Practical Concerns and Controversies in the Management of Alcoholic Hepatitis

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Abstract: Recent advances in the treatment of alcoholic hepatitis (AH) have reinforced the utility of glucocorticoids, a treatment that has been in use for nearly 4 decades, to enhance short-term survival. As multi-institutional consortia research new therapeutic advances, this orphan disease, which afflicts younger patients and has poor outcomes, continues to be difficult to manage. AH has a protean clinical presentation and course, with various prediction models and treatment approaches that can challenge even experienced providers. This review addresses 4 key controversies and other practical issues associated with the diagnosis, prognosis, management, and treatment of patients with AH.

Alcoholic hepatitis (AH) is an acute, inflammatory syndrome of jaundice and liver injury that occurs in a subset of patients after decades of heavy alcohol use (mean intake, approximately 100 g/day).[1-3] The presentation of AH can be quite varied, but when it is severe and not responding to medical therapies, it has a dismal prognosis. There has been a resurgence of interest in this condition with the publication of several important studies addressing long-unresolved issues regarding the treatment of AH and the introduction of early liver transplantation (LT) for severe AH. In addition, several U01 research project cooperative agreements involving large multi-institutional consortia funded by the National Institute on Alcohol Abuse and Alcoholism are well underway to identifying new therapeutic targets and performing clinical trials to develop and test drugs for AH. While there has been an abundance of recent review articles on AH, few have focused on the more practical concerns and controversies that arise regarding the diagnosis, prognosis, management, and treatment of patients with AH.[4-7]

Burden of Alcoholic Liver Disease

Alcohol use is ubiquitous in the United States. It is estimated that two-thirds of the US adult population consumes some alcohol, with 44% having at least 12 drinks in the prior 12 months.[8] However, a recent report suggests an alarming rise of the 12-month and lifetime

prevalences (13.9% and 29.1%, respectively) of the Diagnostic and Statistical Manual of Mental Disorders (5th edition) alcohol use disorder classification in the United States.[9] Although only a minority of heavy drinkers develop AH and/or cirrhosis, the prevalence of alcoholic liver disease is likely to increase.

Alcoholic liver disease is a major cause of mortality and morbidity both in the United States and globally. Almost 6% of all deaths worldwide in 2012 were attributable to alcohol.[10] In 2012, the proportion of deaths due to cirrhosis stemming from alcoholic liver disease was 50% globally, 60% in the United States, and greater than 70% in the United Kingdom and Eastern Europe.[10] In the United States, alcoholic cirrhosis is the eighth most common cause of all mortality and the second most common among all gastrointestinal diseases.[2] In 2007, 0.71% of all hospital admissions in the United States were for AH as the primary diagnosis, with an in-hospital mortality rate of 6.8%.[2] The average total charges in 2011 during hospitalization for AH were $37,769, higher than for acute myocardial infarction and stroke.[11] Data from combined treatment studies of severe AH have shown a 28-day mortality rate of 34% in patients not receiving corticosteroids.[7] These statistics highlight the need for improving education, prevention, diagnosis, and treatment of alcohol-related disease in its various forms: AH, alcohol use disorder, and alcoholic liver disease–related cirrhosis.

Diagnosis

Because there are no diagnostic tests for AH, eliciting an accurate history of alcohol use from a patient is paramount to its diagnosis. This process may be challenging for several reasons. First, a patient may not be forthright in providing a factual drinking history. Second, a provider should ask about current and past alcohol consumption in a nonjudgmental way to obtain an accurate response, as patterns of alcohol use can change over time.[12] Patients with AH commonly stop alcohol use for weeks prior to their presentation.[1] Therefore, it is important to elicit alcohol use histories over discrete time periods, particularly in association with recent life stressors that may lead to increased consumption.[13,14] This approach is particularly useful in assessing the impact of alcohol in more equivocal situations of liver injury where concomitant conditions such as nonalcoholic fatty liver disease, drug-induced liver injury, or hepatitis C virus infection may be confounding. Third, even agreeing upon what constitutes a standard drink can be confusing and is often influenced by the use of colloquial terms or jargon such as jigger, forty, handle, quart, and fifth, and by provider unfamiliarity.[12,15-17]

Table 1. Standard Drink Definitions and Drink Equivalents in the United States

Standard Drink Definitions[a]	Standard Drink Equivalents
Beer or cooler (12 oz, approximately 5% alcohol)	12 oz = 1 drink
	40 oz = 3.3 drinks
Malt liquor or beer (8-9 oz, approximately 7% alcohol)	12 oz = 1.5 drinks
	40 oz = 4.5 drinks
Wine (5 oz, approximately 12% alcohol)	1 bottle (750 mL or 25 oz) = 5 drinks
Hard liquor or spirits (1.5 oz, approximately 40% alcohol)	1 pint (16 oz) = 11 drinks
	1 fifth (25 oz) = 17 drinks
	1 handle (1.75 L or 59 oz) = 39 drinks

[a]A standard drink is any drink that contains approximately 14 grams of pure alcohol (approximately 0.6 fl oz or 1.2 tbsp).

