Management of alcohol withdrawal

Key concepts and statements

6. AWS should be stratified and managed as per Clinical Institute Withdrawal Assessment for Alcohol protocol (45–49).
7. In patients with severe AWS and ALD, benzodiazepines are the treatment of choice.

AWS is a common condition affecting alcohol-dependent patients who abruptly discontinue or markedly decrease alcohol consumption. Light or moderate AWS usually develops within 6–24 h after the last drink and symptoms may include nausea/vomiting, hypertension, tachycardia, tremors, hyperreflexia, irritability, anxiety, and headache. These symptoms may progress to more severe forms of AWS, characterized by delirium tremens, generalized seizures, coma, and even cardiac arrest and death. Older patients are at greater risk for delirium tremens.

Patients with moderate or severe alcohol withdrawal should be closely monitored in an intensive care unit (ICU), where vital signs, volume status, and neurological function are monitored on a regular basis. Severity scores for AWS such as the Clinical Institute Withdrawal Assessment for Alcohol score are useful in the management of patients, although they have not been validated in patients with severe ALD and a symptom-triggered approach is preferred (45,46).

Benzodiazepines are the most commonly used drugs to treat AWS. Long-acting benzodiazepines (e.g., diazepam and chlordiazepoxide) predominantly protect against seizures and delirium; short and intermediate-acting benzodiazepines (e.g., lorazepam and oxazepam) are safer for patients with poor liver function. Patients with AWS and concomitant hepatic encephalopathy should be treated for both the conditions. Of note, high-dose benzodiazepines may precipitate and worsen hepatic encephalopathy; thus, careful monitoring and titration is critical for optimal outcomes. Given the side effects of benzodiazepines in patients with advanced liver disease and the potential for abuse in an addictive population, other drugs such as baclofen, clonidine, gabapentin, and topiramate have been proposed to treat AWS in patients with ALD including alcoholic cirrhosis. However, the efficacy and safety of these substances in patients with AH is unknown and therefore prospective studies are required. A promising approach is to use baclofen to prevent and treat moderate AWS first, and continue the medication to prevent alcohol relapse.

Management of liver disease

Alcoholic cirrhosis. It is important to assess the nutritional status of ALD patients as malnutrition is often present in these patients (see section on nutritional supplementation for details). Patients with alcoholic cirrhosis should be screened for varices with upper gastrointestinal endoscopy (50). These patients are also at an increased risk of developing HCC, with a life-time risk of about 3–10% and an annual risk of about 1%. Obesity and cigarette smoking are risk factors for HCC in patients with alcoholic cirrhosis. Patients with alcoholic cirrhosis should undergo screening with ultrasound examination with or without α-fetoprotein testing every 6 months for HCC (51). Immunization against hepatitis A and B, pneumococcal pneumonia and influenza is also recommended (Center for Disease Control and Prevention link on vaccinations).

Patients with decompensated cirrhosis are managed as for any patient with cirrhosis as described below.

Ascites. A diagnostic paracentesis is warranted to rule out spontaneous bacterial peritonitis. A therapeutic paracentesis is carried out as required for symptom relief of tense ascites. Management of ascites and hepatorenal syndrome should follow established guidelines. In addition to antibiotics, albumin 1.5 g/kg is recommended on day 1 and 1 g/kg on day 3 in the presence of spontaneous bacterial peritonitis (52).

Hepatic encephalopathy. This is managed as per prevailing guidelines and includes lactulose and rifaximin therapy, as well as control of infection. Cerebral damage, malnutrition, and infections among patients with alcohol-related cirrhosis and continued alcohol use may lower the threshold in development of hepatic encephalopathy. However, other causes of altered mental status should be screened for, especially among patients who present with atypical neuro-psychiatric features that warrant questioning the diagnosis of hepatic encephalopathy or AWS. For example, seizures, focal neurological deficits, severe headache, and encephalopathy refractory to all measures should point towards an alternate cause for altered consciousness such as stroke, subdural hematoma, drug overdose, meningitis, and fungal infections of the central nervous system. A drug screen is recommended and in selected patients imaging of the head and cerebral spinal fluid studies may be required (53).

