TOPIC HIGHLIGHT

Ashwani K Singal, MD, *Series Editor*

General aspects of the treatment of alcoholic hepatitis

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Received: October 28, 2010   **Revised:** March 6, 2011
Accepted: March 13, 2011
Published online: May 27, 2011

INTRODUCTION

The approach to general treatment of patients with acute alcoholic hepatitis (AH) is similar irrespective of the disease severity.

ABSTINENCE FROM ALCOHOL

Abstinence is of paramount importance in the treatment of AH and has been shown to significantly improve long-term survival[1,2]. The success rate of achieving abstinence varies from 30%-90%. The most important factor associated with long-term abstinence is the patient's awareness of the consequences of alcohol consumption. Other factors such as adequate social support, lack of illicit drug use and appropriate psychiatric evaluation and help predict successful outcome[3]. Incorporation of behavior modification and support groups, such as Alcoholics Anonymous, increases the likelihood of sustained sobriety and is recommended for patients who have difficulty in abstaining.

Pharmacological therapy such as naltrexone (an opioid receptor antagonist), acamprosate (GABA analog) and baclofen (GABA agonist) can be used to maintain abstinence[4]. However, only baclofen has been tried in patients with cirrhosis and liver failure. In the study reported from Italy, patients with alcoholic decompensated cirrhosis were randomized to receive baclofen ($n = 42$) or placebo ($n = 42$). At the end of 3 m, results by intention to treat analysis favored baclofen with a higher proportion of patients remaining abstinent (71% *vs* 29%; $P = 0.0001$) and longer cumulative abstinence duration (63 d *vs* 31 d; $P = 0.001$).

Abstract

General measures for treating patients with alcoholic hepatitis (AH) are similar irrespective of the disease severity. Alcohol abstinence is the cornerstone of treatment and can be achieved with appropriate social support, Alcoholics Anonymous and sometimes pharmacological therapy. Alcohol withdrawal should be anticipated and treatment initiated to prevent this complication. Treatment for complications of cirrhosis should be as for any other patient with cirrhosis. AH patients are particularly prone to infections and malnutrition. These should be identified and treated appropriately using broad spectrum antibiotics and nutritional support respectively.

Key words: Alcoholic hepatitis; Alcohol abstinence; Alcohol withdrawal; Nutritional support; Complications of cirrhosis; Malnutrition; Treatment

Table 1 General approach to treatment of a patient with alcoholic hepatitis			
Complication	**Initial evaluation**	**Treatment**	**Treatment for refractory cases**
Alcohol withdrawal	History of alcohol abuse Ethanol level	Fluid hydration Benzodiazepines Glucose supplementation Vitamin replacement	ICU placement IV benzodiazepines Propofol Phenobarbital Endotracheal intubation
Ascites	LFTs, ascetic fluid analysis, CT abdomen	Diuretics IV albumin Paracentesis	TIPS Liver transplantation
Altered mental status	CBC/BMP LFTs NCCT head Pancultures Lumbar puncture	IV antibiotics Lactulose Treat precipitant	Rifa × imin
Variceal bleeding	CBC LFTs	Blood transfusion octreotide Prophylactic antibiotics EVL	TIPS Shunt surgery for compensated cirrhosis
Infection	CBC/BMP Pancultures	Antibiotics for gram negative coverage	Broad spectrum antibiotics covering both gram positive and negative organisms
Malnutrition	Weight comparison Serum albumin	Oral supplementation	PEG placement Nutritionist consultation

CBC: Complete blood count; BMP: Basic metabolic panel; EVL: Endoscopic variceal ligation; TIPS: Transjugular intrahepatic portosystemic shunt.

No side effects were reported with the use of baclofen in these patients with advanced cirrhosis[5].

MANAGEMENT OF ALCOHOL WITHDRAWAL

In patients with a history of alcohol abuse, it is crucial to recognize symptoms of alcohol withdrawal which may include insomnia, irritability, nausea, vomiting, headache, anxiety, cardiac arrhythmia, hypoglycemia and diaphoresis. Rarely, withdrawal tonic clonic seizures may occur which can proceed to delirium tremens (DT). Symptoms can present within six hours of alcohol cessation in the presence of significant serum alcohol levels. Electrolyte abnormalities such as hypokalemia, hypomagnesemia, hypophosphatemia and hypoglycemia are common due to poor intake or concomitant diarrhea.