Adapted from the National Institute on Alcohol Abuse and Alcoholism at http://pubs.niaaa.nih.gov/publications/Practitioner/PocketGuide/pocket_guide2.htm.

Table 1 lists standard drink definitions and common equivalents.

Controversy #1: Diagnosing Alcoholic Hepatitis by Liver Biopsy

Liver biopsy is considered the gold standard of diagnosis of AH and is required for inclusion in many, albeit not all, AH clinical trials. However, there are challenges that may impede the utilization of liver biopsy in clinical practice. Most patients with severe AH are already cirrhotic, and many have portal hypertension, either chronically or as a consequence of AH. Therefore, many of these patients have a prolonged international normalized ratio (INR), a low platelet count, or a combination of both, and present a bleeding risk. In order to diminish the risk of bleeding, most liver programs in the United States have adopted a transjugular route. Nevertheless, liver biopsies are not routine in the United States as part of the evaluation of a patient with putative severe AH, whereas they are common practice in Spain, France, and Germany.[1,6,18] The reported inaccuracy rate of diagnosing AH clinically without liver biopsy varies from 4% to 46%.[19-24] In addition, the histopathologic features of AH may persist for several months after alcohol cessation, and 70% to 98% of patients have concomitant histologic evidence of cirrhosis.[19,20,25] A review of 11 randomized, controlled trials

of biopsy-proven AH demonstrated that 1409 of 1668 (84.5%) biopsies showed histologic evidence of AH and that the addition of a total bilirubin greater than 80 μmol/L (>4.7 mg/dL) increased the accuracy of AH diagnosis to 96%.[24] Dhanda and colleagues suggested that a liver biopsy is not essential for diagnosing AH using this bilirubin threshold.[24]

A further component surrounding the need for and utility of liver biopsy in the diagnosis of AH revolves around the distinction between acute-on-chronic liver failure (ACLF) and AH. ACLF is a relatively new concept in hepatology, with varying definitions proposed. In most definitions, ACLF describes a subset of cirrhotic patients with rapidly progressive decompensation, multiorgan failure, and high short-term mortality.[26-29] While the etiologies of ACLF seem to vary between Asia and the Western world, a common theme is the implication of recent alcohol use as a precipitating factor in the pathogenesis of ACLF. Because nearly all patients with severe AH are already cirrhotic and often present with multiorgan dysfunction, it is possible that the majority of ACLF is simply severe AH.[29-31] In addition, given the diagnostic difficulties described above, alcohol-related ACLF is likely underreported and possibly constitutes a significant proportion of the ACLF caused by unknown origin, regardless of geography.[27-29] Whether conventional AH-specific therapies are effective in patients with alcohol-related ACLF is unknown and requires further study.

Although liver biopsy is not essential to diagnose AH, it is useful in cases of diagnostic uncertainty, as differentiating severe AH from nonalcohol-related liver diseases based upon clinical parameters alone can lead to different management plans.[24,31,32]

Controversy #2: Choosing a Prediction Model in Alcoholic Hepatitis

There is no shortage of protocols designed to predict the outcome of a patient with severe AH, and it is important to learn how to use the prediction models currently available, as they share many similar elements (Table 2).

Discriminant Function

The discriminant function (DF) was first described by William Maddrey in 1978.[33] It was derived from a prospective, double-blind, placebo-controlled trial of prednisolone for AH and later modified. Patients with a DF of at least 32 had a 1-month mortality of 30% to 50% with a survival benefit if given prednisolone.[33] The components of the DF are known laboratory markers of hepatic synthetic function. The DF is highly sensitive to identifying patients with AH at risk of early mortality and has decades of study as the key inclusion criterion for numerous prospective clinical trials of AH treatment. However, its specificity is suboptimal, as many patients with a DF of 32 or higher survive even without AH-specific treatment. The DF is also limited as a static, dichotomous variable calculated at the time of admission. Additionally, the DF uses prothrombin time (PT) and control PT rather than INR. In the United States, the control PT is not commonly reported and usually requires a managing provider to contact a laboratory to confirm the correct value (usually the mean of the reference range). Because control PT values can differ by laboratory and change over time based upon reagents used and methodology, attention should be paid to this issue, especially in retrospective clinical research.[34-40] While the DF calculation can be a source of confusion in clinical use, the model is still widely used in both clinical practice and research.

