PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 November 21; 12(43): 6909-6921
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Current concepts and controversies in the treatment of alcoholic hepatitis

Catherine Rongey, Neil Kaplowitz

Catherine Rongey, Robert Wood Johnson Clinical Scholars Program, University of California at Los Angeles, 911 Broxton Avenue, Los Angeles, CA 90024, United States
Neil Kaplowitz, Department of Gastroenterology and Hepatology, University of Southern California, 2011 Zonal Avenue, Los Angeles CA 90033, United States
Correspondence to: Catherine Rongey, MD, Robert Wood Johnson Clinical Scholars Program, University of California at Los Angeles, 911 Broxton Avenue, Los Angeles, CA 90024, United States. crongey@mednet.ucla.edu
Telephone: +1-310-7948309 Fax: +1-310-7943288
Received: 2005-10-14 Accepted: 2005-11-18

Abstract

The treatment of alcoholic hepatitis remains one of the most debated topics in medicine and a field of continued research. In this review, we discuss the evolution of scoring systems, including the recent development of the Glasgow alcoholic hepatitis score, role of liver biopsy and current treatment interventions. Studies of treatment interventions with glucocorticoids, pentoxifylline, infliximab, s-adenosyl-methionine, and colchicine are reviewed with discussion on quality. Glucocorticoids currently remain the mainstay of treatment for severe alcoholic hepatitis.

Key words: Alcoholic hepatitis; Treatment; Glucocorticoid; Biopsy; Scoring system

Rongey C, Kaplowitz N. Current concepts and controversies in the treatment of alcoholic hepatitis. *World J Gastroenterol* 2006; 12(43): 6909-6921

http://www.wjgnet.com/1007-9327/12/6909.asp

INTRODUCTION

The treatment of alcoholic hepatitis is one of the most debated topics in medicine. The prevalence of the disease, its high fatality rate, and the elusiveness of cure keeps this disease in the forefront of topic reviews and scientific investigations.

Alcoholic liver disease accounts for over 12 000 deaths per year and 300 000 years of potential life lost in the United States[1]. Age adjusted death rate from alcohol induced liver disease accounts for 40% of deaths from cirrhosis or 28% of all deaths from liver disease[2]. Alcoholic liver disease is one of the top ten leading causes of death in developed countries, responsible for 3% (1.8 million) of all deaths[3]. While alcoholic hepatitis is common, its pathogenesis, predictors for survival, and treatment remain debated.

There have been several excellent reviews on the treatment of alcoholic hepatitis in the past year[4,5]. The focus of our review is to expand on the treatment of alcoholic hepatitis while addressing the role of scoring systems and liver biopsy.

PATHOGENESIS

While the histology of alcoholic hepatitis is well characterized, the pathogenesis remains uncertain. A number of hepatocellular and inflammatory processes including the potential involvement of innate and adaptive immunologic responses are under investigation.

The variety of treatment options in alcoholic hepatitis share a common treatment goal of blocking the myriad of innate immunologic responses which include macrophage release of chemokines and cytokines, TNF-α, IL-1β, IL-6 and IL-8, in addition to adaptive immune responses to acetaldehyde and hydroxyethyl radical formation[6,7].

While the immunologic responses are varied, they share similar end results of apoptosis, necrosis, inflammation and fibrosis. The history and basis of treatment interventions in alcoholic hepatitis are centered on blocking one or more of the harmful mechanisms found in the animal model with the hope, in human trials, of providing survival benefit (Table 1).

SCORING SYSTEMS

There are several scoring systems applied toward predicting survival in alcoholic hepatitis. Many clinically employed scoring systems, however, are derived from related liver diseases and later validated for alcoholic hepatitis. As patient risk stratification and allocation of treatment are entirely dependent on a system to gauge short-term mortality, it is important to develop a scoring system that accurately predicts survival versus mortality.

First developed as risk stratification method for patients undergoing shunt surgery and later refined[8,9], the Child Turcotte Pugh (CTP), score has evolved as the

Table 1 Immunologic responses and directed therapies in alcoholic hepatitis

Cytokines	Mechanism	Mediators	Treatment
Cytokines			
TNFα	Via TNFR1 signaling in hepatocytes and Kupffer cells (KC)	Apoptosis, necrosis, KC production of cytokines, potential cytoprotective effect	Glucocorticoids; Pentoxifylline; Infliximab
IL-6, 8	Lymphocyte and neutrophil activation, release of acute phase reactants	Inflammation, fibrosis	Glucocorticoids
Antigenic adduct	Oxidation of ethanol, binding to proteins forming antigenic adducts	Adaptive immunity	Glucocorticoids
Chemokines	Attract leukocytes and increase adhesion molecules	Inflammation	Glucocorticoids
Oxidative Injury			
S-adenosyl-methionine (SAMe)	Precursor for glutathione, defense mechanism against oxidative stress, increase methylation	Protective role of SAMe	SAMe
Hypoxia/ischemic injury	Hypermetabolic state	Insufficient oxygen	Propylthiouracil

most clinically used prognostic tool in cirrhotic patients. Patients are stratified into three categories based on point assignment of objective and subjective measures of liver function (Appendix A). The clinical application of the CTP score applied to cirrhotic patients has been validated[10,11]. Cited over 1700 times, the CTP score remains one of the most important clinical predicting tools in patients with cirrhosis[12]. However, in the setting of alcoholic hepatitis, there is evidence that other scoring systems may better predict survival.

The Maddrey Discriminant Function (DF) score, unlike the CTP, is derived from a clinical trial studying the efficacy of corticosteroid therapy in patients with alcoholic hepatitis[13]. Admission prothrombin time and serum bilirubin are independently and significantly associated with mortality and serve as the key variables in calculating the DF score. Further modified, in combination with the presence of encephalopathy, a DF score greater than 32 predicts greater than 50% mortality[14]. The DF score has subsequently been used to stratify patients in trials studying the efficacy of corticosteroid treatment in patients with alcoholic hepatitis[14,15]. While the DF score provides risk stratification, concerns of center to center variability of prothrombin time measurement[16], significant mortality in patients with DF score less than 32 and low test specificity have led some investigators to suggest alternative scoring systems[17].

The Mayo Endstage Liver Disease (MELD) Score, like the CTP score, was developed to predict survival in patients undergoing decompressive therapy for portal hypertension[18,19] (Appendix A). Unlike the CTP score, the MELD score is derived from prospective data and lacks subjective measurements of liver function. Using a derived formula, the MELD score is calculated using prothrombin time, creatinine and bilirubin. All of which are factors Maddrey *et al* found to be significant in his original study. However, unlike the Maddrey Discriminant Function, the MELD score is employed as a continuous assessment of liver function and includes creatinine, a marker of development of hepatorenal syndrome. It would be interesting to evaluate the Maddrey DF as a continuous marker of liver function.

The MELD score has been validated in predicting survival in patients with end-stage liver disease and chronic liver disease[19,20]. Three retrospective studies suggest that MELD is equivalent to DF in predicting survival in patients with alcoholic hepatitis[22,23]. One study found MELD to be more predictive of survival if calculated after the first week of hospitalization[23]. This result may reflect the fact that patients with a higher likelihood of dying decline in the first few weeks of hospitalization rather than improved test sensitivity. In summary, admission MELD, DF and CPT did not differ significantly from each other (Table 2).

Citing concerns of low specificity of the Maddrey DF score and the difficulty of identifying an optimal cut-off point of the MELD score[24,25], Forrest *et al* introduced the Glasgow alcoholic hepatitis score (GAHS)[16] (Appendix A). Using retrospective data from patients presenting with alcoholic liver disease, the authors use stepwise logistic regression to identify variables associated with mortality. In Table 2, we include the results of Forrest *et al*.'s study with separate comparisons between GAHS *versus* DF and GAHS *versus* MELD from the validation portion of the trial. We compared the accuracies of each test *via* Chi-square analysis. GAHS is more accurate than DF in 28 and 84 d mortality prediction but equivalent to MELD in 28 d mortality prediction. The reported specificities of both MELD and DF in this study are quite low, especially in comparison with other studies. However, the reported low specificity of DF significantly affected its comparative predictive capacity, *via* chi-square analysis, against GAHS.