Alcoholics are also prone to anion gap acidosis due to hormonal disturbances with relative insulin deficiency and high cortisol levels. Anion gap acidosis should, however, be differentiated from lactic acidosis and sepsis as these are also common in alcoholics. Pure acidosis due to fasting and hypoglycemia reverses with administration of appropriate fluids. Hypoglycemia should only be corrected after the administration to thiamine to avoid precipitation of Wernicke's encephalopathy presenting with confusion, delirium and ophthalmoplegia, a consequence of thiamine deficiency which can be prevented by supplementation with thiamine and folic acid.

DT, defined by hallucinations, disorientation, cardiac arrhythmia, hypertension, fever, agitation and diaphoresis, usually occurs 48-96 h after the patient's last alcohol drink. Risk factors for the development of DT include chronic alcohol use, history of DT in the past, elevated serum alcohol levels and presence of concomitant illness Mortality rate of DT approaches 5% and is usually due to arrhythmia and complicating illness (pancreatitis, hepatitis or pneumonia). Benzodiazepines are used for prophylaxis and acute withdrawal. Lorazepam and oxazepam are the preferred drugs in patients with liver disease due to their relatively short half life. Intravenous administration is preferred in the setting of acute withdrawal due to rapid absorption and achievement of therapeutic levels. Intramuscular administration is not recommended due to inconsistent absorption rates. Refractory DT may be treated with the addition of phenobarbital to benzodiazepine therapy. Propofol has also been utilized to control symptoms. Patients who require phenobarbital or propofol will likely need endotracheal intubation and mechanical ventilation.

TREATMENT OF COMPLICATIONS OF CHRONIC LIVER DISEASE

Individuals with alcoholic hepatitis may have underlying cirrhosis and may frequently have complications with decompensated cirrhosis such as ascites, infection, variceal bleeding, altered mental status and renal complications (Table 1).

Ascites

Large volume paracentesis (LVP) is indicated for removal of fluid due to diuretic or diet noncompliance or ascites refractory to diuresis. Large volume paracentesis (removal of over 4-5 L) requires infusion of 6-8 g of albumin for every liter of ascites removed above the minimum. Another option for patients with refractory ascites is the use of transjugular intrahepatic portosystemic shunt (TIPS). Meta-analysis of randomized studies comparing paracentesis and TIPS have shown better control of ascites with less frequent accumulation and significantly impro-

ved transplant free survival with TIPS compared to LVP (year 1: 63% *vs* 52% and year 2: 49% *vs* 35%)[6]. However, increased frequency of hepatic encephalopathy occurred with TIPS compared to LVP (39 ± 21% *vs* 23 ± 14%; *P* < 0.05). After initial placement acute deterioration of hepatic function, increased cardiac output and decrease in vascular resistance is expected with TIPS but resolves approximately 3 mo later. Therefore, TIPS should be avoided in patients with a model for end-stage disease (MELD) score > 18 or Child Pugh class > 9[7-9].

Hepatic hydrothorax develops in approximately 5%-10% of cirrhotic patients. It occurs on the right side in 90% cases. Fluid seeps through defects in the diaphragm and the accumulated fluid in the pleural cavity has features similar to ascitic fluid[10]. Because of the potential for occurrence of volume and electrolyte disturbances in these patients, the placement of a chest tube should be avoided[11].

