Medical Management of Severe Alcoholic Hepatitis

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Importance of Alcoholic Hepatitis in Clinical Practice

Acute alcoholic hepatitis (AH) is a serious form of acute decompensation of alcoholic liver disease (ALD) that develops in heavy drinkers and is characterized by rapid onset of jaundice, malaise, anorexia, tender hepatomegaly, and features of the systemic inflammatory response syndrome (SIRS). Two recent studies suggest the number of patients hospitalized in the U.S. with AH increased during the first decade of the 21st century (1, 2). Although in its most severe form, AH has a high short-term mortality rate if untreated, in 2011, only 28% of more than 1,600 patients admitted to U.S. hospitals were treated with glucocorticoids and 17% with pentoxifylline (PTX), suggesting a lack of widespread confidence in the 2 most frequently used therapies for AH (2). Patients with AH are systemically ill with a high risk of nutritional deficiency, infection, acute kidney injury (AKI), and development of multiorgan failure (MOF) syndrome(3). Recognition of the possible complications and improved understanding of the basic mechanisms of liver injury from alcohol is essential to improve clinical outcomes for patients with severe AH.

Definition of Alcoholic Hepatitis

Histologic features of AH include steatosis and ballooning degeneration of hepatocytes (steatohepatitis), intrahepatic cholestasis (bilirubinostasis), chicken-wire fibrosis, Mallory-Denk bodies, and megamitochondria. Cirrhosis is present in the vast majority of those who are severely ill(4-6).

A recent consensus statement from the Alcoholic Hepatitis Consortium sponsored by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) provided a working definition of AH that includes onset of jaundice within 60 days of heavy consumption (> 50 g/day) of alcohol for a minimum of 6 months, a serum bilirubin > 3 mg/dL, an elevated AST (50-400 U/L), an AST:ALT ratio > 1.5, and no other obvious cause for hepatitis (6). The consensus statement proposed classifying patients with AH as *definite* when a liver biopsy was used to establish the diagnosis; *probable* when the clinical and laboratory features were present without potential confounding problems; and *possible* when confounding problems were present. This proposed classification is intended to improve interpretation of future

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treatment trials in patients with AH, since prior studies indicated that 10-15% of subjects diagnosed with acute AH based on clinical criteria alone did not have characteristic histologic features on a liver biopsy specimen.

Risk Factors

While the exact pathogenesis of AH remains a subject of active investigation, several risk factors have been identified, including female gender, elevated body-mass index (BMI), and genetic risk factors such as having the G allele of *PNPLA3* (patatin-like phospholipase domain containing protein 3). Because elevated BMI is a risk factor for both AH and nonalcoholic steatohepatitis (NASH), distinguishing these 2 entities usually rests on the amount of alcohol consumed and the rapid onset of jaundice (7). Some experts believe that the distinction may be artificial since pre-existing fatty liver due to obesity and the metabolic syndrome could provide the necessary background for additional injury due to alcohol.

The Role of Inflammation in AH

AH is by its definition an inflammatory condition that is often accompanied by features of SIRS: tachycardia, tachypnea, fever and leukocytosis. Infections are common and must be identified and treated in patients with AH, but SIRS may develop in the absence of infection. The presence of SIRS increases the risk of developing MOF that predicts high mortality in AH (3). Numerous basic and translational studies have identified high levels of pro-inflammatory cytokines in patients with AH that may be linked to an increased risk of mortality.

Predicting Prognosis in AH

In 1977, Maddrey and colleagues used the serum bilirubin and prothrombin time to define a group of patients with AH that had a 28-day mortality rate above 50%. This formula, known as the Maddrey Discriminant Function (MDF), was subsequently used to stratify subjects for inclusion into clinical trials (8). Early trials and a subsequent randomized multicenter trial indicated that only those patients with more severe manifestations of AH and an MDF > 32 benefited from treatment with glucocorticoids (8, 9). The MELD score was also shown to predict 28-day and 90-day mortality, and the ABIC score (age, bilirubin, INR, and creatinine) and the Glasgow AH Score also predict 90-day mortality (10-12). All of these scoring systems have been validated to predict severe outcomes with a high degree of reliability.