Variceal bleeding. Management of the acute variceal bleeding episode involves pharmacological therapy with available vasoactive agents (terlipressin or octreotide), antibiotics, and endoscopic therapy. Endoscopy should ideally be carried out at least 30 min after initiation of vasoactive therapy (54).

ALCOHOLIC HEPATITIS

Diagnosis of alcoholic hepatitis

Key concepts and statements

8. Clinical diagnosis of AH is determined in a patient with rapid development or worsening of jaundice and liver-related complications, with serum total bilirubin >3 mg/dL; ALT and AST elevated >1.5 times the upper limit of normal but <400 U/L with the AST/ALT ratio >1.5; documentation of persistent heavy alcohol use until 8 weeks before onset of symptoms; and exclusion of other liver diseases
9. In patients with suspected AH, a transjugular liver biopsy is recommended when the clinical diagnosis is confounded by another liver disease etiology or there is uncertainty on alcohol consumption history
10. Patients with severe AH should preferably be hospitalized for management

Table 3. Proposed definitions and subtypes of alcoholic hepatitis

Definite alcoholic hepatitis: Histological confirmation of features of alcoholic hepatitis.
Probable alcoholic hepatitis: Clinical diagnosis based on (a) heavy alcohol use for >5 years, (b) active alcohol use until 4 weeks prior to presentation, (c) sudden onset or worsening of jaundice, (d) AST/ALT ratio >1.5:1 with levels <400 IU/L, and (e) absence of other causes of liver disease.
Possible alcoholic hepatitis: Clinical diagnosis uncertain due to another confounding etiology of liver disease or unclear history on alcohol consumption.

History. Clinical features of AH include non-specific constitutional symptoms such as fatigue but may also include symptoms attributable to advanced liver disease. The history of alcohol use needs to be carefully documented including the date of last drink. Collateral information from relatives about drinking patterns is often required to confirm the history on alcohol consumption. Suspicion for AH should be high in a patient with recent onset or worsening of jaundice in the setting of chronic heavy alcohol use, which has been active until at least 8 weeks before presentation. History should also include previous admissions for AH, type, duration and amount of alcohol intake, previous alcohol counseling and/or detoxification attempts, recent cocaine and other drug use, potential hepatotoxic drugs, gastrointestinal bleeding, duration of jaundice, and possible source of infection including urinary, pulmonary, cutaneous, and abdominal.

Physical examination. Many physical examination signs overlap with alcoholic cirrhosis reflecting portal hypertension and complications of cirrhosis. Malnutrition of variable degree and sarcopenia is present in most patients with AH. Signs of chronic alcohol intake (e.g., Dupuytren contracture, rhinophyma, etc.), signs of chronic liver disease (spider angioma, palmar erythema, and jaundice), signs of portal hypertension (splenomegaly, ascites, and hepatic encephalopathy), and of alcohol withdrawal (tremors, tachycardia, agitation, seizures in severe AWS, or delirium tremens) may be present (55). Features of systemic inflammatory response syndrome (SIRS) may be present in these patients even in the absence of infection (56). SIRS criteria include the presence of ≥2 of the following: heart rate >100 beats per minute, temperature >38 °C or <36 °C, respiratory rate >12 breaths per minute, and white blood cell count >12,000 or <4,000 mm.

In addition to SIRS criteria, tender hepatomegaly and occasionally, hepatic bruit may be present. A very careful search should be made for a source for potential infection or sepsis, including skin examination for signs of cellulitis and infection around venous lines.

Laboratory abnormalities.Specific laboratory abnormalities to diagnose AH include bilirubin >3 mg/dL; AST >50 but <400 IU/L, with AST/ALT ratio of >1.5. The severity of liver disease should also be documented by measuring the serum bilirubin, creatinine, INR, albumin, and electrolytes to calculate the MELD score, MELD sodium score, and Maddrey discriminate function scores (see section on prognosis and disease severity). As these patients have high risk for infection, diligent infectious work up should be performed including ascitic fluid cell counts with cultures in patients with ascites, urine microscopic examination and cultures, chest X-ray, blood, and sputum cultures as clinically indicated. As SIRS features along with rapidly increasing jaundice may mimic cholangitis, it is prudent to exclude biliary obstruction.