Lille Model

The Lille model was born out of a clinical observation that an early change in bilirubin levels after initiation of glucocorticoids was associated with improved prognosis.[41] The addition of the dynamic variable of comparing bilirubin levels at days 0 and 7 is a key feature of this validated model. The Lille model differs from other prediction models in that it was designed to influence clinical decision-making by augmenting the DF to assess the likelihood of response to glucocorticoids in a well-characterized, biopsy-proven cohort of AH patients with a DF of at least 32.[42] The model helps answer the question of whether a patient with severe AH should continue receiving glucocorticoids after 7 days as a responder to medical therapy. A Lille score of 0.25 or less predicts good response with glucocorticoids and a 25% mortality rate at 6 months, compared with a Lille score of 0.45 or higher, which predicts poor response, supporting cessation of therapy and a 75% mortality rate.[42] A subsequent pooled meta-analysis of individual data confirmed the 28-day survival benefit of glucocorticoids according to a tripartite classification of the Lille score: complete responders (score <0.16; <35th percentile), partial responders (score 0.16-0.56; 35th-70th percentile), and null responders (score >0.56; >70th percentile).[43] Corresponding 28-day mortality rates were 9%, 21%, and 47%, respectively.[43] Glucocorticoids improved survival in responders (complete and partial) but not in patients with a Lille score higher than 0.56, a higher threshold that reduces overestimation of risk.[6]

Model for End-Stage Liver Disease

As in other areas of hepatology, the Model for End-Stage Liver Disease (MELD) has also been applied to AH. MELD accurately predicts outcome in AH and has the benefit of capturing renal function, which has been independently associated with outcomes in severe

Table 2. Prediction Models for Alcoholic Hepatitis

Model	Formula	Interpretation
Discriminant Function	(4.6 × [PT – control PT]) + serum bilirubin	Glucocorticoids are beneficial when discriminant function is >32
Lille	[3.19 – (0.101 × age)] + (0.147 × albumin on day 0) + (0.0165 × change in bilirubin on day 7) – [0.206 × renal insufficiency (rated as 0 if absent and 1 if present)] – (0.0065 × bilirubin level on day 0) – (0.0096 × PT)	Stop glucocorticoid use if score is ≥0.45 (nonresponse)
MELD	3.8 × $\log_e$ (bilirubin in mg/dL) + 11.2 × $\log_e$ (INR) + 9.6 × $\log_e$ (creatinine mg/dL) + 6.4	High 30-day mortality risk with a MELD score >18 or 21
Glasgow Alcoholic Hepatitis Score	1 point / 2 points / 3 points Age: <50 / ≥50 / N/A WBC count: <15 / ≥15 / N/A Urea: <5 / ≥5 / N/A PT ratio: <1.5 / 1.5-2 / >2 Bilirubin: <7.3 / 7.3-14.6 / >14.6	Glucocorticoids are beneficial if score is ≥9 (when discriminant function is ≥32)
ABIC	(age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8)	90-day mortality risk: Low: <6.71 Intermediate: 6.71-9.0 High: >9.0
Alcoholic Hepatitis Histologic Score	Points Fibrosis stage None or portal fibrosis: 0 Expansive fibrosis: 0 Bridging fibrosis or cirrhosis: 3 Bilirubinostasis No: 0 Hepatocellular only: 0 Canalicular or ductular: 1 Canalicular or ductular plus hepatocellular: 2 Polymorphonuclear cell infiltration None or mild: 2 Severe infiltration: 0 Megamitochondria Present: 2 Absent: 0	90-day mortality risk: Mild: 0-3 Intermediate: 4-5 Severe: 6-9

ABIC, age, serum bilirubin, international normalized ratio, and serum creatinine model; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PT, prothrombin time; WBC, white blood cell.

