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Treatment of Severe Alcoholic Hepatitis

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Alcoholic hepatitis (AH) is a syndrome of jaundice and liver failure that occurs in a minority of heavy consumers of alcohol. The diagnosis usually is based on a history of heavy alcohol use, findings from blood tests, and exclusion of other liver diseases by blood and imaging analyses. Liver biopsy specimens, usually collected via the transjugular route, should be analyzed to confirm a diagnosis of AH in patients with an atypical history or presentation. The optimal treatment for patients with severe AH is prednisolone, possibly in combination with N-acetyl cysteine. At present, only short-term increases in survival can be expected—no treatment has been found to increase patient survival beyond 3 months. Abstinence is essential for long-term survival. New treatment options, including liver transplantation, are being tested in trials and results eagerly are awaited.

Keywords: NAC; Alcoholism; Cirrhosis; Steroid.

Alcoholic hepatitis (AH) is a distinct clinical presentation characterized by jaundice and liver failure in patients with prolonged and excessive alcohol consumption.[1] Typically, patients have been drinking up to the time of admission or have stopped drinking only within 4–6 weeks of presentation. Recent onset of jaundice helps to distinguish patients with AH from patients with decompensated cirrhosis. A group of patients with severe AH can be defined using Maddrey's discriminant function (DF), which is based on the serum bilirubin level and prothrombin time.[2] A DF score of 32 or higher has been associated with up to a 30% mortality rate over a 28-day period after admission.

AH usually is diagnosed based on a patient's history and laboratory results, and exclusion of other causes of acute liver injury, based on findings from serologic tests and ultrasound analyses of the liver. Characteristic laboratory findings include a bilirubin level higher than 5 mg/dL (>85 umol/L), an aspartate aminotransferase (AST) level higher than the alanine aminotransferase level, with an AST level usually less than 400 IU/mL, and increased white blood cell counts (>10,000/mm^3, with an increase in polymorphonuclear cells). An incorrect clinical diagnosis of AH may occur in up to 20% of patients; therefore, in cases in which there is diagnostic uncertainty, patients must undergo a liver biopsy.

Rates of alcohol consumption are high in North America, Europe, and some parts of the western Pacific regions. In these areas, the alcohol-related mortality- and disability-adjusted life-years are correspondingly high.[3] There are few data on the incidence of AH; 1 study from Denmark showed an increasing incidence, from 37 cases/million in 1999 to 46 cases/million in 2008 in men, and 24 cases/million increasing to 34 cases/million in women, respectively.[4]

Short-term mortality from AH can be deduced from randomized trials. In studies conducted before 1980, short-term mortality was reported to be as high as 60%.[5] However, in recent trials, mortality among subjects in placebo or steroid treatment groups invariably have been less than 20% after 28 days or 1 month.[6–8]

Who to Treat: Stratification of Patients by Disease Severity

Encephalopathy, renal failure, coagulopathy (based on prothrombin time), and serum levels of bilirubin have served as independent prognostic factors for AH since the early 1970s.[5,9,10] However, Maddrey et al[2] used discriminant analysis to produce a scoring system that reliably defined individuals at highest risk for death in the short term. In the original study describing the DF, a cut-off value of 93 was used to identify patients who died. Subsequently,

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Abbreviations used in this paper: AH, alcoholic hepatitis; AST, aspartate aminotransferase; DF, discriminant function; G-CSF, granulocyte colony–stimulating factor; MELD, model for end-stage liver disease; NAC, N-acetylcysteine; STOPAH, steroids or pentoxifylline for alcoholic hepatitis; TNF, tumor necrosis factor.

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the scoring system was changed (to measure the seconds prolonged in the prothrombin time, rather than the actual prothrombin time); a cut-off value of 32, which corresponded to the old cut-off value of 93, was used to identify patients with severe AH. By using the DF, large variations in mortality were observed between patients with DF values of 32 or more compared with patients with lower DF values.[9] Most trials conducted since that time have used this threshold to identify patients who might benefit from treatment. Most trials conducted before 2000 enrolled relatively small numbers of patients, which would make it difficult to detect a statistically significant difference in mortality rate in patients with a low mortality rate.