Liver biopsy. One area of controversy is the need for a liver biopsy to confirm the diagnosis of AH. In a recent NIH-sponsored consensus meeting of investigators, it was proposed to define AH as definite, probable, or possible based on clinical features, presence of confounding serology for other liver disease etiology, and liver histology (57) (**Table 3** and **Figure 3**). Definite AH was categorized as a compatible clinical diagnosis along with liver biopsy confirming the existence of criteria of AH; probable AH was defined as classic clinical syndrome, as defined above in the absence of confounding serology for another disease; possible AH was defined as clinically suspicious for AH, presence of confounding factors such as ischemic hepatitis, possible drug-induced liver injury, serology positive for another liver disease etiology, or uncertain alcohol use. It was proposed that patients with possible AH should undergo liver biopsy to confirm the diagnosis, especially if specific pharmacologic interventions are proposed. On the other hand, the diagnosis of probable AH may be associated with only a low rate of histologic misclassification and therefore biopsy may not be essential in this population.

Characteristic histological findings of AH include macro vesicular steatosis, lobular infiltration of neutrophils with hepatocyte damage (Mallory–Denk bodies and/or ballooning), bilirubin stasis and liver fibrosis, which is typically described as peri cellular and sinusoidal ("chicken wire" appearance) (58) (**Figure 4**). These features are indistinguishable from non-ASH and the alcohol–non-ALD index (including body mass index, gender, AST, ALT, and mean cell volume of the red blood cells or mean corpuscular volume) can be helpful to distinguish the two in cases of unclear alcohol consumption (59). The majority of AH patients have underlying macronodular cirrhosis, which is not easily distinguishable from other forms of cirrhosis. When cirrhosis is established, steatosis may be less prominent. On electron microscopic examination, megamitochondria may be observed. If liver biopsy is performed for diagnosis of AH, the findings may also have prognostic value. For example, one recent study showed that presence of severe fibrosis, megamitochondria, degree of neutrophil infiltration, and cholestasis could predict prognosis in patients with AH (60).

Prognostic scores and natural history

Many scoring systems have been developed to predict severity of AH. The Maddrey Discriminant Function is the most time tested and validated scoring system, with severe AH defined by Maddrey Discriminant Function ≥32 (61). Retrospective and prospective analysis of this score indicates that Maddrey Discriminant Function ≥32 predicts a mortality rate of ~20–50% over 30 days (62). Most clinical trials for AH have used this score based on its use in the original corticosteroid trials. A number of other scoring