AH.[44] However, creatinine as a model variable can also be misleading, as a patient with mild AH and severe acute kidney injury can have a low DF but a high MELD score. MELD has the added benefit of being a commonly used dynamic and continuous model that can be measured at different time points to assess prognosis. However, there is no consensus as to the MELD threshold value defining poor prognosis at which glucocorticoids or other therapies would be useful.[6,43] In practice, a MELD score greater than 21, particularly with a minimum total bilirubin of 5 mg/dL and a rising MELD score of at least 2 in the first week, likely portends a poor prognosis.[19,45-48] Additionally, its use has been studied and verified in ACLF.[6,28,49]

Glasgow Alcoholic Hepatitis Score

The Glasgow Alcoholic Hepatitis Score (GAHS) was derived and validated in a study population that did not receive glucocorticoids or pentoxifylline. The score

considers age and white blood cell count as shared variables with the other models. Although the GAHS has a higher accuracy and specificity compared with the DF or MELD, it is substantially less sensitive in predicting 1- and 3-month mortality rates. Given the high risk of short-term mortality, an AH model would preferably have a high sensitivity to identifying all AH patients at risk. The GAHS has been shown to be a useful adjunct to a DF of 32 or higher. Additionally, a GAHS of 9 or higher identified patients who benefited from glucocorticoids, compared with a DF of at least 32 and a GAHS less than 9, where no appreciable difference between untreated or glucocorticoid-treated patients was found.[50-52]

Age, Serum Bilirubin, International Normalized Ratio, and Serum Creatinine Model

The age, serum bilirubin, INR, and serum creatinine (ABIC) model is a newer prediction model, derived and validated in a Spanish biopsy-proven AH cohort, that stratifies patients into low, intermediate, and high risk of mortality at 90 days and 1 year.[53,54] Because the ABIC model was developed in a cohort treated with corticosteroids, it is likely limited as a tool to identifying patients best suited to corticosteroids.[6]

Alcoholic Hepatitis Histologic Score

The Alcoholic Hepatitis Histologic Score (AHHS) was developed and refined in a multinational effort as the first histologic AH prediction model.[55] The AHHS is semiquantitative with histologic variables previously correlated with prognosis in AH. Of note, mild or absent neutrophil infiltration confers points toward a higher risk of mortality compared with severe neutrophil infiltration. This may seem contrary to a higher serum white blood cell count conferring higher risk in the GAHS and Lille model, with a feature of systemic inflammatory response syndrome (SIRS) likely playing an unascertained role.[56] The AHHS requires an early liver biopsy obtained within 48 hours of admission to be scored correctly, which limits its practical applicability given patient safety, availability of transjugular biopsy, and cost concerns. While the ABIC model and AHHS are organizationally similar with 3 tiers of risk, caution is advised to directly comparing these or other models. For example, the low-, intermediate-, and high-risk mortality rates for the ABIC model and AHHS vary widely (3% vs 0%, 19% vs 30%, and 51% vs 75%, respectively).[54] Prospective, real-world evaluation of the AHHS is needed.

Real-World Application of Models

Several studies have performed retrospective application of the 6 clinical prediction models discussed above. Using heterogeneous study cohorts, these case series demonstrate that the clinical prediction models perform similarly well at predicting outcomes in AH, with the area under the curve ranging from 0.71 to 0.82 for 28-day mortality.[57-62]

Joint-Effect Combinative Models

A recent study evaluated various combinations of the dynamic Lille model with static models for outcome prediction in AH.[63] These joint-effect combinative models originated in a glucocorticoid-treated European cohort and were validated in a similar multinational cohort. While all combinations performed well, the MELD+Lille combination was better at predicting survival at 2 and 6 months than the DF+Lille or ABIC+Lille combinations and single models, with an area under the curve of 0.77. These combinative models, particularly MELD+Lille, provide a continuum of mortality risk from 0% to 100% rather than a simple yes/no response, allowing for a more nuanced and precise prediction of outcome, including in patients with intermediate risk. Thus, the MELD+Lille joint-effect model has practical value for patient management and the design of future clinical trials.

Controversy #3: The Optimal Treatment for Severe Alcoholic Hepatitis

Treatment of severe AH begins with cessation of alcohol consumption. It is unknown whether a safe lower threshold for alcohol consumption exists for patients with AH. Therefore, all patients with AH are advised to establish and maintain abstinence. The roles of treatments in controlling craving for alcohol or of psychotherapies in supporting abstinence have not been established for AH. Based upon other forms of alcoholic liver disease, for which there are also a paucity of good data, patient-tailored psychotherapies are recommended once the patient has achieved sufficient health to participate.

Abstinence and Nutrition

Many patients with severe AH and underlying cirrhosis have protein-calorie malnutrition, making nutritional replenishment an obvious place to begin treatment. Achieving adequate nutrition can be difficult for patients with severe AH, especially in those with hepatic encephalopathy, tense ascites, and/or lactulose-related ileuses. Enteral nutrition via a nasogastric tube is sometimes considered, although good data to support it are few.[64-66] In a small, multicenter, randomized, prospective Spanish study, enteral nutrition (2000 kcal/day) was compared to prednisolone for 28 days, and similar rates of survival were observed.[67] This finding suggests that enteral nutrition may be noninferior to prednisolone as a therapy for AH. Enteral nutrition may also play a role in reducing bacterial translocation in the gut by maintaining gut barrier function that may reduce the incidence of infections.[68-70] Furthermore, it is not believed that

passage of a nasogastric tube is a risk factor for variceal hemorrhage.