Although an MDF > 32 initially defined a group of patients with a 28-day mortality rate > 50%, the short-term mortality in the placebo group in recent studies (STOPAH) is much better (17%) than the mortality rate in the U.S. multicenter trial (35%), likely because of improvements in best supportive care (BSC)(13) (see later). Importantly, improved outcome with BSC alone makes direct comparisons with historical data from trials more difficult since the time when the trials were completed must be considered.

The Lille score uses data obtained from the first week of treatment with prednisolone to predict whether an individual patient is likely to have a favorable outcome (14). This

information is important since prolonged use of glucocorticoids is associated with an increased risk of infection in patients with AH (13). Combining the Lille model with the MELD score has been proposed as a further refinement (15).

Mechanisms of Action of Current AH Therapy

AH is an inflammatory disease, and proinflammatory mediators, such as tumor necrosis factor (TNF), play a critical role in liver injury. Gut-derived toxins such as lipopolysaccharides (LPS) have been postulated to translocate across a leaky gut barrier and bind to Toll-like receptors with subsequent proinflammatory cytokine production. The two most widely used drug therapies for severe AH both have anti-inflammatory mechanisms of action.

Glucocorticoids, considered the standard of care for severe AH by many gastroenterologists/ hepatologists and professional organizations, bind to receptors (GRs) in the cytoplasm. GRs subsequently translocate to the nucleus and bind to the glucocorticoid response elements (GREs) in the promoter regions of glucocorticoid responsive genes to switch on expression of certain anti-inflammatory genes. Glucocorticoids can also act indirectly to repress activity of a number of relevant transcription factors (e.g., nuclear factor kappa B) with subsequent down-regulation of inflammatory genes. This process requires recruitment of co-repressor molecules, particularly histone deacetylases (HDAC-6,-2) (16, 17).

Unfortunately, some patients are not candidates for glucocorticoid treatment and others develop glucocorticoid resistance by various molecular mechanisms (18, 19), which may differ between patients. For example, inhibition of interleukin 2 (IL-2), a key growth factor secreted by T cells that antagonizes the anti-inflammatory response to glucocorticoids, enhances glucocorticoid sensitivity *in vitro (20).* Levels of GR-B, an alternatively spliced form of GR that essentially acts as a dominant negative inhibitor of glucocorticoid action, are increased in some glucocorticoid-resistant disease states (21, 22). While our knowledge of mechanisms of glucocorticoid action and resistance has expanded, further information is needed to potentially enhance glucocorticoid effectiveness.

PTX, a relatively weak nonspecific phosphodiesterase (PDE) inhibitor has been shown to attenuate liver injury and fibrosis in animal models of liver disease (23, 24). Intracellular levels of cyclic adenosine monophosphate (cAMP) regulate LPS-inducible expression of TNF by monocytes/macrophages (25, 26). PDE inhibitors increase cAMP levels, thereby inhibiting TNF production *in vivo* and *in vitro* (25, 27-30). Importantly, PDE4 inhibitors have also been demonstrated to upregulate the anti-inflammtory/antifibrotic cytokine IL-10 (31-35). Recent studies have shown a pathogenic role of PDE4 enzymes in the development of cholestatic liver injury/fibrosis, and significant protection using a PDE4-specific inhibitor (36). Experimental and clinical studies provide a rationale for targeting PDE4 as a therapeutic strategy for treatment of ALD, but this has been hampered by dose-associated side effects including severe nausea, emesis, and sedative effects caused by the increased cAMP levels in the central nervous system (25, 37). Thus, targeting potent PDE inhibitors directly to the liver may be more effective.

