Alcoholic Hepatitis Clinical Guidelines

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PURPOSE

To delineate clinical guidelines for the diagnosis and management of patients with alcoholic hepatitis (AH). This protocol is only meant to provide a general guideline to care. The clinical circumstances and treatment of each patient will be determined on a case-by-case basis.

RESPONSIBLE PARTIES

- Hepatologists
- ICU Physicians
- Hospitalists
- Pharmacists
- House staff

BACKGROUND

Alcoholic hepatitis is an acute inflammatory condition that occurs in a subset of patients with longstanding and heavy alcohol consumption that carries a high risk of morbidity and mortality (~30%). Observational studies report increased risk of alcoholic cirrhosis with ingestion > 10-20 g of alcohol per day in women and > 20-40 g per day in men (Becker 1996). Age, female gender, and overweight (BMI >27 kg/m2 in men and > 25 kg/m2 in women) are identified as additional risk factors for alcohol-induced liver disease (Becker 1996; Bellentani 1997; Naveau 1997; Raynard 2002). Severe alcoholic hepatitis is associated with binge drinking and malnutrition (Stewart 2001). Typical patients with AAH have been drinking heavily for years and often will report a dramatic increase in alcohol consumption prior to becoming ill (triggered in many cases by life stressors such as loss of job, divorce, or death of a loved one). Patients have often stopped drinking some time prior to their presentation (days or weeks) due to onset of symptoms.

I. Diagnosis of Alcoholic Hepatitis

(Note: not all of the following features may be present with AH but, when present, do help to support the diagnosis)

- a) Recent alcohol use (< 2 months)
- b) Physical exam: jaundice, malnutrition, ascites, spider angiomata, hepatic bruit, tremor, delirium, tachycardia and asterixis may be present
- c) Liver enzymes elevated with AST>ALT (in ratio >1.5) with AST typically >45 but <300
- d) Total bilirubin >2 (often >10)
- e) Leukocytosis (may be mild or severe with WBC up to 40-60K)
- f) Liver biopsy may be indicated to support diagnosis of AH and look for confounding disease if laboratory tests suggest a second diagnosis or otherwise in doubt (especially if being considered for transplantation).
  - o May require Transjugular approach due to ascites and coagulopathy.
  - o Features of AH include sclerosing hyaline, necrosis, macrovesicular steatosis, Mallory-Denk bodies, megamitochondria, and intrahepatic cholestasis (Ishak 1991; Jensen 1994; Bruguera 1977; Uchida 1984)
II. **Determination of Severity and Prognosis**

a) Maddrey Discriminate Function (DF) Calculation:

\[4.6 \times \text{(Prothrombin Time - Control PT)} + \text{bilirubin (mg/dl)} \] ; result >32 identifies patients with mortality >50% without pharmacologic therapy (Maddrey 1978)

b) MELD score ≥ 20 at the time of hospital admission has high sensitivity and specificity for predicting in-hospital mortality (Dunn 2005; Srikureja 2005)

c) The Lille score can be calculated (typically on day 0 and 7 days after initiation of corticosteroids) using either prothrombin time or INR according to the following equations (Louvet 2007). This score may be helpful in monitoring patients who are selected for and who would continue to benefit from ongoing corticosteroid therapy:

Lille model with INR:

\[3.19 - 0.101 \times \text{[age in years]} + 0.147 \times \text{[albumin (g/L) on day 0]} + 0.0165 \times \text{[evolution in bilirubin level in } \mu\text{M]} - [0.206 \times \text{renal insufficiency}] - 0.0065 \times \text{[bilirubin (} \mu\text{M) on day 0]} - 0.0096 \times \text{[INR]}.

The Lille model with PT and Lille model with INR are similar as seen by their AUC of 0.85 +/- 0.038 and 0.85 +/- 0.037 respectively (p = NS).

III. **Treatment**

Mild forms of AH may improve with abstinence and conservative management alone, thus prognostic assessment (described above) should be performed to identify patients with severe disease who should be treated more aggressively (Morgan 1993). Patients with severe AH face an approximately 40% risk of mortality at 6 months, thus we would advocate for more aggressive evaluation and management of this subset of patients.

**Toxicology screening:** Alcohol, drug and acetaminophen levels should be measured on admission

**Alcohol Withdrawal:** May not be present given that many patients with AH have previously discontinued use, but primary service should observe carefully for signs of withdrawal and manage according to standard protocols.