Nutrition Plus Glucocorticoids

European investigators reported the results of a multicenter, randomized, controlled trial comparing 2 arms: the intensive group, which received intensive enteral nutrition plus methylprednisolone, and the control group, which received conventional nutrition plus methylprednisolone.[71] In the intensive group, enteral nutrition of a proprietary formula (1.5 kcal/mL and 7.5 g protein/100 mL) was given via a nasogastric tube for 14 days based upon weight (1 L/day if <60 kg, 1.5 L/day if 60-90 kg, or 2 L/day if >90 kg). The authors reported a significant improvement in 6-month survival rates on a per-protocol analysis (69.8% intensive group vs 46.8% control group; *P*=.015). On intention-to-treat analysis, however, no statistical difference was found in 6-month survival rates.[72] Given these data, adequate and consistent enteral nutrition should be considered a critical treatment for every AH patient who cannot maintain an adequate intake of protein and calories by mouth.[73]

Glucocorticoids

Glucocorticoids are the most extensively studied intervention in AH treatment, with more than 16 clinical trials that date back almost 40 years.[32] The heterogeneity and lack of power of these small trials to detect differences in outcome led to years of controversy regarding the utility of glucocorticoids in AH. Two Cochrane meta-analyses were conflicted; one reported that glucocorticoids decreased 1-month mortality in AH only when severe (DF ≥32) or in patients with hepatic encephalopathy.[74,75] A gold standard meta-analysis of combined individual data of 5 randomized, controlled trials with 418 patients confirmed the efficacy of glucocorticoids in severe AH.[76] The arm receiving glucocorticoids (n=221) had higher 28-day survival rates than the placebo arm (n=197; 80% vs 66%).[76] This represents a 30% relative risk reduction with a number needed to treat of 5 (ie, 5 patients need to be treated to avert 1 death at 28 days). There is currently a general agreement that glucocorticoids should be part of first-line therapy in patients with AH and a DF of at least 32 without contraindications.[32,77,78]

Prednisolone Vs Prednisone

The type, dose, and duration of glucocorticoid treatment used in clinical trials of AH vary significantly, although both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver guidelines recommend use of prednisolone 40 mg/day (usually oral) for 4 weeks, then tapered over 2 to 4 weeks or stopped, depending on the clinical situation.[32,78] Anecdotally, rapid tapering of glucocorticoids in AH does not cause adrenal insufficiency. Aside from the fact that most clinical trials use prednisolone, there is also a pharmacologic concern over the diminished hepatic metabolism of prednisone (the prodrug) to prednisolone in a dysfunctional liver. The putative mechanisms are impairment of the hepatic enzyme 11-beta-hydroxysteroid dehydrogenase, which renders the 11-oxosteroids cortisone and prednisone biologically active, and impairment of ring A reduction of prednisolone, which leads to persistence of this biologically active metabolite.[79] Serum prednisolone levels are also higher after administration of prednisolone vs prednisone in patients with liver dysfunction and low serum albumin levels due to higher circulating unbound corticosteroids.[78] However, subsequent studies did not demonstrate significant differences between prednisolone and prednisone.[80,81] Of note, these studies were performed in the 1970s with small numbers of subjects, varying techniques, and likely various disease etiologies (eg, autoimmune hepatitis or hepatitis C virus infection) that were not yet well defined.

Depending on availability, oral prednisolone comes in liquid form and is often formulated with alcohol, making tapering difficult and prompting questions by pharmacists and patients. Methylprednisolone tablets are another widely available option but require dose conversion, as the drug has a relative potency of 5:4 compared with prednisolone or prednisone. Practically, prednisolone tablets are preferred; however, if they are not available, prednisone may be used to treat severe AH.