Altered mental status

Changes from baseline mentation are common in acute alcoholic intoxication and liver disease. Neurological disorders may stem from malnutrition (thiamine deficiency), ethanol neurotoxicity or acute intracranial abnormality (hemorrhagic or ischemic stroke). Metabolic disorders such as hypoglycemia, hyponatremia or hepatic encephalopathy are additional considerations. Infectious causes such as spontaneous bacterial peritonitis, meningitis or sepsis if suspected require empirical antibiotic coverage. At initial presentation, the patient should have a non-contrast head CT, preferably before lumbar puncture, if clinically indicated. Blood cultures, urinalysis, urine culture and ammonia level should be obtained along with CBC to evaluate acute decrease of hemoglobin or infection and BMP for metabolic abnormalities. Supplementation of thiamine and water soluble vitamins (pyridoxine and folate) should be administered. A major cause of altered mental status in liver disease is noncompliance with medical management. Typical management is the administration of lactulose with a goal of 2-3 bowel movements daily. Many patients are noncompliant with therapy due to the inconvenience of having frequent bowel movements, thus leading to frequent episodes of encephalopathy. Rifaximin is also utilized in the prevention of encephalopathy and has been shown in placebo controlled studies to have higher rates of remission and reduction of hospital admissions due to hepatic encephalopathy[12].

Variceal bleeding

A potential complication of portal hypertension is the development of esophageal and gastric varices. Mortality from esophageal variceal bleeding approaches 20%-40% and in hospital mortality remains about 20% despite optimal medical management[13]. Mortality from gastric variceal bleeding exceeds 50% and, as with esophageal varices, the outcome is linked to factors such as CTP class and the size of varices[14]. Screening for primary prevention is recommended for all patients presenting with cirrhosis. The presence and characteristics of the varices are predictors of bleeding. These include distance from the gastroesophageal junction (proximal *vs* distal), color (blue or white)**,** size and presence of red streaking/hematocystic spots.

Primary prophylaxis can be achieved with nonselective beta blockers such as propranolol for patients with large varices. Individuals who cannot tolerate or are non-compliant to beta blockers have a high risk of bleeding and may benefit from endoscopic variceal ligation.

Acute variceal bleeding can lead to encephalopathy and the patient's airway should be secured at presentation. Pharmacological therapy aims to control acute bleeds from systemic vasoconstriction. Commonly, somatostatin or octreotide infusions are utilized to control active variceal bleeding. Both drugs have an excellent safety profile and studies have shown favorable control of acute bleeding with somatostatin and octreotide versus placebo or vasopressin. The use of these drugs is also comparable to early balloon therapy or endoscopy[15-18]. Current guidelines recommend infusion of somatostatin or octreotide in addition to balloon tamponade, sclerotherapy or endoscopic banding to reduce the risk of recurrent bleeding[19-21]. Patients who are unresponsive to initial pharmacological or endoscopy treatments should be considered for TIPS procedure or surgery as an alternative. Empirical coverage with Cefotaxime or a third generation cephalosporin is recommended during active bleeding to prevent infections, especially spontaneous bacterial peritonitis.

Special considerations

Infection: Alcoholics are more susceptible to infections than other patients with liver disease because of malnutrition, immunosuppression and altered macrophage function. Common infections include pneumonia, meningitis, urinary tract infections, bacteremia and spontaneous bacterial peritonitis. Patients with cirrhosis are also susceptible to fungal infections and *Vibrio vulnificus* or *Listeria monocytogenes*. Cirrhotic patients who are suspected to have an infection should have a proper work up with a chest x-ray, blood cultures and urine analysis and culture. If the physical exam is positive for CNS abnormalities, a lumbar puncture should also be considered. Ascites should be sampled and sent for culture and cell count. An absolute neutrophil count of > 250 in the ascitic fluid of a cirrhotic patient indicates spontaneous bacterial peritonitis (SBP)[22]. The most frequently isolated organisms are enterobacteriaceae but gram positive organisms such as *Streptococcus pneumonia* and *Enterococcus* can also be isolated[22]. Initial antibiotic choice includes a third generation cephalosporin or beta lactam/lactamase. Amino glycosides should be avoided due to the risk of renal toxicity. Intravenous albumin (1.5 g/kg at diagnosis and 1 g/kg 48 h post diagnosis) can also be administered upon clinical suspicion or laboratory confirmation of SBP to prevent potential renal complications and reduce mortality[23]. Bacterial infection or sepsis from upper gastrointestinal bleeding occur in about 20% of patients and should also be treated with empirical antibiotics. Database reviews and trials have demonstrated that overall

complications, recurrent bleeding and mortality from infections were reduced in patients with cirrhosis hospitalized for gastrointestinal bleeding[24-26].