**Diagnostic confirmation:** Perform liver biopsy if fasting iron saturation > 50%, if diagnosis of AH is in doubt, or if an alternate diagnosis is suspected (such as autoimmune hepatitis or drug induced liver injury)

**Electrolyte abnormalities:** Daily monitoring and repletion of magnesium, phosphorus, and potassium should be undertaken. Patients with AH have often been on a diet of alcohol alone for prolonged periods and have substantial deficiencies that may take several days to correct. Patients with electrolyte disturbance and severe malnutrition are at risk for refeeding syndrome and thus electrolyte abnormalities should be corrected prior to initiating nutrition support therapy (enteral or parenteral feeds).

**Nutrition management:** A nutrition consult should be placed whenever a diagnosis of AH is suspected or established. Studies have shown improved outcomes with aggressive nutritional support even when compared to steroids. (Foody 2001)

**Nutritional support goals** include aggressive caloric intake (35-40 kcal/kg/day) and protein intake (1.2-1.5 grams/kg/day) (Plauth 2009)
Use of **nasoenteric tube feeding** is strongly recommend and should be instituted early since the great majority of patients are not able to meet requirements via oral intake (this should be assessed by very early and accurate assessment of calorie and protein intake during the first 1-2 days of hospital admission) (Plauth 2009). Tube feedings in one randomized study reduced mortality by 40%.

**Nocturnal nutrition supplementation** via tube feeding is advised in patients with cirrhosis to help prevent muscle wasting and improve lean muscle mass (Plank 2008).

Consider **intravenous lipids**, 500 ml/day (~1000 kcal/day), as an adjunctive means of nutrition support in those with large caloric requirement and severe AH. It is recommended the lipids IV be administered over 12-20 hours to prevent line related infections. It is recommended that tubing used to administer fat emulsion IV be replaced within 24 hours of initiating the infusion (O’Grady 2011).

Triglycerides should be checked after first dose of intravenous lipids and then 1-2 times per week or as needed. Triglyceride levels should be at least 4 hours after completion of lipid infusion (Szetsycki 2005). If post-infusion triglyceride levels are near baseline levels then it can be assumed IV fat is clearing. If post-infusion triglyceride levels exceed baseline levels then a slower rate of lipid infusion is recommended (e.g. 20 vs. 12 hours) but should not exceed 20 hours. Triglycerides should be held if post-infusion levels are > 400-500 mg/dL.

**Treatment of nutritional deficiencies**: Multivitamin, thiamine, folic acid, zinc, fat-soluble vitamins (A, D, E, K), magnesium, and testosterone (in men). Vitamin K should be administered as 10 mg subcutaneous x 3 days. Magnesium should be administered IV at 1 GM q 6 hours for 4 days, provided that the GFR is >40 ml/Hr.

**Wernicke’s encephalopathy**: Syndrome consisting of ataxia, confusion, nystagmus caused by thiamine (vitamin B1) deficiency should be considered in this patient population, particularly in those with additional risk factors such as prior bariatric surgery.

**Cardiac complications**: An echocardiogram to assess for alcoholic &/or cirrhotic cardiomyopathy should be considered. If cardiomyopathy is identified (depressed ejection fraction or E/A ratio <1), contributing factors such as selenium deficiency or iron overload should be investigated and consideration given to Cardiology consult for further evaluation and management.

**Ascites diagnosis and management**: Paracentesis is required to exclude SBP if significant ascites is present. Ascitic fluid should be tested for cell count and differential, culture, albumin, and total protein. Prophylactic antibiotics are recommended for SBP prevention following a treated episode of SBP or if total protein in ascitic fluid is <1.5. Initial management of large ascites should include sodium restriction (<2 grams/day) and diuretics (if kidney function permits). If potassium stores are not yet replete, initial therapy should be with spironolactone alone (with addition of furosemide later to maintain normal potassium levels).

**Acute kidney injury**: If creatinine is elevated, patients should be evaluated for the diagnosis of hepatorenal syndrome. Initial work-up includes urinalysis, urine electrolytes, renal US, hold diuretics and administer 25% IV albumin 1 gm/kg up to 100 grams on 2 consecutive days, and complete an infectious work-up.
Pharmacotherapy for AH:

1. Corticosteroids

Consider initiation of steroids (Prednisone 40 mg/day) for severe disease (DF ≥32 or MELD >20, especially if encephalopathy is present) if there is no evidence of acute kidney injury, infection or GI bleeding. Corticosteroids have been advocated as first-line therapy for severe AH, although their safety and efficacy continue to be debated. A Cochrane review of 15 RCTs including 721 patients found mortality benefit from corticosteroids only among those with DF ≥32 or encephalopathy (Rambaldi 2008), thus this is the patient population that should be targeted for this therapy.