Starting Corticosteroid Use

Providers are often reticent to start patients with severe AH on glucocorticoids due to side effects and infection risk. There is a significant overlap between the clinical presentations of AH and sepsis. Fever, tachycardia and tachypnea, leukocytosis (sometimes extreme with a white blood cell count >50,000), altered mental status, abdominal pain, and distension may accompany severe AH. These shared features with SIRS present clinical uncertainty, with the role of SIRS being increasingly recognized in influencing outcomes in AH.[56] In addition, up to one-quarter of patients who are hospitalized with severe AH already have a significant infection such as spontaneous bacterial peritonitis, pneumonia, cellulitis, or urinary tract infection.[82] In a French cohort of 246 biopsy-proven patients with AH treated with glucocorticoids, one-quarter were infected at the time of admission, with another one-quarter developing infections during glucocorticoid treatment.[82]

Given these risks, a practical approach should be used in considering patients for glucocorticoids in severe AH. Upon admission, clinicians should obtain blood, urine, ascitic fluid cultures (if present), and chest

radiograph and abdominal imaging (eg, ultrasound with Doppler), and should avoid empiric antibiotics and intravenous contrast. Glucocorticoids should be started if a clinical diagnosis of severe AH is made and if cultures are negative at 24 to 48 hours with a low clinical suspicion of infection and a lack of other contraindications (Table 3). Furthermore, when cultures reveal an infection, glucocorticoids may be started after 48 hours of treatment with appropriate antibiotics.[82]

Just as there is a minimum threshold at which glucocorticoids are useful (DF ≥32), a therapeutic ceiling (DF >54) has been posited beyond which medical therapies aimed at decreasing the inflammatory cascade may cause more harm than benefit.[32] The evidence for this is a commonly cited study of protein-calorie malnutrition in US veterans with AH.[83] However, this study was not powered to examine mortality differences at a DF threshold of 54, nor have subsequent studies substantiated this observation. For example, 5 recent studies of glucocorticoids in severe AH had a median DF ranging from 54 to 71 with similar rates of mortality.[25,82,84-86] Consequently, corticosteroids should not be withheld on the basis of this maximum threshold alone. Nonetheless, it is reasonable that the presence of a DF higher than 54 would cause the provider to thoroughly assess the patient for undiagnosed infection causing cholestasis of sepsis prior to initiation of glucocorticoids.

Stopping Corticosteroid Use

The Lille score should be calculated after 7 days of corticosteroid use. If the score is greater than 0.56, glucocorticoids should be stopped on the dual basis of null response and risk of infection. If any of the common complications of severe AH (Table 3) develop during treatment, particularly infection and acute kidney injury, glucocorticoids should be stopped to avoid exacerbating the infection and because of the lack of data that glucocorticoids are salutary in severe AH with acute kidney injury. In one study, glucocorticoids were not associated with a higher short-term risk of infections.[82] In patients cured of infection and treated with corticosteroids, outcomes were similar for overall and infection-free survival. The authors note that controlled infections may allow for resumption of glucocorticoids, as this strategy enables recovery of liver function, which is ultimately paramount in protecting against future infection and improving survival.[82]

Changes in the Use of Pentoxifylline

Pentoxifylline is a xanthine derivative that weakly mitigates production of tumor necrosis factor alpha in vitro. Because tumor necrosis factor alpha has been proposed to play a major role in the pathogenesis of AH, pentoxifylline gained support as a treatment for AH.[87,88]

Table 3. Common Contraindications to Using Glucocorticoids in Patients With Alcoholic Hepatitis

- Active uncontrolled infection (urine > ascites > pulmonary)
- Acute kidney injury
- Gastrointestinal bleeding
- Acute pancreatitis

This was further supported by a randomized, controlled trial comparing pentoxifylline to placebo in patients with severe AH (DF >32), in which the pentoxifylline group had fewer in-hospital deaths.[89] The effect seemed to be a consequence of protecting the kidneys from developing hepatorenal syndrome.[89,90] Subsequent studies have failed to confirm the benefit. A Cochrane meta-analysis reporting on 5 clinical trials of pentoxifylline in patients with AH and a DF greater than 32 concluded that pentoxifylline could not be supported or rejected for treating AH.[91] Two trials in France failed to show a benefit of pentoxifylline as either a rescue agent in patients who had failed prednisolone (as assessed by Lille score on day 7) or in combination with prednisolone compared to prednisolone alone.[25,92] Additionally, the STOPAH (Steroids or Pentoxifylline for Alcoholic Hepatitis) trial failed to demonstrate any benefit of pentoxifylline.[84]

The Steroids or Pentoxifylline for Alcoholic Hepatitis Trial

Three head-to-head clinical trials comparing pentoxifylline to glucocorticoids in Asia provided conflicting results.[93-95] The STOPAH trial, the findings of which were recently published, was a multicenter, double-blind, randomized trial conducted in 65 hospitals across the United Kingdom with a 2-by-2 factorial design to evaluate the effect of treatment with prednisolone or pentoxifylline on 28-day survival rates (Table 4).[84] A power analysis assuming a 28-day mortality of 30% in the placebo group indicated that in order to achieve 80% power to detect a 9% difference in 28-day mortality with an allowance of approximately 10% withdrawal/drop-out rate, 1200 subjects were needed. The study enrolled 1092 subjects. In brief, the STOPAH trial demonstrated that only prednisolone improved 28-day survival rates and that neither prednisolone nor pentoxifylline alone or in combination improved longer-term survival at 90 days and 1 year. Pentoxifylline was no better than placebo in reducing mortality, but was associated with fewer infections than glucocorticoids.[84]