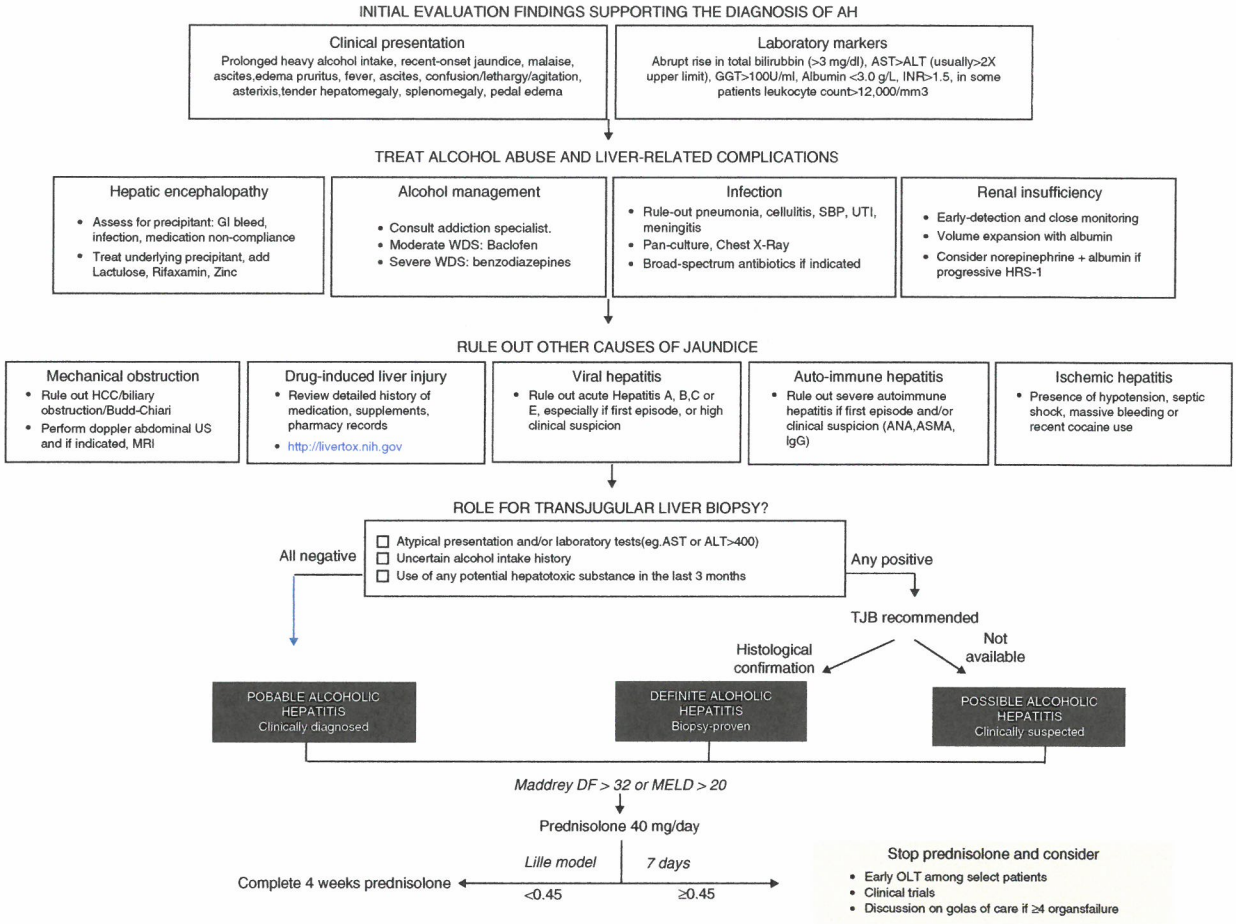

Figure 3. Approach towards the diagnosis and management of alcoholic hepatitis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio.

systems have also been validated and generally performed similar to the Maddrey score, including the MELD score, Age Bilirubin INR Creatinine (ABIC) score, and the Glasgow scale (62). The MELD score is being increasingly used to assess severity of AH given its better accuracy, worldwide use in organ allocation, INR as standard in reporting prothrombin time, and incorporation of renal function and serum creatinine, which is a major determinant of outcomes in AH patients. A MELD score >20 has been proposed as defining severe AH with an ~20% mortality (63). Lille score (a continuous score with a scale from 0 to 1) at 4–7 days of corticosteroids therapy can be used to assess the response to corticosteroids (Lille score <0.45) (64). Most of these scores by themselves do not predict prognosis accurately after 90 days and are most predictive at 30 days. A number of other variables influence prognosis after 30–90 days, most notably the ability to maintain abstinence from alcohol or not (5,6). Recent studies have shown that combination use of MELD at baseline and Lille score at day 7 has best discrimination and calibration for 2-month and 6-month mortality (65). In addition, serum lipopolysaccharide levels, SIRS criteria, and other serum markers may also serve as biomarkers of mortality (56).

Treatment of alcoholic hepatitis

General measures and supportive treatment: provided to all AH patients irrespective of disease severity.