In the recent STOPAH trial, steroids showed a trend towards improvement in mortality at 28 days without statistical significance but no improvement at 90 days or 1 year. However, in a secondary analysis that included adjustments for baseline determinants of prognosis, steroids did confer mortality advantage at 28 days. Thus, steroids should be considered for treatment of severe AH given lack of other beneficial therapies. (Thursz 2015). Provided that the patient meets the Lillle Criteria at day 7 for treatment response.

Once steroids are initiated, all patients should be reassessed at 7 days and if no improvement, the steroids should be discontinued.

Guidelines for discontinuation of corticosteroids for AH:

- Stop prednisone if bilirubin has not decreased 30% by day 7

- The Lille model may help to identify patients who may derive survival benefit from a 28 day course of corticosteroids (based on data from a meta-analysis, Mathurin 2011).

  Lille score (using prothrombin time) = 3.19 - 0.101 x age (years) + 0.147 x albumin (g/l) on day 0 + 0.0165 x change in bilirubin on day 7 (micromol/l) - 0.206 x renal insufficiency (rated as 0 if absent and 1 if present) - 0.0065 x bilirubin level on day 0 (in micromol/l) - 0.0096 x prothrombin time (in seconds)

  A Lille score on day 7 >0.45 signifies failure of steroid therapy and warrants its discontinuation

2. Pentoxifylline

In several recent randomized clinical trials including STOPAH, pentoxifylline has been shown to confer no benefit in those with severe AH. (Thursz 2015, Park 2014, Mathurin 2013) However, a recent meta-analyses has shown that pentoxifylline at a dose of 400 mg three times daily may have some benefit especially in those with contraindications to steroid therapy. Combination pentoxifylline and corticosteroids confers no benefit over corticosteroids alone, pentoxifylline alone, or combination of corticosteroids and N-acetylcysteine. (Singh 2015)

3. NAC (N-acetylcysteine)

Treatment of AH with N-acetylcysteine (NAC) have yielded mixed results. One study of nutrition support with or without IV NAC x 14 days found no survival benefit or biochemical improvement with the addition of NAC (Moreno 2010). Stewart and colleagues found that antioxidant therapy, including NAC, alone or with corticosteroids,
did not improve 6-month survival (Stewart 2007). In contrast, a recent trial comparing 28 days of prednisolone 40mg with or without 5 days of IV NAC (regimen shown below) demonstrated significantly improved short-term (1 month) survival as well as lower rates of infection and hepatorenal syndrome in the group treated with NAC (Nguyen-Khac 2011). No difference was observed in longer term survival (6 months). NAC with corticosteroids is recommended as part of this treatment guideline.

Day 1: 150 mg/kg body weight in 250 mL 5% glucose solution over 30 minutes, 50 mg/kg in 500 mL of 5% glucose over 4 hours, and 100 mg/kg in 1000 mL of 5% glucose over 16 hours
Days 2-5: 100 mg/kg/d in 1000 mL of 5% glucose

While PO NAC may be more cost effective than IV NAC, there are no data to indicate whether the efficacy of this route of administration may be equivalent in patients with AH (though this is an important area for study given cost, ease of administration, and potentially earlier hospital discharge).

4. **GCSF**

G-CSF at a dose of 5 mcg/kg twice daily for 5 days is safe and effective in the mobilization of hematopoietic stem cells and improves liver function as well as survival in patients with severe alcoholic hepatitis (Singh 2014). This is strongly advised in the treatment of acute alcoholic hepatitis.

5. **Other**

There are no consensus data to guide management in patients with severe AH who do not respond to therapies described above. Initiation and monitoring of these treatments does not need to be done in an inpatient setting unless patients meet other criteria for hospitalization. Consider use of **oxandrolone** 40mg PO daily x 30 days only (longer duration should be avoided due to increased risk of prostate cancer and HCC with androgen therapy) in patients who present with DF ≥ 80 or a lack of improvement in DF or MELD score (Mendenhall 1984; Orr 2004; Amini 2010). **S-adenosyl methionine (SAMe)** 400 mg TID is thought to be a potentially important mediator in alcoholic liver disease and is currently being studied for treatment of AH (Mato 1999; Lee 2004)

**Disposition:** Social work assessment is advised early in the course of hospitalization for AH. Goals of this assessment include facilitation of rehabilitation (including a contract for abstinence and referral to AA, inpatient/outpatient alcohol rehab, or other counseling). In cases of severe AH, recovery from acute illness may be slow and accompanied by prolonged requirement for nutrition support and physical therapy. In these cases, patients may be considered for in-home support, where available, or placement in a skilled nursing facility in order to maximize chances for good outcome while avoiding prolonged hospital stay.

**Disclosures:** None

**References**