Alcoholic hepatitis scoring systems are in evolution. MELD and DF appear to be equivalent in predicting mortality. The higher specificity and overall accuracy of the GAHS, if confirmed, may make it a better screening tool in the clinical trial. It would be interesting to review previous studies assessing the efficacy of glucocorticoid treatment using GAHS as the scoring system. For clinicians, however, a test with a higher sensitivity would be desirable as their primary goal is to maximize the number of patients receiving a treatment benefit. Therefore, the DF score may be preferred in the clinical setting as

Table 2 Sensitivity and specificity of scoring systems for alcoholic hepatitis: sensitivities (Sen)/specificities (Spec)

Study	Patients	Study design	Predictive Mortality	MELD Sen/Spec (%)	DF Sen/Spec (%)	CTP Sen/Spec (%)	Glasgow Sen/Spec (%)	Conclusions
Sheth *et al*[21] 2002	34	Retrospective	30 d	⩾ 11 86/82	⩾ 32 86/48	N/A	N/A	MELD equivalent to DF
Kulkarni *et al*[17] 2004	41	Retrospective	28 d	N/A	⩾ 33 66.7/61.5	N/A	N/A	DF ⩾ 32 is appropriate. High mortality in DF < 32
Dunn *et al*[22] 2005	73	Retrospective	90 d	⩾ 21 75/75	⩾ 37 88/65	N/A	N/A	MELD equivalent to DF
Srikureja *et al*[23] 2005	202	Retrospective	Not given	Admission: ⩾ 18 85/84 Wk 1: ⩾ 20 91/85	⩾ 32 83/84	⩾ 12 76/80	N/A	Admission MELD equivalent to DF
Forrest *et al*[16] 2005	134	Retrospective	28 d 84 d	N/A	⩾ 32 28 d 96/27 84 d 95/31	N/A	⩾ 9 28 d 81/61 84 d 78/66	GAHS more accurate in predicting mortality compared to DF
Forrest *et al*[16] 2005	46	Retrospective	28 d 84 d	⩾ 11 28 d 92/29 84 d 92/29	N/A	N/A	⩾ 9 28 d 75/68 84 d 69/67	GAHS more accurate in predicting 84 d mortality GAHS equivalent to MELD in predicting 28 d mortality

it captures more patients at risk of dying than does the GAHS score.

LIVER BIOPSY

Since it was reported first by Mallory *et al*[26] the morphology of alcoholic liver disease has been well described[27]. The details and significance of morphologic progression from steatosis to cirrhosis, as it relates to survival and treatment, continue to be refined.

Employed as part of an entry and stratification criteria in a few clinical trials[13,15,28-31], liver biopsy for staging and predicting survival has been replaced by scoring systems. Although survival did not differ between the glucocorticoid trials that used pre-randomization biopsies versus scoring system, we think that clinical trials should enroll biopsy-proven cases. Biopsy confirmation of alcoholic hepatitis accurately defines the patients eligible for clinical trials and, in our view, is preferred if fever, leukocytosis and hepatic bruit are absent.

While histologic changes from steatosis and steatohepatitis to cirrhosis are known, correlating degree of steatosis with liver function and survival is currently under investigation. A study by Duvoux *et al*[32] finds a correlation between low grade steatosis and advanced liver failure as well as lowered sensitivity to steroid treatment. However, patients with low grade steatosis had higher Maddrey discriminant function scores, which can also predict poor survivals.

The role of liver biopsy in defining prognosis and treatment of alcoholic hepatitis in the clinical setting remains unclear. A thorough patient history and physical examination has a reported sensitivity and specificity of 91% and 96% in diagnosing alcoholic hepatitis[33]. However, from the above study, four cases out of 103 were misdiagnosed as alcoholic hepatitis upon review of biopsy specimen. It is generally accepted to perform a liver biopsy if the diagnosis of alcoholic hepatitis is either in question or a concomitant pathology, such as hepatitis C, is suspected[34]. Approximately 35%-40% of alcoholics are infected with HCV[35,36] and experience higher mortality rates than patients with alcoholic liver disease alone[37,38].

A patient history and physical exam cannot, however, consistently distinguish between and determine the extent of alcoholic hepatitis alone versus alcoholic hepatitis with concomitant cirrhosis. A biopsy can provide useful prognostic and diagnostic information. Patients with alcoholic hepatitis and cirrhosis have significantly higher 1- and 5-year mortality compared to patients with cirrhosis alone[39,40]. Presence of perivenular fibrosis, steatosis and giant mitochondria in a known alcoholic may herald the transition from alcoholic hepatitis to cirrhosis; a transition which could be prevented with abstinence[41-43]. In clinical practice, we recommend transjugular(given the presence of coagulopathy and/or ascites) liver biopsy in cases in which it is difficult to distinguish the contribution of alcoholic hepatitis and end-stage cirrhosis, especially when the hallmarks of alcoholic hepatitis, leukocytosis, fever and hepatic bruit are absent. Since treatments are associated with complications, we believe it is prudent to be confident of the diagnosis before using steroids.

TREATMENT

Glucocorticoids

First studied in the treatment of alcoholic cirrhosis in

Table 3 Randomized controlled glucocorticoid trials in treatment of alcoholic hepatitis (% Death)

Study	Glucocorticoid	Patient	Severity assessment	HE	Placebo All (%) / HE (%)	Steroid All (%) / HE (%)	RRR (95% CI) All % / HE %	NNT (95% CI) All / HE	Quality score
Porter *et al*[125] 1971	Methylprednisolone	20	Self derived	16	7/9 (77)[b] 7/8 (88)[c]	6/11 (55)[b] 6/8 (75)[c]	N/A	N/A	5
Helman *et al*[28][a] 1971	Prednisolone	37	Self derived	15	6/17 (35) 6/6 (100)	1/20 (5) 1/9 (11)	86 (-0.06-0.98) 84 (0.28-0.96)	3 (2-18) 1 (1-2)	2
Campra *et al*[31] 1973	Prednisone	54	Self derived	18	9/25 (36) 8/10 (80)	7/20 (35) 4/8 (50)	N/A	N/A	2
Blitzer *et al*[52] 1977	Prednisolone	28	Self derived	5	5/16 (31) 1/2 (50)	6/12 (50) 2/3 (67)	N/A	N/A	5
Lesesne *et al*[49][a] 1978	Prednisolone	14	Self derived	14	7/7 (100) 7/7 (100)	2/7 (29) 2/7 (29)	67 (0.05-0.88) 67 (0.05-0.88)	2 (1-4) 2 (1-4)	3
Shumaker *et al*[30] 1978	Methylprednisolone	27	Self derived	12	7/15 (47) 4/6 (67)	6/12 (50) 2/6 (33)	N/A	N/A	5
Maddrey *et al*[13][a] 1978	Prednisolone	55	DF	15	6/31 (19) 6/10 (60)	1/24 (4) 1/5 (20)	79 (-0.67-0.97) 67 (-1.1-0.95)	6 (-3-111) 3 (-1-16)	4
Depew *et al*[126] 1980	Prednisone	28	Self derived	28	7/13 (54) 7/13 (54)	8/15 (53) 8/15 (53)	N/A	N/A	4
Theodossi *et al*[53] 1982	Methylprednisolone	55	Self derived	34	16/28 (57) 10/14 (71)	17/27 (63) 17/20 (85)	N/A	N/A	3
Mendenhall *et al*[48] 1984	Prednisolone	178	Self derived	61	50/88 (57) 10/30 (33)	55/90 (61) 11/31 (36)	N/A	N/A	3
Carithers *et al*[14][a] 1989	Methylprednisolone	66	DF	33	11/31 (36) 9/19 (47)	2/35 (6) 1/14 (7)	84 (0.3-0.96) 85 (-0.06-0.98)	3 (2-9) 2 (2-7)	5
Ramond *et al*[15][a] 1992	Prednisolone	61	DF	19	16/29 (55) 7/10 (70)	4/32 (13) 2/9 (22)	77 (0.4-0.9) 68 (-0.15-0.9)	2 (2-5) 2 (1-12)	5

[a]$P < 0.05$ for survival benefit as reported by study authors; Note percent death at 28 d in placebo *versus* steroids is shown in each box for all cases[b] and for those with hepatic encephalopathy. [c]RRR, NNT is calculated from published data of those studies that reported a significant survival benefit. HE: Hepatic Encephalopathy; DF: Maddrey Discriminant Factor; CP: Child Turcotte Pugh; N/A: non significant difference in mortality as reported by study authors; Self derived: Criteria derived by study team not including CP, DF or MELD.

1960[44], the use of glucocorticoids remains perhaps the most studied and debated intervention. Reported successes of glucocorticoids are variable and appear largely dependent on the nature of the trial.

The rationale for the use of glucocorticoids is centered upon blocking the cytotoxic and inflammatory pathways in alcoholic hepatitis. Glucocorticoids decrease circulating inflammatory cytokines such as TNF-α, ICAM-1 expression, and have demonstrated short term histologic improvement in the treatment of alcoholic hepatitis[45].