Recommendation

6. Patients with AH should be considered for nutritional supplementation to ensure adequate caloric intake and to correct specific deficits, yet its effects on patient survival has not been proven (Conditional recommendation, very low level of evidence)

Key concepts and statements

11. Severe AH is identified by Maddrey's discriminant function score >32 or MELD score >20
12. SIRS syndrome at admission predisposes to acute kidney injury and multi-organ failure, which are associated with a poor prognosis. Physicians should take appropriate measures to prevent renal injury, such as avoidance of nephrotoxic drugs, judicious use of diuretics, and low threshold for expanding circulating blood volume with albumin or saline infusions

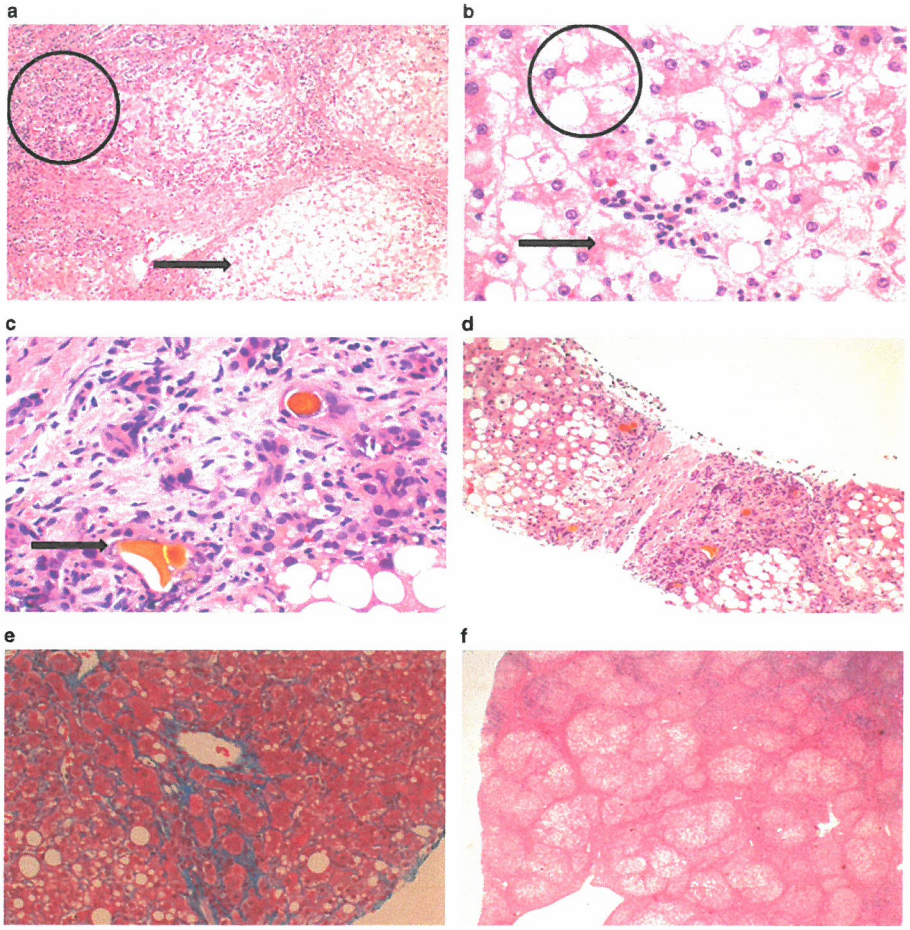

Figure 4. Histologic features of alcoholic hepatitis and Alcoholic Hepatitis Histologic Score. (**a**) Circle represents lobular inflammation and arrow represents steatosis, (**b**) circle and arrow represent cell ballooning, (**c**) arrow represents cholestasis with bile canalicular and hepatocyte plugging, (**d**) steatosis and fibrosis, (**e**) chicken wire and pericellular fibrosis, (**f**) cirrhosis.

13. Infections are common in AH patients and a comprehensive infectious screen is recommended as part of routine work-up of these patients. The development of bacterial infections during hospitalization is associated with poor prognosis

Patients hospitalized with severe AH often have history of active heavy alcohol use and present with manifestations of the SIRS (56). Sepsis and malnutrition are common among this population (4). Ascites, variceal bleeding, and hepatic encephalopathy may also be present. In-patient management should therefore focus on alcohol withdrawal, nutritional supplementation, infections and sepsis, complications of cirrhosis and portal hypertension, and specific treatment of AH. Patients may also develop acute on chronic liver failure, which manifests with hepatic and extrahepatic organ failure requiring intensive care (see below).

