Management and prognosis of alcoholic hepatitis

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INTRODUCTION

Excessive alcohol consumption is associated with a range of hepatic manifestations and takes a significant toll on human health throughout the world [1-4]. Moreover, alcoholic liver disease tends to be diagnosed at later stages than other liver diseases [5]. In the United States, the burden of alcoholic hepatitis is increasing [6]. Hepatic manifestations include alcoholic fatty liver disease (with or without steatohepatitis), alcoholic hepatitis, and cirrhosis. While asymptomatic steatohepatitis due to alcohol could be referred to as "alcoholic hepatitis," the term is typically used to describe the acute onset of symptomatic hepatitis. The amount of alcohol intake that puts an individual at risk for alcoholic hepatitis is not known, but the majority of patients have a history of heavy alcohol use (more than 100 g per day) for two or more decades (figure 1) [7,8].

This topic will review the prognosis and management of patients with alcoholic hepatitis. The pathogenesis of alcoholic liver disease, the clinical manifestations and diagnosis of alcoholic hepatitis, and the approach to patients with alcoholic fatty liver disease or alcoholic cirrhosis are discussed separately.

- (See "Pathogenesis of alcohol-associated liver disease".)
- (See "Alcoholic hepatitis: Clinical manifestations and diagnosis".)
- (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)
- (See "Management of alcohol-associated steatosis and alcohol-associated cirrhosis".)

Guidelines for the management of patients with alcoholic liver disease have been issued by the American Association for the Study of Liver Diseases, the American Gastroenterological Association, and the American College of Gastroenterology [9,10]. The discussion that follows is generally consistent with those guidelines.

DETERMINING DISEASE SEVERITY

Several models have been proposed to determine the severity of a patient's alcoholic hepatitis [11,12]. The Maddrey discriminant function and the Model for End-stage Liver Disease (MELD) score are the most commonly used to help identify patients who are more likely to benefit from pharmacologic therapy. Other validated scores include the Glasgow alcoholic hepatitis score, the ABIC score (which includes age, serum bilirubin, international normalized ratio, and serum creatinine), and the Lille score (which is used to determine if a patient is responding to treatment) [12-14]. (See 'Efficacy' below.)

Maddrey discriminant function — Disease severity and mortality risk in patients with alcoholic hepatitis may be estimated using the Maddrey discriminant function (DF, also known as the Maddrey score), which is calculated as follows (calculator 1) [15,16]:

For bilirubin in conventional units (mg/dL):

DF = (4.6 x [prothrombin time (sec) - control prothrombin time (sec)]) + (serum bilirubin)

For bilirubin in système international units (micromol/L):

DF = (4.6 x [prothrombin time (sec) - control prothrombin time (sec)]) + (serum bilirubin/17.1)

Patients with a DF value ≥32 have high short-term mortality and may benefit from treatment with glucocorticoids, whereas those with lower scores have low short-term mortality and do not appear to benefit from glucocorticoids. (See 'Prognosis' below and 'Efficacy' below.)

MELD score — The MELD score is a statistical model developed to predict survival in patients with cirrhosis that has also been used to predict mortality in patients hospitalized for alcoholic hepatitis [17-19]. The score ranges from 6 to 40 and is based on the serum bilirubin, creatinine, and international normalized ratio (calculator 2 and calculator 3). (See "Model for End-stage Liver Disease (MELD)".)

In one report, a MELD score >11 performed as well as the DF in predicting 30-day mortality [17]. The sensitivity and specificity of MELD for predicting 30-day mortality were 86 and 81 percent,

respectively, and for the DF were 86 and 48 percent, respectively. In a second study, a MELD score of ≥21 had a sensitivity of 75 percent and a specificity of 75 percent for predicting 90-day mortality [18].

In addition, an increase in the MELD score of ≥2 points in the first week of hospitalization may independently predict in-hospital mortality [19].

A proposed scoring system that combines alterations in hepatic gene expression with MELD score (gene signature-MELD) has been used to predict survival at 180 days for patients with severe alcoholic hepatitis [20]. The score requires a liver biopsy, which limits its routine clinical use.

Glasgow alcoholic hepatitis score — The Glasgow alcoholic hepatitis (GAH) score predicts mortality in alcoholic hepatitis and is based on a multivariable model that includes age, serum bilirubin, blood urea nitrogen, prothrombin time, and peripheral white blood cell count (calculator 4) [21,22]. An initial validation study with 195 patients with alcoholic hepatitis found that a GAH score ≥9 had lower sensitivity but higher specificity for predicting 28-day mortality than a DF of ≥32 (81 versus 96 percent and 61 versus 27 percent, respectively) [22]. Similar results were seen when it was compared with the MELD score (using a MELD cutoff of 11).

A subsequent validation study with 225 patients with a DF ≥32 found that patients with a GAH score ≥9 who received glucocorticoids had higher survival rates compared with those who did not receive glucocorticoids (78 versus 52 percent survival at 28 days and 59 versus 38 percent survival at 84 days) [21]. However, no survival benefit with glucocorticoids was seen among the patients with a GAH score <9.