It is difficult to provide a simple summary of results for glucocorticoid trials in alcoholic hepatitis. While all trials appeared to have been controlled, few have high quality scores given the variable definition of randomization and blinding in each trial[46,47].

The trials vary by inclusion/exclusion criteria, glucocorticoid type, scoring system, length of treatment and co-interventions. The study by Mendenhall *et al* is particularly difficult to interpret as essentially three different intervention arms, oxandrolone, prednisolone and prednisone, are employed[48]. Lesesne *et al* compares prednisolone to a 1600 caloric intake diet which is below the estimated caloric needs of most hospitalized patients; his trial is not placebo controlled[49]. Furthermore, the variation in type of glucorticoid, dose, and treatment length makes it difficult to provide treatment guidelines for physicians.

We did a computerized search using the MEDLINE database from 1971 to August 2005 using the search headings of "steroids", "corticosteroids", "alcoholic hepatitis", "hepatitis, alcohol", "randomized" and "English". We obtained additional trials by manually searching through retrieved trials and review articles. Randomized trials including corticosteroids in the treatment of alcoholic hepatitis with the outcome measure of mortality are summarized in Table 3. The trial results are summarized by percentage death in each group including number of patients with hepatic encephalopathy and their percentage mortality. Relative risk reduction (RRR), number needed to treat (NNT) with their associated 95% confidence intervals are calculated for trials that reported a significant benefit in survival. Given that hepatic encephalopathy is a known predictor of mortality, we have also calculated RRR and NNT for those patients; again only in trials that reported a significant survival benefit. We employed the Jadad score as an assessment of trial quality. The Jadad score is one of the few validated measures of randomized trial quality[46,50,51]. Out of a maximum score of five, points are assigned based on the method of randomization, double blinding and description of withdrawals/drop-outs.

The results are variable. Five trials reported a significant

survival benefit with glucocorticoids[13-15,28,49]. RRR ranged from 67% to 86%, with NNT varying between 2 and 6. As reported in the above trials and noted in our table, glucocorticoid treatment significantly reduces mortality in patients with hepatic encephalopathy. The latter trials by Carithers *et al* and Ramond *et al*, selectively treated patients with discriminant function scores greater than 32, supporting a more discriminate use of glucocorticoids[14,15].

Of the trials which reported a non-significant benefit, there are four trials which report higher mortality in the glucocorticoid group[30,48,52,53]. While glucocorticoids are relatively benign in the short term for most patients, the remaining three trials remind clinicians that there are significant complications with their use. Blitzer *et al* reported a higher number of fungal infections in the steroid group contributing to the greater percentage of deaths in the steroid group when compared to placebo. However, his steroid treatment group contains a higher proportion of patients with elevated total bilirubin, when compared to placebo, which may contribute to his study result[52]. Included in our discussion of nutrition in the treatment of alcoholic hepatitis, Cabre *et al*'s study found 31% (11/35) mortality in the steroid group with 91% of deaths attributable to infection[54]. It is important to recognize the potentially serious infectious complications secondary to steroid treatment.

Subsequent meta-analyses, while still yielding conflicting results, began to delineate which patients would most benefit from glucorticoid treatment. The first meta-analysis on this topic, conducted by Imperiale and McCullough in 1990 (which antedates more recent trials), finds a protective efficacy of glucocorticoids in higher quality trials, particularly those that exclude patients with gastrointestinal bleeding but include patients with hepatic encephalopathy[55]. They found a protective efficacy of 34% overall (95% CI, 15%-48%) for patients with hepatic encephalopathy. Imperiale and McCullough's study applies quality scores which are important in the setting of such trial heterogeneity. In their paper, quality scores are assigned by independent assessors. Quality scores we use in this paper are derived from Jadad *et al*, and have been used in assessing the quality of randomized clinical trials[46]. We do not find a significant association between high Jadad score and trial survival benefit. However, Jadad *et al* score does not consider baseline equivalence of compared groups, use of co-therapies and adequate potency of principal therapy. The variance of survival amongst the trials may have more to do with patient inclusion/exclusion criteria and the self-derived scoring systems than trial quality and adherence to randomization and double blinding.

Meta-analysis conducted by Christensen *et al*, did not find an overall treatment benefit, after attempting to control for confounding variables[56]. Controlling for confounding variables without direct access to individual study data can be difficult given the heterogeneity of prior trials. A subsequent study, by Mathurin, Mendenhall, Carithers *et al*[57] pooled raw data from their respective trials based on DF score (greater than 200 patients with DF $\geqslant$ 32 in placebo versus steroids) and found a survival benefit. If the DF < 32, there was a > 90% survival without steroids. The conclusions from the above study provide a more definitive treatment guideline for clinicians. In patients with DF $\geqslant$ 32, treatment with glucocorticoids improves short term, 28 d, survival with mortality decreasing from 35% in controls to 15% with steroids.

The longer term benefit of glucocorticoids are difficult to assess given the variable long- term clinical trial definitions (1.5 mo, 6 mo, 1 year)[54,48,58] and each of the existing three trials reported different outcomes: harm, no benefit and benefit[54,48,58]. It is also difficult to assess long-term benefit as alcoholic hepatitis is likely to recur unless the patient abstains.

Recommendations

A review of the literature supports a more discriminate use of glucocorticoids in patients with a Maddrey discriminant function score $\geqslant$ 32. If there is no evidence of gastrointestinal bleeding or infection, the frequent concomitant presence of hepatic encephalopathy provides an even stronger support for the use of glucocorticoids. A study by Mathurin *et al* suggests a simple method to identify patients who are most likely to respond to glucocorticoids. Patients with an 'early change in bilirubin levels' (ECBL), i.e. a bilirubin level at 7 d lower than the bilirubin level on the first day of treatment, were significantly more likely to survive and respond to steroid treatment[59]. Discontinuation of glucocorticoid treatment in the non-responder group, i.e. patients that did not have an ECBL at 7 d, did not appear to result in adverse events[5]. Devising methods to target the patient groups most likely to benefit are important in maximizing treatment benefit, avoiding unnecessary complications of treatment and streamlining the treatment decision process.

Glucocorticoids, while providing a benefit in a select group of patients, are not without risks and should be used with caution in patients with infectious complications and gastrointestinal bleeding. Further trials that are larger in sample size, involving multiple centers and with an active comparator, i.e. pentoxifylline, are needed to better delineate the true effect of glucocorticoids. Finally, as scoring systems are changing, repeat studies may be needed to reassess the treatment effect of glucocorticoids employing MELD and GAHS.

Anabolic steroids

There is a measurable and clinically apparent decline in gonadal function in patients with alcoholic liver disease[60-62]. In 1938, administration of androgens appeared to enlarge the liver of cirrhotic rats, thereby suggesting that perhaps androgens could reverse the process of fibrosis[63]. This lead to the first clinical trial where 12 patients with alcoholic cirrhosis were injected with large doses of testosterone with 'some improvement'[64].

A 2003 Cochrane systematic review could not demonstrate a significant effect of anabolic-androgenic steroids on the mortality of patients with alcoholic liver disease[65]. Three trials[48,66,67] included in the analysis and two trials[68,69] excluded from the analysis are trials in which all participants have alcoholic hepatitis.

Table 4 Infliximab trials in the treatment of alcoholic hepatitis

Study	Design	Patients	Treatment	Results
Spahr *et al*[76] 2002	Randomized	20	All patients: prednisone for 28 d Randomized d 0 R1: Infliximab 5 mg/kg R2: Placebo	Improved Maddrey score No significant difference in survival, histology or adverse outcomes
Tilg *et al*[77] 2003	Case Series	12	Infliximab 5 mg/kg	83% (10/12) survived at median 15 mo No mention of infection
Mookerjee *et al*[78] 2003	Case Series	10	Infliximab 5 mg/kg times one	72 h assessment Significant reduction in laboratory parameters Increased hepatic and renal blood flow
Naveau *et al*[79] 2004	Randomized	36	All patients: Prednisone for 28 d R1: Infliximab 10 mg/kg R2: Placebo	Significantly higher rate of infections in treated group Non-significantly higher rate of death in treated group Study stopped secondary to adverse events in treatment group

Reflective of the conclusions derived from the systematic review, Bonkovsky *et al*'s study[67] and Mendenhall *et al*'s 1984 study[48] did not find a significant survival advantage in the anabolic steroid group in the placebo. In Mendenhall *et al*'s study, patients in the oxandrolone group were treated for 30 d. They report, however, in subgroup analysis that patients with moderate hepatitis treated with oxandrolone seemed to have survival advantage 6 mo post treatment. As the subgroup analysis did not include patients that had died within the first two months of treatment, the results should be taken with some caution.