Renal failure: Renal failure is an important cause of mortality among patients with AH and will be discussed separately in another section.

Malnutrition: Patients with AH frequently present with protein caloric malnutrition due to a number of factors such as: poor intake, direct interference with small intestinal absorption and alcoholic diarrhea[27]. Nutritional status directly correlates with survival and patient outcome; thus, maintaining an adequate nutritional status in patients with alcoholism and alcoholic hepatitis is paramount[28].

Many studies have assessed the role of nutritional supplementation in the treatment of AH. A randomized control trial compared corticosteroid therapy (40 mg/d) with enteral diet (2000 kcal/d) and the outcomes were assessed at 28 d, 1 year and death. The study concluded that the overall mortality in both groups were similar; however, the enteral nutrition group had a lower incidence of infections[29]. Investigational studies have evaluated the use of anabolic steroids such as oxandrolone and testosterone in addition to high protein diets. In a trial of 263 patients with moderate to severe AH, patients were randomized to receive prednisolone, oxandrolone or placebo. Mortality was not significantly different between placebo and steroid therapy in the first 30 d; however, the group receiving oxandrolone and nutritional supplementation had a better outcome compared to oxandrolone alone[30,31]. It is important to achieve nutritional goals with positive nitrogen balance to improve survival; therefore, an energy intake of 35-40 kcal/kg per day and protein intake of 1.2-1.5 g/kg per day is recommended. Proteins should not be restricted, even in patients with encephalopathy provided they can tolerate the protein load and encephalopathy does not worsen. The use of a daily caloric count and the help of a professional dietitian are crucial in detecting patients who are unable to meet the desired needs and subsequently require additional supplementation[32,33]. Enteral supplementation is preferred and placement of enteral tubes, even in patients with esophageal varices, can successfully achieve the desired nutritional goals[34].

REFERENCES

1 **Pessione F**, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, Valla DC. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. *Liver Int* 2003; **23**: 45-53
2 **Morgan MY**. The prognosis and outcome of alcoholic liver disease. *Alcohol Alcohol Suppl* 1994; **2**: 335-343
3 **Chung T**, Martin CS, Winters KC. Diagnosis, course, and assessment of alcohol abuse and dependence in adolescents. *Recent Dev Alcohol* 2005; **17**: 5-27
4 **Garbutt JC**, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; **293**: 1617-1625
5 **Addolorato G**, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007; **370**: 1915-1922
6 **Salerno F**, Cammà C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. *Gastroenterology* 2007; **133**: 825-834
7 **Salerno F**, Merli M, Cazzaniga M, Valeriano V, Rossi P, Lovaria A, Meregaglia D, Nicolini A, Lubatti L, Riggio O. MELD score is better than Child-Pugh score in predicting 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt. *J Hepatol* 2002; **36**: 494-500
8 **Montgomery A**, Ferral H, Vasan R, Postoak DW. MELD score as a predictor of early death in patients undergoing elective transjugular intrahepatic portosystemic shunt (TIPS) procedures. *Cardiovasc Intervent Radiol* ; **28**: 307-312
9 **Boyer TD**, Haskal ZJ. The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: update 2009. *Hepatology* 2010; **51**: 306
10 **Strauss RM**, Boyer TD. Hepatic hydrothorax. *Semin Liver Dis* 1997; **17**: 227-232
11 **Liu LU**, Haddadin HA, Bodian CA, Sigal SH, Korman JD, Bodenheimer HC, Schiano TD. Outcome analysis of cirrhotic patients undergoing chest tube placement. *Chest* 2004; **126**: 142-148
12 **Bass NM**, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, Teperman L, Hillebrand D, Huang S, Merchant K, Shaw A, Bortey E, Forbes WP. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362**: 1071-1081
13 **Dy SM**, Cromwell DM, Thuluvath PJ, Bass EB. Hospital experience and outcomes for esophageal variceal bleeding. *Int J Qual Health Care* 2003; **15**: 139-146
14 **Aertgeerts B**, Buntinx F, Kester A. The value of the CAGE in screening for alcohol abuse and alcohol dependence in general clinical populations: a diagnostic meta-analysis. *J Clin Epidemiol* 2004; **57**: 30-39
15 **Kravetz D**, Bosch J, Terés J, Bruix J, Rimola A, Rodés J. Comparison of intravenous somatostatin and vasopressin infusions in treatment of acute variceal hemorrhage. *Hepatology* ; **4**: 442-446
16 **Bagarani M**, Albertini V, Anzà M, Barlattani A, Bracci F, Cucchiara G, Gizzonio D, Grassini G, Mari T, Procacciante F. Effect of somatostatin in controlling bleeding from esophageal varices. *Ital J Surg Sci* 1987; **17**: 21-26
17 **Imperiale TF**, Teran JC, McCullough AJ. A meta-analysis of somatostatin versus vasopressin in the management of acute esophageal variceal hemorrhage. *Gastroenterology* 1995; **109**: 1289-1294
18 **Jenkins SA**, Shields R, Davies M, Elias E, Turnbull AJ, Bassendine MF, James OF, Iredale JP, Vyas SK, Arthur MJ, Kingsnorth AN, Sutton R. A multicentre randomised trial comparing octreotide and injection sclerotherapy in the management and outcome of acute variceal haemorrhage. *Gut* 1997; **41**: 526-533
19 **Bañares R**, Albillos A, Rincón D, Alonso S, González M, Ruiz-del-Arbol L, Salcedo M, Molinero LM. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology* 2002; **35**: 609-615
20 **Jenkins SA**, Kingsnorth AN, Ellenbogen S, Copeland G, Davies N, Sutton R, Shields R. Octreotide in the control of post-sclerotherapy bleeding from oesophageal varices, ulcers and oesophagitis. *HPB Surg* 1996; **10**: 1-6