Hepatic histology score — A histologic scoring system has been introduced that may assist in stratifying severity and predicting 90-day mortality [23]. Key parameters that correlate with outcome include the degree of fibrosis and neutrophilic infiltration, type of bilirubinostasis, and presence of megamitochondria. It was developed using predictors of 90-day mortality derived from a study of 121 patients with alcoholic hepatitis. Scores range from 0 to 9. A score of 0 to 3 was associated with a low risk of mortality within 90 days (3 percent), a score of 4 to 5 was associated with a moderate risk of mortality (19 percent), and a score of 6 to 9 was associated with a high risk of mortality (51 percent). The hepatic histology score requires a biopsy, which is not routinely performed in patients with alcoholic hepatitis. (See "Histologic scoring systems for chronic liver disease".)

MANAGEMENT

Treatment considerations for all patients — The management of alcoholic hepatitis includes treatment for alcohol withdrawal and providing hemodynamic and nutritional support. Patients may develop complications such as infections or conditions related to cirrhosis, which also require treatment. Most patients with alcoholic hepatitis require inpatient hospitalization, and some will also need critical care support (eg, those with respiratory failure or sepsis). (See 'Complications of cirrhosis' below and 'Critically ill patients' below.)

Consultation with a gastroenterologist or hepatologist is recommended to assist with management, especially for patients who fail to respond to pharmacologic treatment. (See 'Glucocorticoids' below and 'Pentoxifylline' below.)

Patients should remain hospitalized if there is evidence of active infection, renal failure, severe coagulopathy and/or liver failure, alcohol withdrawal, delirium tremens, or other complications. Once these have been excluded and the patient is hemodynamically stable (with or without ongoing glucocorticoid usage), discharge can be considered, provided that there is sufficient social support and patient insight to ensure good compliance with medications, abstinence from alcohol, and close medical follow-up. The approach to treating alcohol use disorder is presented separately. (See "Alcohol use disorder: Treatment overview" and 'Alcohol abstinence and withdrawal' below.)

Alcohol abstinence and withdrawal — All patients with alcoholic hepatitis should abstain from alcohol. Pharmacologic therapy may aid with abstinence, and this is discussed separately [24-27]. (See "Ascites in adults with cirrhosis: Initial therapy", section on 'Alcohol abstinence'.)

Since many patients have a long history of excessive alcohol use, they are at risk for alcohol withdrawal. Therefore, the prevention and treatment of alcohol withdrawal is an important part of a patient's management. A systematic review of interventions for alcohol abstinence in patients with chronic liver disease found that when combined with comprehensive medical care, psychosocial interventions such as cognitive behavioral therapy, motivational enhancement therapy, can induce abstinence and reduce the risk of relapse [28]. (See "Management of moderate and severe alcohol withdrawal syndromes", section on 'Prophylaxis' and "Management of moderate and severe alcohol withdrawal syndromes", section on 'Management'.)

Hydration — Poor oral intake prior to presentation may result in dehydration, so many patients require fluid resuscitation. We prefer to use albumin rather than crystalloid for patients with prerenal azotemia and underlying cirrhosis, and the management of prerenal disease and/or hepatorenal syndrome is discussed separately [29]. (See "Hepatorenal syndrome".)

Overhydration should be avoided since it may increase the degree of ascites, lower the plasma sodium concentration, and occasionally precipitate gastrointestinal hemorrhage from varices [30]. Thus, patients without prerenal azotemia should not be routinely given maintenance fluids, particularly if they are able to tolerate oral fluids. (See "Maintenance and replacement fluid therapy in adults".)

Nutrition — Most patients with severe alcoholic hepatitis are malnourished and require nutritional support. In a Veterans Administration Cooperative Study that included 284 patients with alcoholic hepatitis who underwent a complete nutritional assessment, signs of tissue wasting and severe protein-calorie malnutrition (eg, hypoalbuminemia, edema) were evident in almost all patients [31]. Indices of malnutrition correlated closely with the clinical severity of liver disease.

The goal of nutritional support is to provide adequate calories and protein, in addition to vitamin (eg, thiamine, folate, and pyridoxine) and mineral (eg, phosphate, magnesium) repletion [32]. Of note, vitamin K is usually given to patients with a prolonged prothrombin time, even though this regimen is often ineffective because the coagulopathy is more a reflection of underlying liver failure than vitamin K deficiency. Oral vitamin K is not well absorbed; a parenteral route of administration is preferred for these patients. Vitamin replacement and management of hemostatic abnormalities in patients with liver disease are discussed in more detail separately:

- (See "Nutritional status in patients with sustained heavy alcohol use", section on 'Supplementation'.)
- (See "Overview of vitamin K", section on 'Vitamin K deficiency'.)
- (See "Hemostatic abnormalities in patients with liver disease".)