Rationale for Current Therapy for Severe AH and Results of Randomized Controlled Trials (RCT) for Treatment of Severe AH

More than 20 RCTs of glucocorticoids have been conducted in patients with severe AH defined by an MDF > 32 (8, 9, 38-43). Several of these studies were used to create the current guidelines of the AASLD and EASL (44, 45). The 1989 U.S. multicenter trial of methylprednisolone vs. placebo for treating severe AH reported that the 28-day mortality rate was significantly lower in those patients treated with methylprednisolone compared with BSC (9). A subsequent trial from France reported similar findings (38, 43). Although some trials failed to show significant survival benefit in subjects treated with glucocorticoids, 2 separate meta-analyses that included primarily high-quality studies concluded that there is a benefit to treatment (39, 46), whereas a third did not (40). A 2008 Cochrane systematic review of 15 trials concluded that there was no benefit from glucocorticoids, except possibly in the group with an MDF > 32, primarily due to substantial variability in bias (41). Those trials with low bias showed benefit, whereas trials with high bias showed no benefit.

PTX was reported to reduce mortality in patients with severe AH (MDF > 32) (47). Subsequent larger trials reached similar conclusions (48, 49). Most of the reduction in mortality appeared to be related to a decrease in the frequency of hepatorenal syndrome (HRS) in the survivors (47). However, 2 meta-analyses of all trials concluded that there were no differences in short-term mortality related to PTX (50, 51). Subsequent studies combining PTX with glucocorticoids did not show any additive benefit (42, 52).

The largest randomized trial to date in patients with severe AH, STOPAH, enrolled 1,103 patients in the U.K. between 2011 and 2014 (13). Inclusion criteria were MDF > 32, onset of jaundice within 2 months, bilirubin > 4.7 mg/dL and AST < 500 U/L, but neither liver biopsy confirmation nor a minimum elevation of the AST were required. Patients with a serum creatinine > 5.7 mg/dL were excluded. Each clinician made individual decisions regarding nutritional supplementation and use of agents such as terlipressin for hepatorenal syndrome. Patients were randomized to receive prednisolone 40 mg (equivalent of 32 mg methylprednisolone) daily, PTX 400 mg 3 times daily, the combination of prednisolone and PTX, or placebo daily. Results are shown in Table 1. The odds ratio for all patients receiving prednisolone (including the combination with PTX) was 0.72 (0.52-1.01) and was not statistically significant (p = 0.06), whereas the odds ratio for all patients receiving PTX was 1.07 (0.77-1.49). The mortality rate for 90 days was 30% and for 1 year 56%, similar in all 4 groups (Table 1). There was no difference in development of AKI, but the groups treated with prednisolone had more infections (13%) than those not treated with prednisolone (7%) (p = .002).

The lower 28-day mortality rate for placebo in this study compared to other studies (39, 53) adversely impacted the calculated power analysis and may explain why the effects of prednisolone narrowly missed achieving statistical significance for improvement in short-term mortality. Furthermore, treatment of AKI with agents such as terlipressin could be a confounding factor and may help explain a lack of benefit for PTX.

Network meta-analysis allows both direct comparisons of interventions and indirect comparisons across trials using a common comparator such as placebo. Although the statistical tools and mathematical analysis are more complex, the potential advantage is that it allows comparison of interventions that may not have been compared directly against each other in trials. Using this technique, various treatments from 22 recent trials involving 2,621 patients with severe AH were compared (53). Based on moderate quality evidence, treatment with glucocorticoids alone or in combination with PTX or the anti-oxidant, N-acetylcysteine (NAC) that is used to restore glutathione (GSH) levels in patients with acetaminophen poisoning, was shown to reduce 28-day, but not 90-day, mortality in patients with AH. Based on lower quality evidence, PTX alone was also shown to reduce 28-day, but not 90-day, mortality. The analysis included the STOPAH trial and showed that the reduction in mortality was comparable for both glucocorticoids and PTX, possibly because the STOPAH trial was not powered to detect differences among all 4 groups.