Table 4. Effect of Treatment With Prednisolone or Pentoxifylline on 28-Day Survival Rates in the STOPAH Trial[a]

	Placebo	Pentoxifylline	
Placebo	17% (45/269)	19% (50/258)	
Prednisolone	14% (38/266)	13% (35/260)	Odds ratio, 0.72 (95% CI, 0.52-1.01; *P*=.06)
		Odds ratio, 1.07 (95% CI, 0.77-1.49; *P*=.69)	

[a]28-day mortality, % (number of deaths/total in subgroup).

STOPAH, Steroids or Pentoxifylline for Alcoholic Hepatitis.

There have been several criticisms of the STOPAH trial. In order to achieve the necessary enrollment, recruitment was extended to community hospitals lacking the facilities to undertake transjugular liver biopsy. Therefore, the diagnosis of AH was based on clinical grounds alone. The lack of liver biopsy confirmation of AH may have diluted the study population by including subjects without AH, thereby diminishing the study power. The rates of infection (approximately 11%), acute kidney injury (approximately 3%), and overall mortality (approximately 16%) were also considerably lower than expected based upon prior studies despite high risk scores (mean DF, 62.6; MELD, 21; GAHS, 8). This indirectly supports the notion that the heterogeneity of severe AH made enrollment difficult despite its optimal study design and large size. The trial has largely shown that pentoxifylline is a failed therapy for AH while also demonstrating that prednisolone is ineffective beyond 1 month to improve survival. The latter result is not unexpected, as return to alcohol use is the greatest risk to the patient's heath after the first 90 days.[96] However, these results further demonstrate that the treatment of AH has not progressed much for almost 4 decades, leaving a dire need for new therapies for AH.

Real-World Applicability of Existing Alcoholic Hepatitis Therapies

Clinical trials of AH treatments typically exclude patients with active infection, acute kidney injury (usually hepatorenal syndrome), gastrointestinal bleeding, and acute pancreatitis, all of which are frequent concomitant problems arising in this patient population. Thus, there is a high rate (approximately 50%) of patient ineligibility to receive AH-specific therapies in the clinic.[97] The management of patients with confounding factors is complex and understudied. In a recent retrospective French study comparing patients with AH to those with AH and gastrointestinal bleeding, the latter group had a lower rate of infections, but no difference was found in 6-month survival rates with acceptable performance of the Lille model.[98]

New Controversies and Future Therapies

N-Acetylcysteine Plus Glucocorticoids

In mouse models of acute and chronic AH, N-acetylcysteine (NAC) has been shown to be ameliorative, presumably by reconstituting glutathione reserves to reduce oxidative stress.[99-102] Intravenous NAC in combination with prednisolone compared with prednisolone plus intravenous placebo has been studied in a multicenter, randomized, controlled trial in France.[85] The dosing of NAC was similar to that used in patients with acetaminophen toxicity, but with the 16-hour maintenance dose extended to a total of 5 days. The prednisolone/NAC arm improved 1-month survival compared with prednisolone/placebo (8% vs 24%; *P*=.006), although this benefit was not seen at 3 or 6 months. The infection rate and mortality attributable to hepatorenal syndrome were lower in the prednisolone/NAC arm. Because 6-month mortality was the primary endpoint, the study was considered a negative trial for this combination therapy. The STOPAH trial also demonstrated that glucocorticoids reduce mortality in AH only at 1 month; thus, this trial of prednisolone/NAC should be reconsidered as an important study.

Granulocyte-Colony Stimulating Factor

Targeting the regenerative aspects of the liver in AH, granulocyte-colony stimulating factor (G-CSF) mobilizes hematopoietic stem cells, induces liver regeneration, and improves survival in experimental models.[103] Two small, randomized, controlled trials of biopsy-proven alcoholic steatohepatitis and cirrhosis demonstrated that 5 days of G-CSF in the treatment arm mobilized CD34+ cells, increased hepatocyte growth factor, and induced hepatic progenitor cells to proliferate within 7 days of administration.[103,104] Subsequent trials of G-CSF