Protein intake is well tolerated and should not be restricted in patients with alcoholic hepatitis. In patients who develop encephalopathy associated with protein feeding, the use of branched-chain amino acids may be helpful. (See "Hepatic encephalopathy in adults: Treatment", section on 'Nutritional support' and "Hepatic encephalopathy in adults: Treatment", section on 'Branched-chain amino acids'.)

If the patient cannot maintain adequate oral intake, enteral tube feeding is generally preferred over intravenous nutrition. In our experience, patients with severe alcoholic hepatitis have very poor oral intake without regular assistance from nursing staff, relatives, or friends. If calorie counts demonstrate inadequate oral intake, a postpyloric feeding tube can greatly improve calorie intake. If the patient pulls the tube out unintentionally, a bridle can be used to keep the tube in place.

Efficacy of nutrition therapy in alcoholic hepatitis has been evaluated in multiple clinical trials [33-37], and most studies have demonstrated improvement in liver function and histology but without a consistent reduction in mortality. Nutrition therapy has been studied in combination with or as an alternative to glucocorticoids [38-40]:

- A pilot, open-label study suggested that combining nutritional therapy with glucocorticoids might allow for a shorter course of glucocorticoids, but further studies are needed [38].
- One randomized trial assigned 71 patients with severe alcoholic hepatitis to prednisolone or enteral tube feeding for 28 days and then followed the patients for one year [40]. Early mortality during treatment was similar in patients who received prednisolone and in those who received enteral tube feeding (25 versus 31 percent, respectively), although deaths occurred later in those who received prednisolone (median 23 versus 7 days). Among the 51 patients who were discharged from the hospital, mortality over the long term was higher in the prednisolone group (37 versus 8 percent).

Complications of cirrhosis — Patients with alcoholic hepatitis may also have underlying cirrhosis. These patients may present with complications of cirrhosis and portal hypertension such as hepatic encephalopathy, ascites, or variceal bleeding. The management of complications of cirrhosis are discussed separately. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

For patients with typical symptoms of hepatic encephalopathy, a trial of lactulose and/or rifaximin should be given, with further evaluation (including head imaging) to exclude other diagnoses if the patient does not improve. The clinical manifestations, diagnosis, and treatment of hepatic encephalopathy is discussed in more detail separately. (See "Hepatic encephalopathy in adults: Clinical manifestations and diagnosis" and "Hepatic encephalopathy in adults: Treatment".)

Critically ill patients — Admission to an intensive care unit should be considered in patients who are unstable or combative. In addition, patients who are inebriated or have hepatic encephalopathy may require airway protection. Critical care support also includes sepsis surveillance and stress ulcer prophylaxis. Ulcer prophylaxis can be discontinued upon discharge from the hospital unless there is another indication for continuation.

Infection surveillance — Patients with evidence of possible infection (eg, fever, worsening mental status, hemodynamic instability) should have blood and urine cultures obtained. Sputum cultures should be obtained if the patient has a productive cough or is intubated, and cerebrospinal fluid examined and cultured in those patients with fever and neurologic signs or

symptoms suggestive of central nervous system infection rather than typical hepatic encephalopathy (eg, headache with fever, nuchal rigidity, or lateralizing neurologic deficits). In addition, if present, ascitic fluid should be obtained for culture, cell count with differential, total protein, and albumin level. Cultures are required because it is often impossible to distinguish between the fever of hepatitis and that of infection based solely on clinical criteria. (See "Alcoholic hepatitis: Clinical manifestations and diagnosis", section on 'Signs and symptoms'.)

While not yet translated into changes in clinical management, there is growing recognition that the microbiome (both bacteria and fungi) are altered in patients with alcoholic hepatitis and may contribute to disease severity because of toxin production by either bacteria or fungi [41-45].

Renal failure and acute kidney injury — Critically ill patients with alcoholic hepatitis may develop renal failure, which is associated with increased mortality [46,47]. The goal is to identify and treat conditions (eg, sepsis) that may lead to acute kidney injury or renal failure. Hepatorenal syndrome is a potential etiology in patients with a rising creatinine despite fluid resuscitation and discontinuation of diuretics. The approach to the diagnosis and treatment of hepatorenal syndrome is discussed in detail elsewhere. (See "Hepatorenal syndrome".)

Ulcer prophylaxis — We give patients prophylaxis against gastric mucosal bleeding with a proton pump inhibitor, histamine-2 receptor antagonist, or sucralfate, particularly if the patient is in an intensive care unit, is receiving glucocorticoids, or has occult blood detected in the stool. Choosing an agent for ulcer prophylaxis in the critically ill patient is discussed separately. (See "Stress ulcers in the intensive care unit: Diagnosis, management, and prevention", section on 'Prophylaxis' and "Evaluation of occult gastrointestinal bleeding", section on 'Testing for occult blood'.)