Subsequently, model for end-stage liver disease (MELD) scores (a score >20 indicates that a patient should be treated) and several additional scoring systems specific for AH have assessed risk of death within 1 month in patients with AH.[11,12] These scoring systems often incorporate the same variables (such as bilirubin level, prothrombin time [or international normalize ratio], creatinine, and age) and appear to have similar efficacy in predicting short-term survival. The Lille score, calculated after 1 week of treatment with prednisolone, includes baseline variables as well as response to treatment, assessed by a change in bilirubin level after 1 week of prednisolone.[13] In the initial analysis, prednisolone treatment did not increase survival among patients with Lille scores of 0.45 or more; a subsequent analysis suggested that prednisolone was ineffective in patients with Lille scores of 0.56 or more—either of these scores can be used to discontinue prednisolone. Short-term mortality might be better predicted by combining MELD and Lille scores.[12] The MELD score is a strong measure of disease severity at baseline, whereas the Lille score is a strong measure of response to therapy.

Recommended Treatments

Corticosteroids

From 1971 through 2014 there were 13 randomized trials and 4 meta-analyses that investigated the effects of corticosteroids in patients with AH.[14–17] Although these studies produced many results, controversy persisted over the use of corticosteroid therapy in these patients. Advocates cited reductions in short- to medium-term mortality, whereas detractors raised concerns about the risks of sepsis and gastrointestinal hemorrhage.

The largest placebo-controlled study of the effects of corticosteroids in 90 patients with AH found prednisolone to provide no benefit compared with placebo.[9] This study was hampered by its inclusion of patients with moderate and severe AH or end-stage alcoholic liver disease. In studies that required histologic confirmation of AH, prednisolone was associated with a short-term decrease in mortality, but there was no reduction in mortality over 6 months.[18,19] Systematic reviews of these clinical trials generated conflicting results. A Cochrane meta-analysis reported a trend toward, although not statistically significant, increase in survival. However, a re-analysis of the 3 largest studies indicated that corticosteroids significantly increased the survival of patients with AH.[16] In this study, 15% of patients with DF values of 32 or higher given prednisolone died within 28 days, compared with 35% of patients given placebo.

In an attempt to resolve the controversy regarding the use of steroids or pentoxifylline, a double blind, factorial 2 × 2, multicenter trial was conducted in the United Kingdom between 2011 and 2014 in patients with a diagnosis of AH (the Steroids or Pentoxifylline for Alcoholic Hepatitis [STOPAH] trial).[20] This study reported a borderline reduction in mortality at 28 days for patients given prednisolone 40 mg daily for 28 days compared with control patients.[8] However, survival curves converged after 28 days such that prednisolone therapy provided no benefit to patients after 90 days or 1 year. Data from this trial and previous studies were incorporated into a network meta-analysis, which confirmed that corticosteroids do not benefit patients beyond the first month of treatment.[17]

Two factors potentially limit the efficacy of corticosteroid use: increased susceptibility to infection and recidivism. In the STOPAH trial, incident infections classified as serious adverse events were more common among subjects given prednisolone than controls.[8] Infections of the respiratory tract were particularly more common. However, in the meta-analysis of Singh et al,[17] infection was not any more common among patients treated with vs without corticosteroids. This apparent discrepancy could have been caused by different methods of trial reporting. On the other hand, a study comparing corticosteroids with intensive enteral nutrition found that the short-term gains in survival in the steroid group were lost after the first month owing to an increased incidence of infections, which resulted in patient deaths.[21]

Nutrition

Deficiencies in protein, vitamins, and minerals have been described in patients with alcohol use disorders but these are not associated specifically with liver disease. High body weight and arm muscle area are associated with AH and cirrhosis, indicating a role for obesity alongside alcohol consumption in the etiology of these conditions.[22] Nevertheless, protein calorie malnutrition, assessed using 8 nutritional parameters, is associated with significantly higher 30-day, 6-month, and 12-month mortality rates.[23]

A number of trials have attempted to assess the therapeutic value of nutritional supplementation using either enteral or parenteral routes. In a small randomized study in which both groups were offered 3000 kCal/100 g protein orally, the effect of supplementing the diet with 70–85 g intravenous amino acid supplement was evaluated in the treatment arm. Patients receiving the supplemented diet had lower mortality rates and lower rates of ascites and encephalopathy, and greater improvements in serum levels of albumin and bilirubin, than controls.[24] However, in a smaller study of 15 patients with AH, 5 were given amino acids and glucose and 10 were given glucose alone. Patients given the amino acids had improved nitrogen balance and