Currently, anabolic steroids are not recommended for the treatment of alcoholic hepatitis.

Pentoxifylline

Pentoxifylline is a suppressor of tumor necrosis factor alpha (TNF-α), prevents leukocyte adherence to vascular endothelium and down regulates the expression of intercellular adhesion molecule-1 in monocytes[70]. The main signaling pathway is through type 1 tumor necrosis factor receptor, TNFR1. Elevated levels of TNF-α are predictive of poor survival in alcoholic hepatitis[71,72]. Other effects of this drug may contribute to its action such as its effects on membrane fluidity which determine its use in peripheral vascular disease.

First studied by McHutchison *et al* in 1991, in patients with severe alcoholic hepatitis (defined as DF score $\geqslant$ 32), pentoxifylline reduced the development of hepatorenal syndrome, and as a consequence mortality, in comparison to patients who received placebo[73]. A subsequent double blind placebo controlled trial, Akriviadis *et al*, from the same center, supports McHutchison's findings[74]. There did not appear to be any complications as a consequence of pentoxifylline treatment. As noted by Dr. Mathurin[5], the latter study showed no improvement in liver function tests. The reported improved survival was accounted for by a reduction in the development of hepatorenal syndrome in the treatment group. This finding is in sharp contrast to the glucocorticoid trials which demonstrate an improvement in liver function and in survival compared to placebo.

A small sample size, retrospective, observational study by McAvoy *et al*, published as an abstract, finds a treatment benefit with pentoxifylline only in patients stratified to GAHS $\geqslant$ 9, but not in patients with DF $\geqslant$ 32[75]. As raw numbers are not available at press time, it is difficult to draw a meaningful conclusion from his study.

Recommendations: Pentoxifylline may reduce mortality from hepatorenal syndrome in the setting of severe alcoholic hepatitis but further studies are needed to confirm these findings. Aside from the need for head to head comparative trials with steroids, one wonders if the combination of the two treatments might exhibit an additive benefit.

Infliximab

Infliximab, used in the treatment of Crohn's disease, rheumatoid arthritis and psoriasis, is a chimeric mouse/human antibody which binds to tumor necrosis alpha, blocking its effects[76]. Preliminary trial data was encouraging. Three trials reported either better survival than predicted, improved Maddrey score or laboratory parameters[76-78]. The largest and most comprehensive trial studying the efficacy of prednisone and infliximab in the treatment of alcoholic hepatitis was terminated early when a significantly higher number of deaths occurred in the treatment group[79]. The study received some criticism for its use of high dose of infliximab and infusion protocol which varied from previous studies. In this study, investigators cited prior studies in Crohn's[80] and rheumatoid arthritis[81] in which there did not appear to be a relationship between dose of infliximab and rate of infection[78]. Furthermore, Dr. Naveau contends, perhaps infliximab is not the TNF-α blocking agent for alcoholic hepatitis (Table 4).

An open label uncontrolled pilot study on etanercept in the treatment of moderate to severe alcoholic hepatitis was completed[82]. Of the 13 patients treated, 7 had Maddrey DF greater than 32 and two of the seven died within 32 d. Etanercept was discontinued in 3 patients secondary to infection, hepatorenal decompensation and gastrointestinal bleeding. Therefore, there is no particular evidence one way or the other to suggest a beneficial or detrimental effect of treatment. As etanercept targets soluble TNF, whereas infliximab targets both soluble and

membrane bound TNF, it is uncertain what the advantages/disadvantages are of this distinction in the setting of this specific disease target.

Infliximab is not currently recommended for the treatment of alcoholic hepatitis, outside of clinical trials. Although concerns have been raised about increased risk of infection, the more disturbing aspect has been recent warnings of acute liver failure in patients with Crohn's disease and rheumatoid arthritis treated with infliximab[83]. This risk may preclude its use in patients with underlying severe liver injury who are less capable of withstanding an additional insult to the liver.

Nutrition

There are multiple etiologies for weight loss and malnutrition in patients with years of alcohol abuse. Weight loss can be reflective of years of substitution of alcohol for more than 50% of other calories[84], malabsorption of dietary fat and nutrients[85] and the induction of a catabolic state resulting in skeletal muscle depletion[86].

Recently reviewed[4] parenteral and enteral nutrition, while improving liver function in a few studies in alcoholic hepatitis[87-89] has yet to demonstrate a change in clinical outcome.

Mendenhall *et al* have done the most extensive assessment on the effect of protein calorie malnutrition (PCM) and protein energy malnutrition (PEM) on survival and liver function. The results of their interventional studies are shown in Table 5. The observed associations between degree of malnutrition, as calculated by PCM or PEM score, and severity of liver disease[90-92] as well as improvement of survival with improved PCM score[93] serve as the basis for determining the effect of nutritional intervention on survival and liver function in alcoholic hepatitis[69,94].

Nutritional interventions such as caloric amount, type, mode and duration of supplementation vary among the trials. For example, the 1600 caloric nutritional intervention in Lesesne *et al*'s study is below that of most hospitalized patients. A positive correlation between nutritional intake and survival, if present, would not be expected. Much as in the case of the glucocorticoid literature, it would be difficult to provide clinical recommendations when the treatment interventions and outcomes vary. Furthermore, it is difficult to draw meaningful clinical conclusions. While nitrogen balance improves in the nutrition intervention arm, survival remains unchanged.

The majority of trials did not find a survival advantage in nutritional support. There are two trials which showed a survival advantage. Nasrallah *et al*'s study is smaller and both groups receive a 3000 kCal diet with protein, which is an intervention treatment in some studies. Mendenhall *et al,* found a later survival advantage, 6 mo post treatment, in the moderately malnourished group. This is in contrast to Mezey *et al*'s study which did not find a survival advantage up to two years after treatment.

Recommendations: It is important to assess nutritional status of patients in order to recognize and treat the distinct nutritional deficiencies inherent in alcoholic cirrhosis and hepatitis. At this time, however, nutritional supplementation during acute presentation of alcoholic hepatitis does not appear to affect survival.

Colchicine

The final histologic stage in alcoholic liver disease is cirrhosis. Found to inhibit liver fibrosis in rats[95], colchicine's anti-fibrotic activity presented a theoretical possibility of preventing liver fibrosis in humans.

Three clinical trials in the setting of alcoholic hepatitis[96,97] and a Cochrane database review in the setting of alcoholic and non-alcoholic liver fibrosis[98] fail to find a benefit in the treatment of alcoholic hepatitis with colchicine. Recently published and not included in the cochrane review, the largest trial studying long-term colchicine in the setting of alcoholic cirrhosis did not find a therapeutic benefit when compared to placebo, in concordance with prior literature[99]. Colchicine is not currently recommended for the treatment of alcoholic hepatitis.

S-adenosyl-methionine

SAMe, produced from methionine by adenosylmethionine synthetase, is important in the metabolism of nucleic acids, structure and function of cell membranes and as a precursor of glutathione. Glutathione may be protective in alcohol induced liver injury[100]. However, in liver disease there is an impairment of enzyme activation of methionine which cannot be corrected by methionine supplementation[101]. In the setting of alcoholic hepatitis, there is a measurable decrease in hepatic methionine, SAMe and glutathione levels[102]. In animal studies, administration of SAMe increased glutathione levels, attenuated ethanol induced liver injury as well as liver injury caused by other hepatotoxins[103-106].

In a 2001 Cochrane systematic review[107], SAMe has yet to consistently demonstrate a significant beneficial effect on the mortality in the setting of alcoholic liver disease. None of the analyzed trials in the systematic review targeted patients with alcoholic hepatitis. The largest multi-center and highest Jadad quality scoring trial, by Mato *et al*, treated patients with alcoholic cirrhosis with SAMe for up to two years[108]. There was an overall decline in mortality in the treatment group compared to placebo, but did not reach significance. Excluding patients with Child's C cirrhosis, however, did yield a significant mortality benefit.

There are currently two NIH funded trials studying the effect of SAMe on the mortality in the setting of alcoholic cirrhosis. There has yet to be a trial studying the effect of SAMe administration on survival in the setting of acute alcoholic hepatitis.

SAMe is currently not recommended in the treatment of acute alcoholic hepatitis.

Propylthiouracil (PTU)

Found to reduce hypoxic hepatocellular injury in ethanol fed rats[109], subsequent animal studies confirm PTU's protective role against oxidative and ischemic liver injury[110]; similar hepatic injuries are found in patients with alcoholic hepatitis[111].