Nutrition and fluid replacement. Malnutrition and sarcopenia are common among hospitalized AH patients with negative impact on outcome (66–68). Many randomized controlled studies have shown improvement in nutritional status, but with controversial data on survival benefit with enteral supplementation (69–73) or parenteral supplementation. Although enteral supplementation in severe AH did not show survival benefit in a recently reported randomized study, there were more deaths with daily caloric intake of <21.5 kcal/kg per day compared with higher intake of calories. The enteral route due to its low cost, safety, and lower risk for infections is the preferred route. Feeding tube can be safely placed in the presence of esophageal varices without active bleeding or who have not undergone recent endoscopic variceal banding (74). Patients with severe AH need daily protein intake of 1.2 to 1.5 g/kg and caloric intake of 35 Kcal/kg. Zinc and other trace elements may need to be replaced. Thiamine and B complex vitamins need to be replaced. Albumin is preferred to crystalloid for volume replacement.

Intensive care. The patient may require transfer to the ICU in the presence of extrahepatic organ failure. Indications for transfer to the ICU include stage III or stage IV hepatic encephalopathy and the need for ventilation, respiratory failure, hemodynamic instability, and septic shock. Scoring systems to predict mortality in ICU patients include the SOFA score (75) and the CLIF SOFA

Table 4. Specific pharmacological therapies for management of alcoholic hepatitis

A) Therapies with proven efficacy
1. Corticosteroids
2. Nutritional supplementation
B) Therapies with potential efficacy
1. Pentoxifylline
2. *N*-acetyl cysteine
3. Granulocyte colony stimulating factor
C) Therapies with no efficacy
1. Tumor necrosis factor-α inhibitors
2. Antioxidant cocktail and vitamin E
3. Hepatic mitogens: insulin and glucagon, anabolic steroids
4. Propylthiouracil

score (76). The North American Consortium for Study of End Stage Liver Disease-Acute on Chronic Liver Failure (NACSELD ACLF) score is the easiest to use—patients with two or more extra-hepatic organ failures, second infections, and higher MELD score are at greatest risk of mortality (77).

Sepsis surveillance should be performed and broad-spectrum antibiotics should be administered before transfer to the ICU, or within one hour of admission. The choice of antibiotics depends on prevailing local antimicrobial resistance patterns. Piperacillin-tazobactam is generally the preferred drug used for sepsis, although vancomycin and meropenem may be considered in patients with penicillin hypersensitivity. As sepsis is difficult to diagnose in this group and about 40– 50% of patients may be culture negative, there should be a low threshold for diagnosis of infection and initiation of antibiotic therapy. Diagnosis of infections in patients with AH and cirrhosis should be performed using standardized definitions and guidelines (78). It is important to differentiate community acquired infections from nosocomial infections (onset after 48 h of admission to hospital) or healthcare-associated infections (within first 48 h of admission in patients with hospitalization within past 6 months, clinic visit within past 30 days, or those residing in nursing homes), as the empiric antibiotics for nosocomial or healthcare-associated infections should cover broadly for multidrug resistant bacteria, and in select high-risk cases for atypical organisms and fungal infections.

Ulcer prophylaxis is recommended using proton pump inhibitors. Both proton pump inhibitors and H2 antagonists increase the risk of infections such as aspiration pneumonia and clostridium difficile, but decrease the risk of chemical pneumonitis and gastrointestinal bleeding. Proton pump inhibitors are superior to H2 antagonists for the prevention of gastrointestinal bleeding. Glucose control is targeted to levels <200 mg/dL and transfusion is required with the hemoglobin target of 7–8 g/dL.