A number of potential treatments including vitamin E and an antioxidant cocktail including NAC have been tried with little success in severe AH (54, 55). However, the combination of prednisolone plus NAC given intravenously over the first 5 days of the trial resulted in the most significant improvement in 1-month mortality (53, 56) of the studies included in the network meta-analysis (53). The mortality rate in patients treated with prednisolone 40 mg daily plus NAC was 8% compared with 24% for those treated with prednisolone alone (56). Patients treated with the combination had fewer infections (19%) in 6 months than those treated with prednisolone alone (42%) (p = 0.001) and a lower incidence of HRS (12% vs. 25%, p = 0.02). These important findings remain to be confirmed by additional studies.

Levels of TNF-α are often elevated in patients with severe AH (57, 58). Although preliminary evidence suggested that anti-TNF therapy might be beneficial in severe AH (59, 60), subsequent larger trials of etanercept (antibody to TNF receptor) and the combination (anti-TNF) with glucocorticoids led to a higher risk of infections and higher mortality rate than BSC (61, 62). These trials have generally led to an abandonment of anti-TNF therapy in AH..

Best Practice Advice for Treatment of AH (Table 2)

Jaundice is an important clinical manifestation of decompensated ALD and is often the first indication of serious AH. Patients with underlying ALD who become jaundiced should be hospitalized to encourage abstinence and to exclude serious bacterial infections.

Abstinence remains the cornerstone of therapy for AH. Numerous studies have shown that patients who return to heavy drinking have a far worse prognosis than those who remain abstinent or have reduced alcohol consumption. Although abstinence is important at all stages, it is particularly important to emphasize abstinence beyond 90 days when many patients are regaining normal functioning. A team approach to achieve this goal is optimal.

Infection may be both a precipitating event and a factor leading to a poor outcome in AH. Although glucocorticoids may improve short-term survival in severe AH, the increased risk of infection leads to no change in survival at 90 days and 1 year after diagnosis (3, 53, 56,

61-63). Infections often precede development of AKI and MOF, which has a high mortality rate (3, 64). A high index of suspicion is required to identify both bacterial and fungal infections in patients with AH, since fever may not always be present and an elevated white blood cell count is an unreliable indicator of infection. The presence of SIRS on admission is a risk factor for subsequent development of MOF (3).

AKI can develop in patients with severe AH for many reasons, including infection, changes in hemodynamics particularly intravascular volume depletion, and as a consequence of nephrotoxic drugs. Administration of iodinated contrast dye is a risk factor for AKI in patients with diabetes mellitus, heart failure, and other conditions and is likely to cause similar problems in patients with cirrhosis (65).

Malnutrition is common in AH and impairs recovery from AH (66). One multicenter study indicated that enteral nutrition was comparable to glucocorticoids in reducing 28-day mortality and more effective in reducing long-term mortality (67). However, another multicenter study reported that adding enteral supplementation via nasogastric (NG) tube to glucocorticoid therapy was no more effective than glucocorticoids alone (68). This study was under-powered, and there was a higher than expected rate of NG tube complications. Importantly, nutritional intake (regardless of the arm of the study) was a major determinant of mortality, with those consuming < 21.5 Kcal/kg/day having lower survival (68). Therefore, all patients with AH should be encouraged to meet their nutritional goals as early as possible. Whether NG tubes should be used to provide enteral nutrition is a subject of controversy. Normal-to-high protein diets are safe and do not increase the risk of encephalopathy in patients with AH. Further studies are needed to define the role of specific micronutrients such as zinc and probiotics in management of AH (69, 70).

Although many studies favor the use of glucocorticoids, the appropriate duration for use is a subject of controversy. If used, glucocorticoids should be discontinued in patients who fail to improve based on Lille criteria (14). Those who have a MELD score > 26 should be considered for liver transplantation, which may be life saving (44, 71, 72). Some transplant centers have policies that require a defined period of abstinence, and all require the willingness of a patient with a history of heavy drinking to remain abstinent after transplantation. Several studies have demonstrated that the outcomes of liver transplantation in patients with AH are similar to those of other transplanted patients with similar MELD scores(71, 72). Relapse following transplantation appears to be no more frequent than it is in patients with alcoholic cirrhosis who do not have AH.