In a 2001 Cochrane systematic review[112], PTU did

Table 5 Interventional studies on nutrition and alcoholic hepatitis

Study	Design	Patients	Intervention	Findings
Lesesne *et al*[49] 1978	Randomized	14 patients, alcoholic hepatitis and encephalopathy	7 controls, 1600 Kcal diet 7 study, prednisolone	Reduction in mortality in the prednisolone arm
Galambos *et al*[127] 1979	Case series	11 patients, alcoholic hepatitis	4, enteral hyperalimentation 7, parenteral hyperalimentation	No difference in mortality Increased nitrogen balance in study group
Nasrallah *et al*[128] 1980	Randomized	35 patients, alcoholic hepatitis	All received 3000 kcal 100g protein diet 18 control 17 study, 70-85 gram of intravenous amino acid	Lower mortality in the study group
Diehl *et al*[129] 1985	Randomized	15 patients, alcoholic hepatitis	All allowed to consume hospital diet ad libitum 10 controls, glucose solution 5 study, glucose solution + amino acids	Increased nitrogen balance in study group No difference in clinical and biochemical markers of liver disease
Mendenhall *et al*[94] 1985	Randomized	57 patients, moderate-severe alcoholic hepatitis	34 controls, 2500 cal diet 23 study, Hospital diet + Hepatic Aid	No difference in mortality Improvement in nutritional parameters in intervention group
Calvey *et al*[130] 1985	Randomized	64 patients, alcoholic hepatitis	32 controls, standard diet 32 study, standard diet + 2000 kCal + 10 g nitrogen	No difference in biochemical or clinical parameters
Soberon *et al*[131] 1987	Case series	14 patients, alcoholic hepatitis	6 with adequate nutritional status, hospital diet 8 with poor baseline nutritional status, nasoduodenal diet, 35 kCal/kg per day	No difference in mortality Increased nitrogen balance in study group
Simon *et al*[87] 1988	Randomized	12 patients, moderate alcoholic hepatitis 22 patients, severe alcoholic hepatitis	Moderate Group 6 control, standard diet 6 study, PPN Severe Group 12 control, standard 10 study, PPN	No difference in mortality Improved in biochemical tests in severe group
Bonkovsky *et al*[67] 1991	Randomized	39 patients, moderate to severe alcoholic hepatitis	9, standard therapy 8, oxandrolone + standard therapy 10, PPN 12, oxandrolone + standard therapy + PPN	Improved biochemical parameters
Mezey *et al*[88] 1991	Randomized	52 patients, alcoholic hepatitis	28 control, dextrose solution 26 study, dextrose + amino acid	No difference in mortality during hospitalization and 2 yr after treatment
Mendenhall *et al*[69] 1993	Randomized	273 patients, severe alcoholic hepatitis	136 control 137 study, oxadrolone + enteral nutrition	No difference in mortality overall Improvement in mortality in moderately malnourished group(19%) versus control (51%) at 6 mo post treatment
Cabre *et al*[54] 2000	Randomized	71 patients, severe alcoholic hepatitis	36, prednisolone 35, enteral tube 2000 kCal/d	No difference in overall mortality Higher early mortality in nutrition *versus* higher follow up mortality on steroids
Alvarez *et al*[132] 2004	Case series	13 patients, severe alcoholic hepatitis	13, prednisolone + TEN 2000 kCal/d	15% death during treatment 67% of patients developed infections during treatment -no deaths due to infections

not provide a significant survival benefit in the setting of alcoholic liver disease. All of the analyzed six studies (3 of which were published only in abstract) included patients with alcoholic hepatitis[110,113-117].

Contrary to animal studies, hepatic histologic improvement with PTU administration is not replicated in clinical trial literature. PTU also does not appear to have a measurable effect on splanchnic hemodynamics in the setting of alcoholic cirrhosis[118].

While the systematic review did not find a significant association between PTU and adverse events, one trial was discontinued when higher mortality rates were observed in the PTU group[110]. Furthermore, there are case reports and several reviews on fulminant hepatic failure and hepatitis[119-123] secondary to PTU in addition to leukopenia[124] Propylthiouracil is not recommended for the treatment of alcoholic hepatitis.

CONCLUSIONS

The treatment of alcoholic hepatitis continues to evolve as our understanding of the disease process expands. As it does so, however, it is important that our clinical trials attempt to achieve the highest quality possible. Trials

designed to replicate treatment effect should be done with treatment dosages and duration that can be employed in the clinical setting.

Further modification of scoring systems and streamlining methods to identify patients most likely to respond to treatment continue to improve as we seek to minimize risk of treatment while maximizing survival gain.

At the present, we recommend corticosteroids for patients with alcoholic hepatitis and DF $\geqslant$ 32, providing there is not evidence of gastrointestinal bleeding. In patients with active infection, we delay treatment until antibiotic control of infection is achieved. Given the various glucocorticoids and dosages employed in clinical trials, it is difficult to provide clinicians evidence based guidelines on type of glucocorticoid, dosage and length of treatment. We currently recommend using the lowest effective dose of prednisone or prednisolone studied in the literature. As prednisone is less costly, we prescribe prednisone 40 mg daily for up to 28 d. If no improvement in bilirubin is seen after 7 d, we recommend stopping glucocorticoids as suggested by Mathurin[59]; switching to pentoxifylline is a reasonable alternative in that situation. Although primary treatment with pentoxifylline holds some promise, the evidence of its efficacy is not as robust as that with steroids.

Although the focus of this article is treatment, preventing the occurrence of disease is important. From physician screening for alcohol abuse to community wide education in a culturally sensitive manner on the risks of alcohol abuse are important health service fields.

APPENDIX A

Child-Turcotte with pugh modification

Score	1	2	3
Prothrombin time (INR)	< 4 s (< 1.7)	4-6 s (1.7-2.3)	> 6 s (> 2.3)
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/dL)	> 3.5	3.5-2.8	< 2.8
Ascites	None	Slight	Moderate
Encephalopathy	0	1-2	3-4

Maddrey criteria

	Score indicating
Initial	Poor prognosis
4.63 × prothrombin time (seconds) + serum bilirubin (mg/dL)	> 93
Modified	
4.6 (patients prothrombin time-control time) + serum bilirubin (mg/dL)	> 32

Glasgow alcoholic hepatitis score

Score	1	2	3
Age	< 50	$\geqslant$ 50	-
WCC (10^9 /L)	< 15	$\geqslant$ 15	-
Urea (mmol/L)	< 5	$\geqslant$ 5	-
PT ratio	< 1.5	1.5-2.0	> 2.0
Bilirubin (mmol/L)	< 125	125-250	> 250

GAHS $\geqslant$ 9 predictive of poor prognosis. MELD = 3.8 × $\log_e$ (bilirubin (mg/dL)) + 1.2 × $\log_e$ (INR) + 9.6 × $\log_e$ (creatinine (mg/dL)); One can also calculate the MELD score at the following internet address: www.mayoclinic.org/gi-rst/mayomodel7.html.

REFERENCES

1 Alcohol-attributable deaths and years of potential life lost--United States, 2001. *MMWR Morb Mortal Wkly Rep* 2004; **53**: 866-870
2 **Kim WR**, Brown RS Jr, Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. *Hepatology* 2002; **36**: 227-242
3 **Rehm J**, Room R, Monteiro M, Gmel G, Graham K, Rehn N, Sempos CT, Jernigan D. Alcohol as a risk factor for global burden of disease. *Eur Addict Res* 2003; **9**: 157-164
4 **O'Shea RS**, McCullough AJ. Treatment of alcoholic hepatitis. *Clin Liver Dis* 2005; **9**: 103-134
5 **Mathurin P**. Corticosteroids for alcoholic hepatitis--what's next? *J Hepatol* 2005; **43**: 526-533
6 **McClain CJ**, Barve S, Deaciuc I, Kugelmas M, Hill D. Cytokines in alcoholic liver disease. *Semin Liver Dis* 1999; **19**: 205-219
7 **Hansen J**, Cherwitz DL, Allen JI. The role of tumor necrosis factor-alpha in acute endotoxin-induced hepatotoxicity in ethanol-fed rats. *Hepatology* 1994; **20**: 461-474
8 **Child III CG**, Surgery and portal hypertension. Child III CG, editor. The Liver and Portal Hypertension. Philadelphia: Saunders; 1964: 50
9 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649
10 **Christensen E**, Schlichting P, Fauerholdt L, Gluud C, Andersen PK, Juhl E, Poulsen H, Tygstrup N. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. *Hepatology* 1984; **4**: 430-435
11 **Sarin SK**, Chari S, Sundaram KR, Ahuja RK, Anand BS, Broor SL. Young v adult cirrhotics: a prospective, comparative analysis of the clinical profile, natural course and survival. *Gut* 1988; **29**: 101-107
12 **Forman LM**, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from child to MELD. Mayo End-stage Liver Disease. *Hepatology* 2001; **33**: 473-475
13 **Maddrey WC**, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**: 193-199
14 **Carithers RL Jr**, Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon HJ, Maddrey WC. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. *Ann Intern Med* 1989; **110**: 685-690
15 **Ramond MJ**, Poynard T, Rueff B, Mathurin P, Théodore C, Chaput JC, Benhamou JP. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992; **326**: 507-512
16 **Forrest EH**, Evans CD, Stewart S, Phillips M, Oo YH, McAvoy NC, Fisher NC, Singhal S, Brind A, Haydon G, O'Grady J, Day CP, Hayes PC, Murray LS, Morris AJ. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. *Gut* 2005; **54**: 1174-1179
17 **Kulkarni K**, Tran T, Medrano M, Yoffe B, Goodgame R. The role of the discriminant factor in the assessment and treatment of alcoholic hepatitis. *J Clin Gastroenterol* 2004; **38**: 453-459
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**: 864-871
19 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage

liver disease. *Hepatology* 2001; **33**: 464-470
20 **Said A**, Williams J, Holden J, Remington P, Gangnon R, Musat A, Lucey MR. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol* 2004; **40**: 897-903
21 **Sheth M**, Riggs M, Patel T. Utility of the Mayo End-Stage Liver Disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. *BMC Gastroenterol* 2002; **2**: 2
22 **Dunn W**, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KV, Malinchoc M, Kamath PS, Shah V. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology* 2005; **41**: 353-358
23 **Srikureja W**, Kyulo NL, Runyon BA, Hu KQ. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. *J Hepatol* 2005; **42**: 700-706
24 **Forrest EH**. Prognostic evaluation of alcoholic hepatitis. *J Hepatol* 2005; **43**: 738-739
25 **Tilg H**, Kaser A. Predicting mortality by the Glasgow alcoholic hepatitis score: the long awaited progress? *Gut* 2005; **54**: 1057-1059
26 **Mallory F**. Cirrhosis of this liver. Five differnt types of lesions from which it may arise. *Bull Johns Hopkins Hospital* 1911; **22**: 69-74
27 **Lefkowitch JH**. Morphology of alcoholic liver disease. *Clin Liver Dis* 2005; **9**: 37-53
28 **Helman RA**, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. *Ann Intern Med* 1971; **74**: 311-321
29 **Bories P**, Guedj JY, Mirouze D, Yousfi A, Michel H. [Treatment of acute alcoholic hepatitis with prednisolone. 45 patients]. *Presse Med* 1987; **16**: 769-772
30 **Shumaker JB**, Resnick RH, Galambos JT, Makopour H, Iber FL. A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. *Am J Gastroenterol* 1978; **69**: 443-449
31 **Campra JL**, Hamlin EM Jr, Kirshbaum RJ, Olivier M, Redeker AG, Reynolds TB. Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. *Ann Intern Med* 1973; **79**: 625-631
32 **Duvoux C**, Radier C, Roudot-Thoraval F, Maille F, Anglade MC, Van Nhieu JT, Rosa I, Hospitel S, Abd-Alsamad I, Sitruk V, Seror O, Ziol M, Blondon H, Dhumeaux D, Richardet JP. Low-grade steatosis and major changes in portal flow as new prognostic factors in steroid-treated alcoholic hepatitis. *Hepatology* 2004; **40**: 1370-1378
33 **Van Ness MM**, Diehl AM. Is liver biopsy useful in the evaluation of patients with chronically elevated liver enzymes? *Ann Intern Med* 1989; **111**: 473-478
34 **Sougioultzis S**, Dalakas E, Hayes PC, Plevris JN. Alcoholic hepatitis: from pathogenesis to treatment. *Curr Med Res Opin* 2005; **21**: 1337-1346
35 **Caldwell SH**, Jeffers LJ, Ditomaso A, Millar A, Clark RM, Rabassa A, Reddy KR, De Medina M, Schiff ER. Antibody to hepatitis C is common among patients with alcoholic liver disease with and without risk factors. *Am J Gastroenterol* 1991; **86**: 1219-1223
36 **Rosman AS**, Waraich A, Galvin K, Casiano J, Paronetto F, Lieber CS. Alcoholism is associated with hepatitis C but not hepatitis B in an urban population. *Am J Gastroenterol* 1996; **91**: 498-505
37 **Mendenhall CL**, Seeff L, Diehl AM, Ghosn SJ, French SW, Gartside PS, Rouster SD, Buskell-Bales Z, Grossman CJ, Roselle GA. Antibodies to hepatitis B virus and hepatitis C virus in alcoholic hepatitis and cirrhosis: their prevalence and clinical relevance. The VA Cooperative Study Group (No. 119). *Hepatology* 1991; **14**: 581-589
38 **Mendenhall CL**, Moritz T, Rouster S, Roselle G, Polito A, Quan S, DiNelle RK. Epidemiology of hepatitis C among veterans with alcoholic liver disease. The VA Cooperative Study Group 275. *Am J Gastroenterol* 1993; **88**: 1022-1026
39 **Orrego H**, Blake JE, Blendis LM, Medline A. Prognosis of alcoholic cirrhosis in the presence and absence of alcoholic hepatitis. *Gastroenterology* 1987; **92**: 208-214
40 **Levitsky J**, Mailliard ME. Diagnosis and therapy of alcoholic liver disease. *Semin Liver Dis* 2004; **24**: 233-247
41 **Van Waes L**, Lieber CS. Early perivenular sclerosis in alcoholic fatty liver: an index of progressive liver injury. *Gastroenterology* 1977; **73**: 646-650
42 **Worner TM**, Lieber CS. Perivenular fibrosis as precursor lesion of cirrhosis. *JAMA* 1985; **254**: 627-630
43 **Teli MR**, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. *Lancet* 1995; **346**: 987-990
44 **WELLS R**. Prednisolone and testosterone propionate in cirrhosis of the liver. A controlled trial. *Lancet* 1960; **2**: 1416-1419
45 **Spahr L**, Rubbia-Brandt L, Pugin J, Giostra E, Frossard JL, Borisch B, Hadengue A. Rapid changes in alcoholic hepatitis histology under steroids: correlation with soluble intercellular adhesion molecule-1 in hepatic venous blood. *J Hepatol* 2001; **35**: 582-589
46 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12
47 **Moher D**, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 1995; **16**: 62-73
48 **Mendenhall CL**, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff LB, Sorrell M, Tamburro C, Weesner R, Zetterman R. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *N Engl J Med* 1984; **311**: 1464-1470
49 **Lesesne HR**, Bozymski EM, Fallon HJ. Treatment of alcoholic hepatitis with encephalopathy. Comparison of prednisolone with caloric supplements. *Gastroenterology* 1978; **74**: 169-173
50 **Khan KS**, Daya S, Jadad A. The importance of quality of primary studies in producing unbiased systematic reviews. *Arch Intern Med* 1996; **156**: 661-666
51 **Moher D**, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352**: 609-613
52 **Blitzer BL**, Mutchnick MG, Joshi PH, Phillips MM, Fessel JM, Conn HO. Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. *Am J Dig Dis* 1977; **22**: 477-484
53 **Theodossi A**, Eddleston AL, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. *Gut* 1982; **23**: 75-79
54 **Cabré E**, Rodríguez-Iglesias P, Caballería J, Quer JC, Sánchez-Lombraña JL, Parés A, Papo M, Planas R, Gassull MA. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. *Hepatology* 2000; **32**: 36-42
55 **Imperiale TF**, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. *Ann Intern Med* 1990; **113**: 299-307
56 **Christensen E**, Gluud C. Glucocorticoids are ineffective in alcoholic hepatitis: a meta-analysis adjusting for confounding variables. *Gut* 1995; **37**: 113-118
57 **Mathurin P**, Mendenhall CL, Carithers RL Jr, Ramond MJ, Maddrey WC, Garstide P, Rueff B, Naveau S, Chaput JC, Poynard T. 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**: 480-487
58 **Mathurin P**, Duchatelle V, Ramond MJ, Degott C, Bedossa P, Erlinger S, Benhamou JP, Chaput JC, Rueff B, Poynard T. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. *Gastroenterology*