in alcohol- and hepatitis B virus–related ACLF in Asia demonstrated an additional benefit of improving liver function and survival with G-CSF at 2 and 3 months, respectively.[105,106] A recent randomized pilot study of 46 patients in India with severe AH receiving pentoxifylline plus G-CSF for 5 days compared outcomes with pentoxifylline alone.[107] A statistically significant increase was noted in the number of CD34+ cells in peripheral blood (marker of hematopoietic stem cells) in the G-CSF arm after 5 days of G-CSF therapy. There was a significant reduction in Child-Pugh, MELD, and DF scores and mortality at 90 days in the G-CSF arm. This potential therapy for severe AH is intriguing given its promotion of hepatic regeneration rather than abrogation of inflammation. However, the origin of functional hepatic progenitor cells (eg, liver, peripheral blood) leading to regeneration is still in debate.[108-112] The ability of G-CSF to provide indirect evidence of regeneration through biomarkers and in small trials is encouraging but requires more study (including cohorts outside of Asia) prior to wider clinical use.[113]

Controversy #4: The Role for Early Liver Transplantation in Treating Severe Alcoholic Hepatitis

Until very recently, patients with severe AH were not considered appropriate candidates for LT, mainly on account of a lack of 6-month sobriety prior to LT.[114] Mathurin and colleagues reported on a multicenter European trial of early LT for severe AH in carefully selected candidates with nonresponse to glucocorticoids.[115] Candidate selection was rigorous and required the complete consensus of medical team circles prior to candidate acceptance for listing. Comprehensive psychosocial assessments by an addiction specialist were performed to identify those with lower risk of alcohol relapse. The authors used 2 methods to construct historical controls. The study demonstrated a survival benefit of early LT for severe AH compared to controls (77 ± 8% vs 23 ± 8%; $P<.001$). Three of the surviving 20 recipients (15%) returned to drinking, although only one at harmful levels (>50 g/day). While this pilot trial demonstrated the medical and surgical feasibility of early LT for severe AH, adoption of this strategy has been cautious given the uncertainty of the psychosocial assessment process and the ethical ramifications of this essentially new indication for LT.[116]

A single center in the United States recently evaluated early LT for severe AH.[117] While the inclusion criteria were essentially the same as those in the European trial, the candidate selection methodology was adapted to account for differences in medical training and organization in the United States. This study found similar low rates of candidate acceptance (20%) and a survival benefit of early LT for severe AH compared to historical controls (89% vs 11%). The alcohol relapse rate to harmful drinking was low (11%), although the study featured a smaller number of patients and shorter follow-up than the European trial. The complex psychosocial profiles of potential candidates were also examined in detail. Candidate acceptance for early LT was more likely with a profile that included presentation as a first liver decompensating event with demonstration of good insight into the patient's addiction. Importantly, the recipient who relapsed failed to meet these 2 criteria. These results and analysis provide an early roadmap for other LT centers considering this indication as a rescue therapy for severe AH.[118] Further studies are needed to assess the outcomes of a wider application of this strategy and to better predict the risk of alcohol relapse in potential AH candidates for early LT.

Future Insights and Therapies for Alcoholic Hepatitis

Due to the paucity of treatment options for AH, a major initiative from the National Institute on Alcohol Abuse and Alcoholism has spearheaded large multi-institutional consortia with the task of identifying new therapeutic targets and performing early-phase clinical studies to develop and test new drugs for managing AH. A review of these rational and targeted potential therapies has been published.[5] The agents attempt to influence different pathophysiologic mechanisms in AH, including disrupted gut-barrier function leading to bacterial and endotoxin translocation; innate immune system activation in the liver; and hepatocellular apoptosis, necrosis, and injury. An early example is from a clinical trial in which daily oral zinc (220 mg), a known stabilizer of gut-barrier function, improved liver inflammation, fibrosis biomarkers, liver function, and clinical parameters (albumin levels, Child-Pugh scores) in alcoholic cirrhosis.[119]

Summary

This review of AH identified 4 key controversies that impact the diagnosis, prognosis, management, and treatment of patients with severe AH. Liver biopsy can be useful in cases of diagnostic uncertainty with milder hepatic decompensation, but it is not required in order to diagnose AH. The DF, MELD score, and Lille model perform well in combination to guide AH-specific treatment and response and to predict survival at different time points. Oral prednisolone can be used with intravenous NAC to improve short-term survival in patients with severe AH. Concurrent enteral nutrition is emphasized, along with patient-centered psychotherapy when medically

appropriate, to improve long-term survival. Patients with severe AH who are nonresponders to medical therapy with good psychosocial profiles may be referred to transplant centers that are performing early LT for this indication. Looking forward, the ongoing multi-institutional consortia yielding new insights and treatments will shape the management of AH for years to come.

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