Organ failure scores are used to determine severity of acute on chronic liver failure. Patients with renal failure and acute kidney injury should receive diligent care with the aim to identify and reverse precipitating factors and improve renal function. Renal replacement therapy is recommended in the presence of acute kidney injury in the presence of sepsis-associated acute tubular necrosis, or if the cause of acute kidney injury is unclear. In the presence of hepatorenal syndrome, a therapeutic trial of renal replacement therapy may be considered in patients who are potential liver transplant candidates. Patients requiring pulmonary support should receive low tidal volume to avoid lung injury. Vasoconstrictors and pressor may be needed to maintain mean blood pressure of >65 mm Hg.

Specific pharmacologic therapies. Pharmacological therapies examined for AH patients are listed in **Table 4**.

Recommendations

7. Patients with severe AH should be treated with corticosteroids if there are no contraindications for their use (Strong recommendation, moderate level of evidence)
8. The existing evidence does not support the use of pentoxifylline for patients with severe AH. (Conditional recommendation, low level of evidence)

Key concepts and statements

14. Response to treatment with corticosteroids should be determined at 7 days using the Lille score. Treatment should be discontinued among non-responders to therapy, defined as those with a Lille score >0.45
15. Patients non-responsive to corticosteroids, ineligible for early LT, and with multiple organ failures may be considered for palliative therapy.

Corticosteroids. As the first randomized controlled study to assess efficacy of corticosteroids in the treatment of AH in 1971 (79), a total of 14 randomized studies (12 against placebo, 1 against enteral supplementation, and 1 against antioxidant cocktail) have reported conflicting data, likely to be due to variations on inclusion/exclusion criteria and the use of liver biopsy for confirming the diagnosis of AH (61,79–90). In a pooled analysis, using individual patient data from the five largest randomized controlled studies (85–88,91), corticosteroids provided survival benefit at 28 days (80% vs. 66%, $P<0.0001$) in half of the patients (92). The largest randomized placebo controlled multicenter study from the United Kingdom (the STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH) study) on 1,103 severe AH patients showed only a trend for mortality benefit at 28 days with prednisolone, compared with patients receiving placebo (13.8% vs. 18%, $P=0.056$). A meta-analysis of randomized studies (including the STOPAH study) showed that corticosteroids were effective in reducing short-term mortality by 46%.

Prednisolone is preferred over prednisone, as the latter requires conversion to prednisolone, which may be impaired in patients with impaired liver synthetic function. Moreover, prednisone did not improve patient survival in a randomized clinical trial (89). Prednisolone is used in a dose of 40 mg per day for a total duration of 4 weeks. Methylprednisolone 32 mg per day by intravenous route is used for patient unable to take oral medications. There are no studies examining different doses

and durations of corticosteroid therapy. Response to therapy is determined at 1 week of therapy using the Lille score. About 50–60% of patients do not respond to steroids (Lille score>0.45) and these patients do not derive further benefit from continuing steroids (**Figure 3**) (64). Recently, the Lille score at day 4 of corticosteroid therapy has been shown to be as accurate as day 7 Lille score in predicting the outcome and response to treatment, although this observation needs further validation studies (93). Unpredictable response to corticosteroids combined with fear of adverse effects, especially risk of infections limit the use of these drugs in routine clinical practice, with only 25–45% providers using them as reported in two different surveys (94,95). There is a clear unmet need for development of safer effective pharmacological options for management of AH patients and for biomarkers to predict response to corticosteroids at the time of presentation (96–98).

Active hepatitis B virus infection and active tuberculosis are contraindications for use of corticosteroids (99). Although HCV infection may potentially worsen the outcome of AH patients (30,100–102), there are no data on whether 4 weeks of corticosteroid therapy will increase HCV replication or that HCV infection worsens the response to corticosteroids. Active infection or sepsis, uncontrolled diabetes mellitus, and gastrointestinal bleeding remain relative contraindications to the use of corticosteroids. In these situations, corticosteroids can be used once the contraindication has been reversed with appropriate therapy. For example, use of corticosteroids after adequate control of infection has been reported to provide similar benefit as in uninfected patients (103). However, development of infections remains a concern among patients treated with corticosteroids, as these drugs compromise the immune status of an individual, putting them at risk for infections (104). In pooled data from 12 randomized studies comparing corticosteroids and placebo, infections during treatment occurred in about 20%, with steroid use associated with risk of fungal infections (105). In one study comprising patients with high bacterial DNA levels (>18.5 pg/mL) enrolling in the STOPAH study, the use of prophylactic antibiotics improved patient survival in corticosteroids treated patients (106). There remains an unmet need to determine accurate biomarkers with a potential for earlier diagnosis of infections, and randomized studies exploring benefit of antibiotics used as prophylaxis or as adjuvant to corticosteroids among patients with AH at high risk for development of infections (56).