Mild to moderate alcoholic hepatitis — Abstinence from alcohol is the mainstay of treatment in patients with mild to moderate alcoholic hepatitis (Maddrey discriminant function [DF] <32) (calculator 1). In addition, general supportive care (eg, nutritional support and hydration) should be provided, but pharmacologic treatment with glucocorticoids is not recommended in patients with mild to moderate alcoholic hepatitis [10]. While glucocorticoids may provide a short-term survival benefit in alcoholic hepatitis, patients with mild to moderate disease have a relatively favorable prognosis, and therefore, potential benefits do not outweigh potential harm. Pentoxifylline has only been studied in patients with severe alcoholic hepatitis. (See 'Treatment considerations for all patients' above and 'Efficacy' below and 'Mortality' below.)

Severe alcoholic hepatitis

Glucocorticoids

Indications and contraindications — In addition to general supportive care, we suggest treatment with glucocorticoids (40 mg per day) for patients with severe alcoholic hepatitis (DF ≥32 (calculator 1)) [48]. However, not all authorities agree with this recommendation, instead favoring pentoxifylline in certain populations in light of inconclusive evidence of glucocorticoid efficacy [49]. Prednisolone has traditionally been given, provided there are no contraindications to its use (eg, active bacterial or fungal infection or chronic hepatitis C virus or hepatitis B virus infection) [10].

Glucocorticoids must be used cautiously, particularly in patients who are unlikely to return for follow-up after discharge from the hospital. In the absence of a clinician guiding treatment, these patients are at risk for continuing glucocorticoids long term (with all of the associated side effects). In such patients, the benefits of glucocorticoids must be weighed against the risk of the patient's failing to receive follow-up medical care.

Careful monitoring for evidence of infection, gastrointestinal bleeding, or glucose intolerance is essential while the patient is on glucocorticoid therapy. In one report, infection developed in 24 percent of 57 patients who received glucocorticoids and was more likely to develop in those who did not respond to glucocorticoids (43 versus 11 percent) [50]. (See "Major side effects of systemic glucocorticoids".)

Administration — We treat selected patients with severe alcoholic hepatitis with prednisolone 40 mg per day. Prednisone is an alternative if prednisolone is unavailable [48]. Prednisolone is preferred over prednisone because the latter requires conversion to prednisolone (the active form) in the liver, a process that may be impaired in alcoholic hepatitis. Methylprednisolone 32 mg daily by intravenous route is used for patients who cannot take oral medications and if intravenous prednisolone is not available (ie, North America).

For patients who respond to treatment, we continue prednisolone for 28 days [48].

Response and early termination of treatment — For patients who receive glucocorticoids, the duration of treatment is 28 days. However, we stop therapy in patients who fail to show signs of improvement after one week (ie, those who fail to have improvement in their bilirubin or DF) (calculator 1).

The Lille score is another method to determine if patients with alcoholic hepatitis are responding to glucocorticoid therapy. We do not use the Lille score when deciding whether to continue treatment, but since it incorporates a bilirubin decrease in response to steroids, it may also be used. The score was derived using a cohort of 295 patients with alcoholic hepatitis who were treated with glucocorticoids [13]. It combines six variables: age, renal insufficiency (Cr >1.3 or creatinine clearance <40 mL/minute), albumin, prothrombin time, bilirubin, and evolution of

bilirubin at day 7 (bilirubin at day 7 – bilirubin at day 0). Online calculators are available for the calculating the Lille score. A score >0.45 suggests that a patient is not responding to glucocorticoid therapy.

In a validation cohort of 118 patients, the 40 percent of patients who had a Lille score >0.45 had a higher mortality at six months compared to those with a lower score (75 versus 15 percent) [13]. In addition, the Lille score performed better than the DF, Child-Pugh score, or Glasgow alcoholic hepatitis score in predicting survival at six months. In another study using individual patient data from five clinical trials, a Lille score ≥0.56 predicted no response to glucocorticoid therapy as measured by hazard ratio for 28-day mortality [51].

Efficacy — The efficacy of glucocorticoids in alcoholic hepatitis has been evaluated in multiple randomized trials and meta-analyses, with mixed results [15,49,51-67]. Mortality rates after one to six months among patients treated with glucocorticoids in these trials ranged from 15 to 63 percent. Some of the variability may be related to differences in disease severity among the trials. Adding to the uncertainty is that many studies did not provide good documentation on complications of glucocorticoids in this setting [49]. (See 'Determining disease severity' above.)

In a 2017 meta-analysis of 15 randomized trials including 1861 patients with alcoholic hepatitis, mortality risk was not significantly different for patients treated with glucocorticoids compared with those given placebo (28 versus 30 percent; RR 0.90, 95% CI 0.70-1.15) [49]. When the analysis was restricted to trials with patients with severe alcoholic hepatitis (DF ≥32 or hepatic encephalopathy), there was also no significant difference in mortality risk (RR 0.92, 95% CI 0.73-1.16). The investigators assessed the quality of the evidence as low due to high risk of bias; they also noted that adverse events and complications of treatment were not clearly reported in many trials.