1996; **110**: 1847-1853
59 **Mathurin P**, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, Valla D, Poupon R, Chaput JC, Naveau S. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. *Hepatology* 2003; **38**: 1363-1369
60 **Gluud C**, Dejgaard A, Clemmensen I. Plasma fibronectin concentrations in patients with liver diseases. *Scand J Clin Lab Invest* 1983; **43**: 533-537
61 **Gluud C**, Christoffersen P, Eriksen J, Wantzin P, Knudsen BB. No effect of long-term oral testosterone treatment on liver morphology in men with alcoholic cirrhosis. *Am J Gastroenterol* 1987; **82**: 660-664
62 **Kishimoto Y**, Yamamoto T, Kato S, Wakushima T, Hirayama C. Gonadal function in male patients with alcoholic and non-alcoholic liver disease. *Jpn J Med* 1987; **26**: 41-45
63 **Hall KKV**. Histological changes produced by castration and by sex hormones in the adrenals of normal and of castrated male rats. *Nature* 1937; **140**: 318
64 **ROSENAK BD**, MOSER RH, KILGORE B. Treatment of cirrhosis of the liver with testosterone proprionate. *Gastroenterology* 1947; **9**: 695-704 [Discussion 749-5]
65 **Rambaldi A**, Iaquinto G, Gluud C. Anabolic-androgenic steroids for alcoholic liver disease. *Cochrane Database Syst Rev* 2003; (**1**): CD003045
66 **Goldberg SJ**, Mendenhall CL, Connell AM, Chedid A. "Nonalcoholic" chronic hepatitis in the alcoholic. *Gastroenterology* 1977; **72**: 598-604
67 **Bonkovsky HL**, Fiellin DA, Smith GS, Slaker DP, Simon D, Galambos JT. A randomized, controlled trial of treatment of alcoholic hepatitis with parenteral nutrition and oxandrolone. I. Short-term effects on liver function. *Am J Gastroenterol* 1991; **86**: 1200-1208
68 **Ludwig J**, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc* 1980; **55**: 434-438
69 **Mendenhall CL**, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. *Hepatology* 1993; **17**: 564-576
70 **Shirin H**, Bruck R, Aeed H, Frenkel D, Kenet G, Zaidel L, Avni Y, Halpern Z, Hershkoviz R. Pentoxifylline prevents concanavalin A-induced hepatitis by reducing tumor necrosis factor alpha levels and inhibiting adhesion of T lymphocytes to extracellular matrix. *J Hepatol* 1998; **29**: 60-67
71 **Bird GL**, Sheron N, Goka AK, Alexander GJ, Williams RS. Increased plasma tumor necrosis factor in severe alcoholic hepatitis. *Ann Intern Med* 1990; **112**: 917-920
72 **Felver ME**, Mezey E, McGuire M, Mitchell MC, Herlong HF, Veech GA, Veech RL. Plasma tumor necrosis factor alpha predicts decreased long-term survival in severe alcoholic hepatitis. *Alcohol Clin Exp Res* 1990; **14**: 255-259
73 **McHutchison JG**, Draguesku RB. Pentoxifylline may prevent renal impairment (hepatorenal syndrome) in severe acute alcoholic hepatitis. *Hepatology* 1991; **14**: 96A
74 **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**: 1637-1648
75 **McAvoy NC**, Forrest EH, Hayes PC. The glasgow alcoholic hepatitis score and the effect of pentoxifylline in alcoholic hepatitis. *Gut* 2005; **54** (Supplement 2): 44A
76 **Spahr L**, Rubbia-Brandt L, Frossard JL, Giostra E, Rougemont AL, Pugin J, Fischer M, Egger H, Hadengue A. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2002; **37**: 448-455
77 **Tilg H**, Jalan R, Kaser A, Davies NA, Offner FA, Hodges SJ, Ludwiczek O, Shawcross D, Zoller H, Alisa A, Mookerjee RP, Graziadei I, Datz C, Trauner M, Schuppan D, Obrist P, Vogel W, Williams R. Anti-tumor necrosis factor-alpha monoclonal antibody therapy in severe alcoholic hepatitis. *J Hepatol* 2003; **38**: 419-425
78 **Mookerjee RP**, Tilg H, Williams R, Jalan R. Infliximab and alcoholic hepatitis. *Hepatology* 2004; **40**: 499-500; author reply 500-501
79 **Naveau S**, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, Davion T, Oberti F, Broët P, Emilie D. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004; **39**: 1390-1397
80 **Present DH**, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, Podolsky DK, Sands BE, Braakman T, DeWoody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340**: 1398-1405
81 **Lipsky PE**, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, Smolen JS, Weisman M, Emery P, Feldmann M, Harriman GR, Maini RN. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; **343**: 1594-1602
82 **Menon KV**, Stadheim L, Kamath PS, Wiesner RH, Gores GJ, Peine CJ, Shah V. A pilot study of the safety and tolerability of etanercept in patients with alcoholic hepatitis. *Am J Gastroenterol* 2004; **99**: 255-260
83 Remicade(infliximab) for IV injection. 2005. Available from: www.fda.gov/medwatch/SAFETY/2005/may05.htm
84 **Patek AJ Jr**. Alcohol, malnutrition, and alcoholic cirrhosis. *Am J Clin Nutr* 1979; **32**: 1304-1312
85 **Linscheer WG**, Patterson JF, Moore EW, Clermont RJ, Robins SJ, Chalmers TC. Medium and long chain fat absorption in patients with cirrhosis. *J Clin Invest* 1966; **45**: 1317-1325
86 **Halsted CH**. Nutrition and alcoholic liver disease. *Semin Liver Dis* 2004; **24**: 289-304
87 **Simon D**, Galambos JT. A randomized controlled study of peripheral parenteral nutrition in moderate and severe alcoholic hepatitis. *J Hepatol* 1988; **7**: 200-207
88 **Mezey E**, Caballería J, Mitchell MC, Parés A, Herlong HF, Rodés J. Effect of parenteral amino acid supplementation on short-term and long-term outcomes in severe alcoholic hepatitis: a randomized controlled trial. *Hepatology* 1991; **14**: 1090-1096
89 **James LP**, Farrar HC, Darville TL, Sullivan JE, Givens TG, Kearns GL, Wasserman GS, Simpson PM, Hinson JA. Elevation of serum interleukin 8 levels in acetaminophen overdose in children and adolescents. *Clin Pharmacol Ther* 2001; **70**: 280-286
90 **Mendenhall CL**, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. *Am J Med* 1984; **76**: 211-222
91 **Mendenhall C**, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. *Alcohol Clin Exp Res* 1995; **19**: 635-641
92 **Mendenhall CL**, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. The VA Cooperative Study Group #275. *JPEN J Parenter Enteral Nutr* 1995; **19**: 258-265
93 **Mendenhall CL**, Tosch T, Weesner RE, Garcia-Pont P, Goldberg SJ, Kiernan T, Seeff LB, Sorell M, Tamburro C, Zetterman R. VA cooperative study on alcoholic hepatitis. II: Prognostic significance of protein-calorie malnutrition. *Am J Clin Nutr* 1986; **43**: 213-218
94 **Mendenhall C**, Bongiovanni G, Goldberg S, Miller B, Moore J, Rouster S, Schneider D, Tamburro C, Tosch T, Weesner R.