Conclusions and Gaps in Information

AH is a potentially severe form of ALD with evidence of systemic inflammation that requires anti-inflammatory and supportive treatment to prevent progression and death. The Maddrey DF, MELD, ABIC, and Glasgow scoring systems all predict prognosis accurately. Nutritional deficiencies and infections are both common in patients with AH and require prompt recognition and treatment to prevent devastating complications such as AKI and MOF. Current anti-inflammatory therapy with glucocorticoids modestly improves short-term mortality, but this endpoint of treatment is clearly suboptimal. The 1-year mortality rate was

56% in the STOPAH trial, and the 4-year mortality rate from the VA Cooperative Study for patients with AH superimposed on cirrhosis was 65%, worse than that for many common forms of cancers such as colon and breast (73). Both dose and duration of therapies for AH generally have been empiric. Perhaps the concept of very high, short-term bursts of glucocorticoids to induce "immune paralysis," as is used to treat lupus nephritis, should be considered. Furthermore, relatively safe drugs such as NAC or PTX could be used for a longer duration to treat ongoing hepatic inflammation, since VA Cooperative studies documented residual histologic AH after more than a year of abstinence. Combination therapy may be optimal; we have focused mainly on inflammation, but there are multiple other targets such as gut-barrier dysfunction, cell death, liver regeneration, and fibrosis. One potential reason for the high long-term mortality is a return to drinking. New treatments need to be tested, and continued support from the NIH (NIAAA Alcoholic Hepatitis Consortium) and new industry support are necessary. Potential treatments should include drugs repurposed to treat AH as well as drugs and approaches to decrease alcohol abuse.

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Table 1

Mortality at 28 days, 90 days, and 1 year in alcoholic hepatitis in the STOPAH trial

End Point	Prednisolone	No Prednisolone	Pentoxifylline	No Pentoxifylline	Prednisolone		Pentoxifylline	
					Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
28-Day mortality—no./total no. (%)	73/526 (14)	95/527 (18)	85/518 (16)	83/535 (16)	0.72 (0.52-1.01)	0.06	1.07 (0.77-1.49)	0.69
90-Day mortality or liver transplantation — no./total no. (%)	144/484 (30)	141/484 (29)	139/478 (29)	146/490 (30)	1.02 (0.77-1.35)	0.87	0.97 (0.73-1.28)	0.81
1-Year mortality or liver transplantation — no./total no. (%)	210/371 (57)	211/376 (56)	205/365 (56)	216/382 (57)	1.01 (0.76-1.35)	0.94	0.99 (0.74-1.33)	0.97

From Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med. 2015 Apr 23;372(17):1619-28.

Table 2

Current recommendations for the diagnosis and treatment of acute alcoholic hepatitis (AH)