These results are somewhat at odds with conclusions derived from an earlier (2011) meta-analysis that examined patient-level data from five randomized trials (221 patients with severe alcoholic hepatitis) and found that glucocorticoid treatment was associated with lower 28-day mortality rates compared with placebo (20 versus 34 percent) [51]. In a subsequently published randomized trial (STOPAH), which included 1103 patients with severe alcoholic hepatitis, prednisolone showed a trend toward improving 28-day survival (odds ratio 0.72, 95% CI 0.52-1.01) [52]. A 2015 meta-analysis that included the STOPAH trial among the eight included trials found that 28-day mortality was reduced in patients who received glucocorticoids (RR= 0.54; 95% CI 0.33- 0.84) [53]. Data on long-term outcomes is more limited, but do not show a benefit for glucocorticoid treatment [49,51-53].

Pentoxifylline — Pentoxifylline is an alternative to glucocorticoids for patients who have contraindications to glucocorticoids or who are at risk for sepsis or for failing to follow up after discharge (and thus may not be tapered off of prednisolone, which could result in serious adverse effects). In addition, some authorities favor pentoxifylline because it may provide more benefit for certain subgroups of patients (eg, those with renal failure) compared with glucocorticoids [10].

Pentoxifylline is given as 400 mg three times per day (400 mg once per day in patients with a creatinine clearance <30 mL per minute). A bilirubin less than 5 mg/dL may be an appropriate time to stop therapy. Pentoxifylline should be stopped earlier in patients who develop dyspepsia that limits oral intake. Pentoxifylline inhibits tumor necrosis factor (TNF) synthesis, which is increased in patients with alcoholic hepatitis.

Pentoxifylline has a good safety profile; however, the use of pentoxifylline in the management of alcoholic hepatitis remains controversial because the data are inconsistent [52,53,68,69]. Several studies and meta-analyses failed to show a benefit with regard to mortality [68,70-74], while other studies and meta-analyses have suggested that pentoxifylline may prevent hepatorenal syndrome and/or decrease mortality [53,71,75,76].

Short- and medium-term mortality:

- The STOPAH trial did not show a mortality benefit with pentoxifylline, but it had several important limitations [52]. The STOPAH trial included 1103 patients with a DF ≥32 who were randomly assigned to receive placebo, prednisolone, pentoxifylline, or both prednisolone and pentoxifylline. The odds ratio for mortality for patients receiving pentoxifylline (with or without prednisolone) was 1.07 (95% CI 0.77-1.49). However, it is important to note that the mortality rate seen in patients who did not receive prednisolone or pentoxifylline (17 percent) was significantly lower than seen in the placebo arms from other trials (approximately 25 to 45 percent at one month) [15,51,75,77].

  This lower-than-expected mortality rate in patients who received placebo suggests that the patients included in the trial may not be representative of patients with severe alcoholic hepatitis in general; it could also reflect generally improved care of patients in the trial. Ways in which the patients may not have been representative include the possible inclusion of patients with diagnoses other than alcoholic hepatitis and the exclusion of patients with renal failure, active gastrointestinal bleeding, untreated sepsis, or the need for inotropic support if their condition did not stabilize within the first seven days.

Importantly, the exclusion of patients with renal failure may have biased the results against pentoxifylline because much of the benefit with pentoxifylline appears to be related to preventing or reversing hepatorenal syndrome.

- A meta-analysis of four trials including 350 patients showed a trend toward a lower risk of mortality with pentoxifylline compared with placebo (RR 0.74, 95% CI 0.46-1.18) [53]. A meta-analysis of four trials including 459 patients showed that the combination of a glucocorticoid and pentoxifylline was not superior to treatment with a glucocorticoid alone with regard to short- or medium-term mortality (RR 0.94, 95% CI 0.69-1.30).

Acute kidney injury (AKI):

- In the STOPAH trial, AKI occurred in nine of 546 patients (2 percent) who received pentoxifylline compared with 14 of 546 patients (3 percent) who did not [52].

- In a meta-analysis of four trials including 347 patients, there was a trend toward decreasing the risk of AKI with pentoxifylline compared with placebo (RR 0.45, 95% CI 0.17-1.16) [53]. When glucocorticoids combined with pentoxifylline were compared with glucocorticoids alone, there was a trend toward decreasing the risk of AKI with dual therapy (RR 0.24, 95% CI 0.24-1.15).

Among patients who fail to respond to glucocorticoid therapy, substituting pentoxifylline for prednisolone does not appear to be effective [78].

Discontinue nonselective beta blockers — In patients with severe alcoholic hepatitis, the use of nonselective beta blockers has been associated with an increased risk of acute kidney injury (AKI) [79]. As a result, we discontinue beta blockers in patients with severe alcoholic hepatitis. In a study of 139 patients with severe alcoholic hepatitis, the cumulative incidence of AKI at nearly six months was higher in patients who received nonselective beta blockers compared with those who did not (90 versus 50 percent) [79].

In addition, beta blockers should not be started in patients with alcoholic hepatitis; thus, we suggest deferring screening endoscopy for varices until the patient has fully recovered.

Possibly effective treatments — Several other medical therapies have been investigated for the treatment of severe alcoholic hepatitis, but whether they will have a role in the routine treatment of alcoholic hepatitis is unclear [12,80,81].