Pentoxifylline. A phosphodiesterase inhibitor, pentoxifylline inhibits tumor necrosis factor-α activity, one of the major cytokines speculated in the pathogenesis of AH (107,108). As the first seminal study on the benefit of pentoxifylline used as 400 mg 3 times a day (109), many other randomized studies have failed to show survival benefit in severe AH patients (110–113). However, pentoxifylline has consistently shown benefit in reducing the risk of renal injury and deaths from hepatorenal syndrome (109,114). Although pentoxifylline is known to inhibit tumor necrosis factor, levels of tumor necrosis factor did not change with pentoxifylline (PTX) in the reported seminal study (109). Pentoxifylline compared with corticosteroids showed benefit in one study (115) and no difference in another study (116). Pentoxifylline was not effective when examined as salvage option for steroid non-responders, (117) or as an adjuvant therapy to corticosteroids (118,119). In a meta-analysis of 10 randomized studies, pentoxifylline failed to show survival benefit at 1 month, but was effective in reducing the occurrence of hepatorenal syndrome by 53% (120). The exact mechanism of renal protection with pentoxifylline remains unclear. The STOPAH study showed no survival benefit with pentoxifylline (90). In a network meta-analysis of 22 studies including the STOPAH study, there was low-quality evidence for benefit of pentoxifylline in reducing the short-term mortality at 28 days by 30% (121). It is possible that subgroups of patients (i.e., kidney failure) with AH may benefit from pentoxifylline, but this needs to be examined prospectively.

Tumor necrosis factor-α inhibitors. Based on pre-clinical efficacy and beneficial effects in open label pilot studies (122–125), trials examining infliximab and etanercept in the management of severe AH had to be terminated prematurely due to higher number of deaths in the treatment arm, with most deaths due to infections (126,127). The mechanisms of these findings are speculated to be due to blocking the beneficial effects of tumor necrosis factor on hepatic regeneration (128).

Antioxidants. Oxidative stress is a major player in the pathogenesis of ALD and AH (129). Antioxidant cocktails and vitamin E examined earlier have not shown beneficial effects in the management of severe AH (88,130,131). N-acetylcysteine infusion showed improved survival at 1 month, when used as an adjuvant to prednisolone in a multicenter randomized controlled study (132). There was no survival advantage with *N*-acetylcysteine at 3 or 6 months from presentation. A network meta-analysis comparing various pharmacological agents showed moderate quality evidence that combination of prednisolone and *N*-acetylcysteine provides best survival benefit at 28 days with 85% risk reduction of death from AH (121). However, more data on the efficacy of *N*-acetylcysteine in severe AH patients are needed before recommending its routine use in practice.

Miscellaneous drugs. Hepatic regenerative capacity supported by bone marrow-derived stem cells and hepatic progenitor cells is a major determinant of the outcome of patient with AH (133,134). However, drugs targeting this pathway including insulin and glucagon (135,136), anabolic steroid, oxandrolone (137), and propylthiouracil (138,139) failed to demonstrate a mortality benefit. Recently, the use of growth factors with granulocyte colony stimulating factor and erythropoietin have shown encouraging data in improving liver disease, reducing infectious complications, and patient survival (140,141). Molecular adsorbent recycling system safely improves liver disease, renal function, and portal hypertension, without any significant improvement in survival (142). Fecal transplantation has also been tested in eight subjects with contraindications to steroid therapy with encouraging results in a preliminary analyses (143). Patients with ≥4 failed organs being treated in ICU, who are not candidates for LT, are unlikely to survive beyond 3–6 months. Continuing further intensive treatment in these patients may be futile (**Figure 3**) (144).