. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1790–800.

48. Spahr L, Rubbia-Brandt L, Frossard JL, Giostra E, Rougemont AL, Pugin J, et al. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. J Hepatol. 2002;37(4):448–55.

49. Paladugu H, Sawant P, Dalvi L Role of pentoxifylline in treatment of severe acute alcoholic hepatitis—a randomized controlled trial. J Gastroenterol Hepatol 2006;21:A459.

50. Lebrec D, Thabut D, Oberti F, Perarnau JM, Condat B, Barraud H, et al. Pentoxifylline does not decrease short-term mortality but does reduce complications in patients with advanced cirrhosis. Gastroenterology. 2010;138(5):1755–62.

51. Sidhu SS, Goyal O, Singla P, Gupta D, Sood A, Chhina RS, et al. Corticosteroid plus pentoxifylline is not better than corticosteroid alone for improving survival in severe alcoholic hepatitis (COPE trial). Dig Dis Sci. 2012;57(6):1664–71.

52. Mathurin P. Addition of pentoxifylline to prednisolone for severe alcoholic hepatitis does not improve 6-month survival: results of the Corpentox trial. Hepatology. 2011;54(Suppl 1):81A.

53. Garcia JG, Hernandez GS, Lopez AM, Barrera CIE, Vargas LS. Pentoxifilina versus esteroide en la sobrevivencia a corto plazo en hepatitis aguda alcoholica severa. Medicina Interna de Mexico. 2012;28:228.

54. Mathurin P, Louvet A, Duhamel A, Nahon P, Carbonell N, Bousier J, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. JAMA. 2013;310(10):1033–41.