- **N-acetylcysteine (NAC)** – The combination of NAC, an antioxidant, with prednisolone has been studied for the treatment of severe alcoholic hepatitis, but it may not be more effective than prednisolone alone. A randomized trial with 174 patients compared

treatment with either four weeks of prednisolone or four weeks of prednisolone plus NAC given on days one through five [82]. There was no difference in six-month mortality (the primary endpoint) between those who received prednisolone and those who received prednisolone plus NAC (38 versus 27 percent). While mortality was higher among those treated with prednisolone alone at one month (24 versus 8 percent), the difference was no longer statistically significant at three months (34 versus 22 percent). However, given the trend toward increased survival in those treated with NAC, additional study is warranted.

- **Granulocyte colony-stimulating factor (GCSF)** – The theory behind using GCSF in patients with severe alcoholic hepatitis is that GCSF may mobilize bone marrow-derived stem cells and promote hepatic regeneration. In a randomized, nonblinded trial with 46 patients with severe alcoholic hepatitis, patients were assigned to receive standard medical care (pentoxifylline with other supportive measures) plus GCSF (5 mcg/kg subcutaneously every 12 hours for five days) or standard medical care alone [83]. Survival at 90 days was higher in the patients who received GCSF than in those who did not (78 versus 30 percent). However, it should be noted that the survival rate for patients in the standard care alone arm was lower than what has been seen in other studies of pentoxifylline (with variable lengths of follow-up). Survival rates with pentoxifylline in other trials have ranged from 71 percent at 28 days to 75 percent at six months.

Ineffective treatments — Ineffective treatments for alcoholic hepatitis that have been studied include anti-TNF antibodies and anabolic steroids.

- **Anti-TNF antibodies** – TNF-alpha is believed to play a role in the pathogenesis of alcoholic hepatitis, but trials using anti-TNF antibodies have had disappointing results. (See "Pathogenesis of alcohol-associated liver disease", section on 'Injurious cytokines'.)

  Etanercept is a soluble TNF receptor: FC fusion protein that binds to and neutralizes soluble TNF. While initial observational studies of etanercept showed a possible benefit [84], a randomized controlled trial in patients with moderate to severe alcoholic hepatitis did not [85]. Compared with placebo, etanercept was associated with significantly higher mortality (mainly due to infection) after six months (58 versus 23 percent).

  Another anti-TNF antibody, infliximab, has also been studied for the treatment of severe alcoholic hepatitis. Infliximab is a chimeric mouse-human anti-TNF monoclonal antibody that was associated with clinical improvement in open-label trials [86,87]. Infliximab was then studied in a randomized trial with 36 patients with severe alcoholic hepatitis [88]. The patients were assigned to infliximab (10 mg/kg at days 0, 14, and 28) or placebo. All patients also received prednisolone (40 mg daily) for 28 days. The study was stopped early

due to higher mortality at two months in the infliximab group (39 versus 18 percent), though the increase was not statistically significant. Infections were more common in the infliximab group (72 versus 17 percent, p = 0.002), with severe infections accounting for half of the deaths. The study was criticized because high doses of infliximab were used (10 mg/kg at days 0, 14, and 28), though the open-label studies that used lower doses also found high infection rates [86,87]. In addition, it is not known if the increased infection rate in the infliximab group was due to the infliximab alone or due to the combined effects of infliximab plus prednisolone.

- **Anabolic steroids** – Androgens have been used in an attempt to improve nutritional status in patients with alcoholic hepatitis, but they are likely ineffective. Promising results were seen in a subset of patents from a multicenter Veterans Administration trial of oxandrolone that included 263 patients with moderate or severe alcoholic hepatitis [57]. While there was no benefit in short-term survival, there was some benefit in long-term survival among patients who survived for at least one month. However, no benefit could be demonstrated in a systematic review of five randomized trials of patients with alcoholic hepatitis and/or cirrhosis [89].

Liver transplantation — Patients with severe alcoholic hepatitis who fail to respond to treatment with glucocorticoids or pentoxifylline may require liver transplantation [90,91]. However, because alcoholic hepatitis implies recent alcohol abuse, such patients usually do not receive transplantations, and the issue presents an ethical dilemma to providers and patients [92] (see "Liver transplantation for alcohol-associated liver disease"). Nonetheless, an increasing number of centers are performing liver transplantation in highly selected patients with severe alcoholic hepatitis [93]. A model study reinforces the extension of survival for patients with alcoholic hepatitis who receive a liver transplantation [94].

Moreover, harmful drinking after transplantation is associated with severe recurrent disease [95]. Nonetheless, in two small trials of highly selected patients, liver transplantation was associated with six-month survival rates of 77 [96] and 100 percent [97]. In one of these studies, the six month alcohol relapse rate in patients receiving early liver transplant was similar to that in a control group who underwent transplant after six months of abstinence (24 versus 29 percent) [97]. Greater emphasis on substance abuse training before and after transplant may also reduce the alcohol relapse rate among those who are transplanted [98].