21   **Jenkins SA**, Baxter JN, Critchley M, Kingsnorth AN, Makin CA, Ellenbogen S, Grime JS, Love JG, Sutton R. Randomised trial of octreotide for long term management of cirrhosis after variceal haemorrhage. *BMJ* 1997; **315**: 1338-1341

22   **Sheer TA**, Runyon BA. Spontaneous bacterial peritonitis. *Dig Dis* 2005; **23**: 39-46

23   **Sort P**, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Ginès P, Rodés J. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; **341**: 403-409

24   **Soares-Weiser K**, Brezis M, Tur-Kaspa R, Paul M, Yahav J, Leibovici L. Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials. *Scand J Gastroenterol* 2003; **38**: 193-200

25   **Chavez-Tapia NC**, Barrientos-Gutierrez T, Tellez-Avila FI, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010; **9**: CD002907

26   **Pauwels A**, Mostefa-Kara N, Debenes B, Degoutte E, Lévy VG. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. *Hepatology* 1996; **24**: 802-806

27   **Mendenhall CL**, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. *Am J Med* 1984; **76**: 211-222

28   **Leevy CM**, Moroianu SA. Nutritional aspects of alcoholic liver disease. *Clin Liver Dis* 2005; **9**: 67-81

29   **Cabré E**, Rodríguez-Iglesias P, Caballería J, Quer JC, Sánchez-Lombraña JL, Parés A, Papo M, Planas R, Gassull MA. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. *Hepatology* 2000; **32**: 36-42

30   **Mendenhall CL**, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. *Hepatology* 1993; **17**: 564-576

31   **Mendenhall CL**, Moritz TE, Roselle GA, Morgan TR, Nemchausky BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. The VA Cooperative Study Group #275. *JPEN J Parenter Enteral Nutr* 1995; **19**: 258-265

32   **Morgan TR**, Moritz TE, Mendenhall CL, Haas R. Protein consumption and hepatic encephalopathy in alcoholic hepatitis. VA Cooperative Study Group #275. *J Am Coll Nutr* 1995; **14**: 152-158

33   **Kearns PJ**, Young H, Garcia G, Blaschke T, O'Hanlon G, Rinki M, Sucher K, Gregory P. Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology* 1992; **102**: 200-205

34   **Plauth M**, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, Ferenci P, Holm E, Vom Dahl S, Müller MJ, Nolte W. ESPEN Guidelines on Enteral Nutrition: Liver disease. *Clin Nutr* 2006; **25**: 285-294