General aspects of the treatment of alcoholic hepatitis

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ABSTINENCE FROM ALCOHOL

Abstinence is of paramount importance in the treatment of alcoholic hepatitis and has been shown to significantly improve long-term survival. 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. 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. 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).
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 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).

**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, Benzdiazepines, Glucose supplementation, Vitamin replacement | ICU placement, IV benzodiazepines, Propofol, Phenobarbital, Endotracheal intubation |
|                      |                                                                                     |                                                                                              | Liver transplantation                      |
| Ascites              | LFTs, ascetic fluid analysis, CT abdomen                                             | Diuretics, IV albumin, Paracetamis            | TIPS                                       |
|                      |                                                                                     |                                                                                              | Liver transplantation                      |
|                      |                                                                                     |                                                                                              |                                             |
| Altered mental status| CBC/BMP, LFTs, NCCT head, Pencultures, 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, Pencultures                                                                | Antibiotics for gram negative coverage, EVL                                                  | Broad spectrum antibiotics covering both    |
| Malnutrition         | Weight comparison, Serum albumin                                                    | Oral supplementation                          | gram positive and negative organisms       |
|                      |                                                                                     |                                                                                              | Nutritionist consultation                  |

CBC: Complete blood count; BMP: Basic metabolic panel; EVL: Endoscopic variceal ligation; TIPS: Transjugular intrahepatic portosystemic shunt.
ved transplant free survival with TIPS compared to LVP (year 1: 63% vs 52% and year 2: 49% vs 35%)\cite{10}. 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\cite{13}.

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\cite{14}. Because of the potential for occurrence of volume and electrolyte disturbances in these patients, the placement of a chest tube should be avoided\cite{15}.

**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\cite{16}.

**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\cite{17}. 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\cite{18}. 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 vasodistraction. 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\cite{19-22}. Current guidelines recommend infusion of somatostatin or octreotide in addition to balloon tamponade, sclerotherapy or endoscopic banding to reduce the risk of recurrent bleeding\cite{19-22}. 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)\cite{22}.

The most frequently isolated organisms are enterobacteriaceae but gram positive organisms such as *Streptococcus pneumoniae* and *Enterococcus* can also be isolated\cite{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\cite{24}. 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 [29,30]. 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 energy intake of 35-40 kcal/kg per day and protein supplementation [29,30]. Enteral supplementation is preferred and placement of enteral tubes, even in patients with esophageal varices, can successfully achieve the desired nutritional goals [30].

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