VA Cooperative Study on Alcoholic Hepatitis. III: Changes in protein-calorie malnutrition associated with 30 days of hospitalization with and without enteral nutritional therapy. *JPEN J Parenter Enteral Nutr* 1985; **9**: 590-596
95 **Mata JM**, Kershenobich D, Villarreal E, Rojkind M. Serum free proline and free hydroxyproline in patients with chronic liver disease. *Gastroenterology* 1975; **68**: 1265-1269
96 **Trinchet JC**, Beaugrand M, Callard P, Hartmann DJ, Gotheil C, Nusgens BV, Lapiere CM, Ferrier JP. Treatment of alcoholic hepatitis with colchicine. Results of a randomized double blind trial. *Gastroenterol Clin Biol* 1989; **13**: 551-555
97 **Akriviadis EA**, Steindel H, Pinto PC, Fong TL, Kanel G, Reynolds TB, Gupta S. Failure of colchicine to improve short-term survival in patients with alcoholic hepatitis. *Gastroenterology* 1990; **99**: 811-818
98 **Rambaldi A**, Gluud C. Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis. *Cochrane Database Syst Rev* 2005; (**2**): CD002148
99 **Morgan TR**, Weiss DG, Nemchausky B, Schiff ER, Anand B, Simon F, Kidao J, Cecil B, Mendenhall CL, Nelson D, Lieber C, Pedrosa M, Jeffers L, Bloor J, Lumeng L, Marsano L, McClain C, Mishra G, Myers B, Leo M, Ponomarenko Y, Taylor D, Chedid A, French S, Kanel G, Murray N, Pinto P, Fong TL, Sather MR. Colchicine treatment of alcoholic cirrhosis: a randomized, placebo-controlled clinical trial of patient survival. *Gastroenterology* 2005; **128**: 882-890
100 **Lieber CS**. Role of S-adenosyl-L-methionine in the treatment of liver diseases. *J Hepatol* 1999; **30**: 1155-1159
101 **Lieber CS**. S-adenosyl-L-methionine: its role in the treatment of liver disorders. *Am J Clin Nutr* 2002; **76**: 1183S-1187S
102 **Lee TD**, Sadda MR, Mendler MH, Bottiglieri T, Kanel G, Mato JM, Lu SC. Abnormal hepatic methionine and glutathione metabolism in patients with alcoholic hepatitis. *Alcohol Clin Exp Res* 2004; **28**: 173-181
103 **García-Ruiz C**, Morales A, Colell A, Ballesta A, Rodés J, Kaplowitz N, Fernández-Checa JC. Feeding S-adenosyl-L-methionine attenuates both ethanol-induced depletion of mitochondrial glutathione and mitochondrial dysfunction in periportal and perivenous rat hepatocytes. *Hepatology* 1995; **21**: 207-214
104 **Lieber CS**, Casini A, DeCarli LM, Kim CI, Lowe N, Sasaki R, Leo MA. S-adenosyl-L-methionine attenuates alcohol-induced liver injury in the baboon. *Hepatology* 1990; **11**: 165-172
105 **Gassó M**, Rubio M, Varela G, Cabré M, Caballería J, Alonso E, Deulofem R, Camps J, Giménez A, Pajares M, Parés A, Mato JM, Rodés J. Effects of S-adenosylmethionine on lipid peroxidation and liver fibrogenesis in carbon tetrachloride-induced cirrhosis. *J Hepatol* 1996; **25**: 200-205
106 **Bray GP**, Tredger JM, Williams R. S-adenosylmethionine protects against acetaminophen hepatotoxicity in two mouse models. *Hepatology* 1992; **15**: 297-301
107 **Rambaldi A**, Gluud C. S-adenosyl-L-methionine for alcoholic liver diseases. *Cochrane Database Syst Rev* 2001; CD002235
108 **Mato JM**, Cámara J, Fernández de Paz J, Caballería L, Coll S, Caballero A, García-Buey L, Beltrán J, Benita V, Caballería J, Solà R, Moreno-Otero R, Barrao F, Martín-Duce A, Correa JA, Parés A, Barrao E, García-Magaz I, Puerta JL, Moreno J, Boissard G, Ortiz P, Rodés J. S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol* 1999; **30**: 1081-1089
109 **Israel Y**, Kalant H, Orrego H, Khanna JM, Videla L, Phillips JM. Experimental alcohol-induced hepatic necrosis: suppression by propylthiouracil. *Proc Natl Acad Sci USA* 1975; **72**: 1137-1141
110 **Rodríguez-Rodríguez E**, González-Reimers E, Santolaria-Fernández F, Milena-Abril A, Rodríguez-Moreno F, Oramas-Rodríguez J, Martínez-Riera A. Cytokine levels in acute alcoholic hepatitis: a sequential study. *Drug Alcohol Depend* 1995; **39**: 23-27
111 **Iturriaga H**, Ugarte G, Israel Y. Hepatic vein oxygenation, liver blood flow, and the rate of ethanol metabolism in recently abstinent alcoholic patients. *Eur J Clin Invest* 1980; **10**: 211-218
112 **Rambaldi A**, Gluud C. Meta-analysis of propylthiouracil for alcoholic liver disease--a Cochrane Hepato-Biliary Group Review. *Liver* 2001; **21**: 398-404
113 **Orrego H**, Kalant H, Israel Y, Blake J, Medline A, Rankin JG, Armstrong A, Kapur B. Effect of short-term therapy with propylthiouracil in patients with alcoholic liver disease. *Gastroenterology* 1979; **76**: 105-115
114 **Serrano-Cancino H**. Treatment of severe alcoholic hepatitis with propylthiouracil (PTU). *Am J Gastroenterol* 1981; **76**: 194
115 **Hallé P**, Paré P, Kaptein E, Kanel G, Redeker AG, Reynolds TB. Double-blind, controlled trial of propylthiouracil in patients with severe acute alcoholic hepatitis. *Gastroenterology* 1982; **82**: 925-931
116 **Orrego H**, Blake JE, Blendis LM, Compton KV, Israel Y. Long-term treatment of alcoholic liver disease with propylthiouracil. *N Engl J Med* 1987; **317**: 1421-1427
117 **Pierrugues R**. Short-term therapy with propylthiouracile (PTU) for alcoholic hepatitis (AH). A clinical, biochemical and histological randomized trial about 29 patients. *J Hepatol* 1989; **9**: S72
118 **Sogni P**, Hadengue A, Moreau R, Le Moine O, Soupison T, Oberti F, Farinotti R, Lebrec D. Acute effects of propylthiouracil on hemodynamics and oxygen content in patients with alcoholic cirrhosis. *J Hepatol* 1997; **26**: 628-633
119 **Mihas AA**, Holley P, Koff RS, Hirschowitz BI. Fulminant hepatitis and lymphocyte sensitization due to propylthiouracil. *Gastroenterology* 1976; **70**: 770-774
120 **Limaye A**, Ruffolo PR. Propylthiouracil-induced fatal hepatic necrosis. *Am J Gastroenterol* 1987; **82**: 152-154
121 **Ruiz JK**, Rossi GV, Vallejos HA, Brenet RW, Lopez IB, Escribano AA. Fulminant hepatic failure associated with propylthiouracil. *Ann Pharmacother* 2003; **37**: 224-228
122 **Deidiker R**, deMello DE. Propylthiouracil-induced fulminant hepatitis: case report and review of the literature. *Pediatr Pathol Lab Med* 1996; **16**: 845-852
123 **Ichiki Y**, Akahoshi M, Yamashita N, Morita C, Maruyama T, Horiuchi T, Hayashida K, Ishibashi H, Niho Y. Propylthiouracil-induced severe hepatitis: a case report and review of the literature. *J Gastroenterol* 1998; **33**: 747-750
124 **Dai WX**, Zhang JD, Zhan SW, Xu BZ, Jin H, Yao Y, Xin WC, Bai Y. Retrospective analysis of 18 cases of antithyroid drug (ATD)-induced agranulocytosis. *Endocr J* 2002; **49**: 29-33
125 **Porter HP**, Simon FR, Pope CE 2nd, Volwiler W, Fenster LF. Corticosteroid therapy in severe alcoholic hepatitis. A double-blind drug trial. *N Engl J Med* 1971; **284**: 1350-1355
126 **Depew W**, Boyer T, Omata M, Redeker A, Reynolds T. Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. *Gastroenterology* 1980; **78**: 524-529
127 **Galambos JT**, Hersh T, Fulenwider JT, Ansley JD, Rudman D. Hyperalimentation in alcoholic hepatitis. *Am J Gastroenterol* 1979; **72**: 535-541
128 **Nasrallah SM**, Galambos JT. Aminoacid therapy of alcoholic hepatitis. *Lancet* 1980; **2**: 1276-1277
129 **Diehl AM**, Boitnott JK, Herlong HF, Potter JJ, Van Duyn MA, Chandler E, Mezey E. Effect of parenteral amino acid supplementation in alcoholic hepatitis. *Hepatology* 1985; **5**: 57-63
130 **Calvey H**, Davis M, Williams R. Controlled trial of nutritional supplementation, with and without branched chain amino acid enrichment, in treatment of acute alcoholic hepatitis. *J Hepatol* 1985; **1**: 141-151
131 **Soberon S**, Pauley MP, Duplantier R, Fan A, Halsted CH. Metabolic effects of enteral formula feeding in alcoholic hepatitis. *Hepatology* 1987; **7**: 1204-1209
132 **Alvarez MA**, Cabré E, Lorenzo-Zúñiga V, Montoliu S, Planas R, Gassull MA. Combining steroids with enteral nutrition:

a better therapeutic strategy for severe alcoholic hepatitis? Results of a pilot study. *Eur J Gastroenterol Hepatol* 2004; **16**: 1375-1380

S- Editor Liu Y **L- Editor** Ma JY **E- Editor** Ma WH