Refractory patients — Patients with severe alcoholic hepatitis who do not respond to supportive care, nutritional therapy, and pharmacologic therapy, who are not candidates for liver transplantation, and who have multiple (≥four) organ failures, may be considered for palliative therapy [10]. (See "Palliative care for patients with end-stage liver disease".)

PROGNOSIS

Mortality — Mortality rates among patients who do not receive pharmacologic therapy (eg, prednisolone) for alcoholic hepatitis are variable. In patients with severe alcoholic hepatitis (typically defined by a Maddrey discriminant function ≥32 (calculator 1)), short-term mortality rates are high (approximately 25 to 45 percent at one month) [15,51,75,77], whereas patients with mild to moderate alcoholic hepatitis have lower short-term mortality rates (<10 percent at one to three months) [36,99]. In one study, the primary causes of death were hepatic failure (55 percent), gastrointestinal bleeding (21 percent), and sepsis (7 percent) [77]. (See 'Determining disease severity' above.)

Multiple risk factors for increased mortality in patients with alcoholic hepatitis have been identified and some have been incorporated into prognostic models. Long-term outcomes are also poor if patients have presented with acute decompensation, with 50 percent five-year mortality [100]. (See 'Determining disease severity' above.)

Risk factors for increased mortality include [12,23,46,100-106]:

- Older age
- Acute kidney injury
- Elevated bilirubin level
- Elevated international normalized ratio
- Leukocytosis
- Alcohol consumption >120 g per day
- Infection (sepsis, spontaneous bacterial peritonitis, pneumonia, urinary tract infection, aspergillosis)
- Hepatic encephalopathy
- Upper gastrointestinal bleeding
- Bilirubin to gamma glutamyl transferase ratio >1
- High hepatic histology score (see 'Hepatic histology score' above)
- Systemic inflammatory response syndrome (see "Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis", section on 'Definitions')

Course after recovery — An important determinant of outcome among patients with alcoholic hepatitis is whether the patients continue to drink alcohol. In a series that included 87 patients with alcoholic hepatitis who survived their index hospitalization, the overall estimated five-year survival rate was 32 percent [107]. However, among those who abstained from alcohol, the

estimated survival rate was 75 percent, whereas for relapsed and continued drinkers it was 27 and 21 percent, respectively.

However, even if patients abstain from alcohol, they remain at risk for progressive liver disease [108,109]. In one series of 61 patients, 18 percent of those who initially had alcoholic hepatitis without cirrhosis progressed to cirrhosis despite alcohol abstinence [108]. In addition, histologic features of alcoholic hepatitis persisted for up to 14 months after discontinuing alcohol, suggesting that resolution of inflammation is slow. Thus, even patients who abstain from alcohol require ongoing evaluation for the development of cirrhosis (see "Cirrhosis in adults: Etiologies, clinical manifestations, and diagnosis", section on 'Clinical manifestations'). Enrollment in an alcohol rehabilitation program within 30 days of discharge can improve outcomes by reducing readmission and death in patients with alcoholic hepatitis [110].

It has been our observation that a marked elevation in serum bilirubin with slow normalization of aminotransferases that remain in an alcoholic pattern (aspartate aminotransferase >alanine aminotransferase) may be seen for many months following an episode of alcoholic hepatitis, even in patients who abstain from alcohol, perhaps reflecting the persistent histologic changes. Thus, the presence of persistently abnormal serum aminotransferases does not necessarily indicate that a patient is continuing to drink alcohol.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Alcoholic liver disease".)

SUMMARY AND RECOMMENDATIONS

- **Determining the severity** – Several prognostic models have been proposed to determine the severity of a patient's alcoholic hepatitis. The Maddrey discriminant function (DF) (calculator 1) and Model for End-stage Liver Disease are the most commonly used to identify patients with severe alcoholic hepatitis (DF ≥32) who are more likely to benefit from pharmacologic therapy (calculator 2 and calculator 3). The Lille score has also been well validated. (See 'Determining disease severity' above.)

  For patients with severe alcoholic hepatitis, short-term mortality rates are high (approximately 25 to 35 percent at one month), whereas patients with mild to moderate alcoholic hepatitis have low short-term mortality rates (<10 percent at one to three months). (See 'Prognosis' above.)

- **Initial management of all patients** – Patients with alcoholic hepatitis require general supportive care, including (see 'Treatment considerations for all patients' above and 'Discontinue nonselective beta blockers' above):

  - Alcohol abstinence
  - Prevention and treatment of alcohol withdrawal
  - Fluid management
  - Nutritional support
  - Infection surveillance
  - Prophylaxis against gastric mucosal bleeding

  In addition, we suggest that nonselective beta blockers are discontinued in patients with severe alcoholic hepatitis (**Grade 2B**).

- **Patients with mild to moderate alcoholic hepatitis** – The mainstay of treatment for patients with mild to moderate alcoholic hepatitis is abstinence from alcohol and supportive care. In patients with mild to moderate alcoholic hepatitis (DF <32), we recommend **against** pharmacologic therapy with prednisolone (**Grade 1B**). Prednisolone does not appear to be beneficial in such patients. In addition, we suggest **against** pharmacologic therapy with pentoxifylline (**Grade 2C**). Pentoxifylline has not been studied in this population, and its efficacy in patients with more severe alcoholic hepatitis has not been established. (See 'Mild to moderate alcoholic hepatitis' above.)