Disease/condition	Acute AH
Target audience	Gastroenterologists, hepatologists, primary care physicians, emergency medicine physicians, and other clinicians.
Target patient population	Adults with rapid onset of jaundice and elevated serum AST levels and a history of drinking more than 40 g (3 standard drinks) of ethanol daily for more than 1 year.
Criteria for diagnosis	Onset of jaundice within 8 weeks of last period of drinking Heavy drinking (> 40 g/day) for more than 6 months, usually for many years Serum bilirubin > 3.0 mg/dL Serum AST > 50 IU/L but < 400 IU/L Serum AST/ALT ratio > 1.5 Liver biopsy specimen showing macrovesicular steatosis, neutrophil infiltration, ballooning degeneration of hepatocytes, megamitochondria, and Mallory-Denk bodies is helpful but not required for the clinical diagnosis.
Assessing severity	Laboratory parameters are more reliable predictors of severe disease than clinical symptoms or signs or imaging criteria. Mathematical equations combining INR (prothrombin time) and serum bilirubin +/− creatinine, +/− age +/− WBC count are effective tools Maddrey discriminant function (MDF) > 32 predicts high mortality within 28 days. MELD score > 20 predicts a high mortality rate within 90 days. ABIC score category C predicts high 28- and 90-day mortality rates. Glasgow alcoholic hepatitis score of 9 predicts a high 28-day mortality rate.
Importance of recognition and treatment	Onset of jaundice indicates decompensation and is an ominous sign in all patients with chronic liver disease, particularly those with alcoholic liver disease. Although the name suggests a process that develops acutely, the majority of patients with AH have cirrhosis at the time of diagnosis of AH. Without treatment and abstinence from drinking alcohol, the mortality rate within 90 days is 40-50%.
Challenges related to treatment	The immune response, particularly neutrophil function, is impaired in patients with AH, placing them at risk of further decompensation following bacterial and fungal infections. Many treatments for AH focus on reducing inflammation through use of glucocorticoids or other drugs that suppress the immune system. Failure to maintain abstinence from drinking alcohol may lead to further deterioration in liver function.
Best Practice Advice (BPA)	*BPA 1:* Abstinence from drinking alcohol is the cornerstone of treatment for AH. *BPA 2:* Patients with jaundice and suspected AH should have cultures of blood, urine, and ascites, if present, to determine the presence of bacterial infections regardless of whether they have fever. *BPA 3:* Patients with AH who have jaundice require further evaluation to determine severity. Those with severe AH or inadequate social and medical support should be admitted to the hospital to encourage abstinence, restore adequate nutrition, and exclude serious infections. *BPA 4:* Imaging of the liver is warranted as part of the evaluation, but caution should be used in administering iodinated contrast dye, as it increases the risk of AKI. *BPA 5:* Patients with AH require a diet with 1-1.5 g protein and 30-40 kcal/kg body weight for adequate recovery. If the patient is unable to eat because of anorexia or altered mental status, a feeding tube should be considered for enteral feeding. Parenteral nutrition alone is inadequate. *BPA 6:* Severity and prognosis of AH should be evaluated using MDF, MELD, ABIC, or Glasgow scoring systems. Current treatments are based on this assessment. *BPA 7:* Presence of SIRS on admission is associated with an increased risk of multi-organ failure (MOF) syndrome. Development of MOF, usually due to infections developing after initial diagnosis of AH, is associated with a very high mortality rate. *BPA 8:* Nephrotoxic drugs, including diuretics, should be avoided or used sparingly in patients with AH, since AKI is an early manifestation of MOF. *BPA 9:* Patients with MDF > 32 or MELD score > 20 without a contraindication to glucocorticoid, such as hepatitis B viral infection, tuberculosis, or other serious infectious diseases, may be treated with methylprednisolone 32 mg daily, but the appropriate duration of treatment remains a subject of controversy. Methylprednisolone does not improve survival beyond 28 days, and the benefits for < 28 days are modest. *BPA 10:* Patients with a contraindication to glucocorticoids may be treated with pentoxifylline 400 mg three times daily with meals. Data regarding the efficacy are conflicting. *BPA 11:* Patients with severe AH, particularly those with a MELD score > 26 with good insight into their alcohol use disorder and good social support should be referred for evaluation for liver transplantation, as the 90-day mortality rate is very high. *BPA 12:* Patients with mild to moderate AH defined by a MELD score < 20 and MDF < 32 should be referred for abstinence counseling and prescribed a high protein diet supplemented with B vitamins and folic acid.
Important points to discuss with patients	Patients should be encouraged to abstain completely from drinking but offered support and encouragement even if they fail to achieve abstinence, as a reduction in alcohol consumption improves survival.

	Adequate nutrition, including calories and protein, is necessary for recovery from AH. Patients who drink alcohol at hazardous levels (> 40 g/day) should be advised to report jaundice as soon as it develops, since this symptom is a harbinger of serious injury.

ABIC, age, bilirubin, INR, creatinine; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.