- **Patients with severe alcoholic hepatitis (DF ≥32)** – In patients with severe alcoholic hepatitis (DF ≥32), we suggest treatment with glucocorticoids (40 mg per day) along with supportive care (**Grade 2C**) (see 'Administration' above). If there are no signs of improvement (ie, decreasing bilirubin or DF) after one week of therapy, we stop glucocorticoid treatment; otherwise we treat for 28 days. (See 'Severe alcoholic hepatitis' above.)

  However, not all authorities agree with this recommendation, instead favoring pentoxifylline in certain populations. This includes patients with contraindications to glucocorticoids (see 'Indications and contraindications' above) as well as those whose social circumstances place them at risk for poor continuity of care.

  As an example, patients who are homeless and given a prescription for glucocorticoids may not receive proper follow-up to ensure that the glucocorticoids are discontinued after 28 days. By contrast, the safety profile of pentoxifylline (400 mg three times per day [or once daily in patients with a creatinine clearance <30 mL/minute]) is relatively favorable in such settings. A bilirubin less than 5 mg/dL may be an appropriate time to stop

pentoxifylline. Pentoxifylline should be stopped earlier in patients who develop dyspepsia that limits oral intake. (See 'Pentoxifylline' above.)

- **Patients who fail medical therapy** – Patients who fail to respond to medical therapy may require liver transplantation before a six-month waiting period. However, such patients must be very carefully selected to ensure a minimal risk of alcohol relapse after transplant. (See "Liver transplantation for alcohol-associated liver disease", section on 'Patients with severe alcohol-associated hepatitis (AH)' and 'Liver transplantation' above.)

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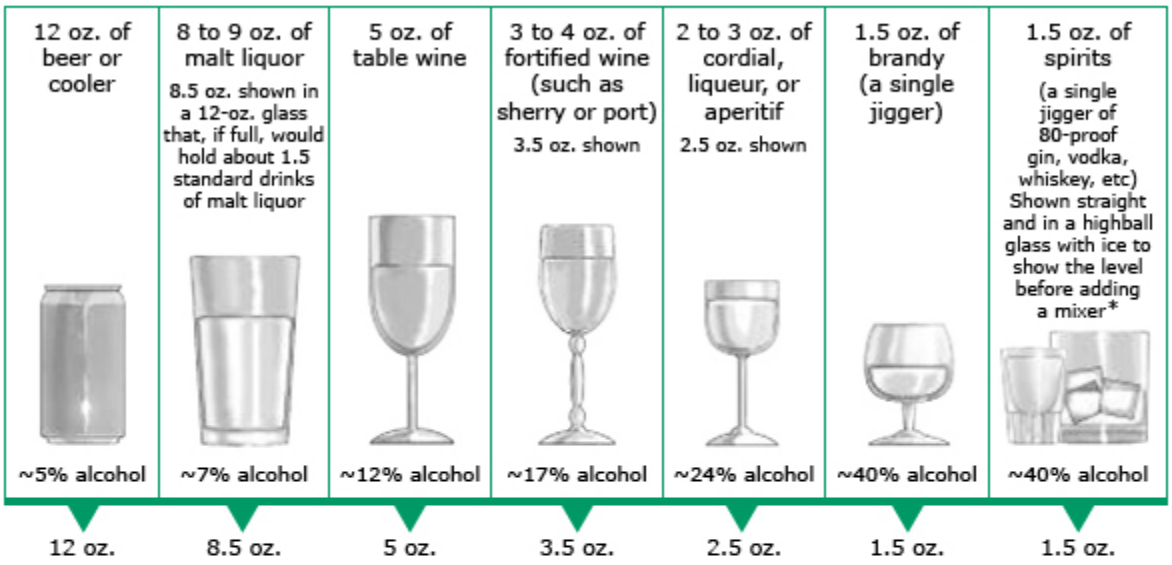
Topic 87052 Version 36.0

GRAPHICS

What is a standard drink?

A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are US standard drink equivalents. These are approximate, since different brands and types of beverages vary in their actual alcohol content.



Many people don't know what counts as a standard drink and so they don't realize how many standard drinks are in the containers in which these drinks are often sold. Some examples:

- For **beer**, the approximate number of standard drinks in:
  - 12 oz. = 1
  - 16 oz. = 1.3
  - 22 oz. = 2
  - 40 oz. = 3.3
- For **malt liquor**, the approximate number of standard drinks in:
  - 12 oz. = 1.5
  - 16 oz. = 2
  - 22 oz. = 2.5
  - 40 oz. = 4.5
- For **table wine**, the approximate number of standard drinks in:
  - a standard 750-mL (25-oz.) bottle = 5
- For **80-proof spirits**, or "hard liquor," the approximate number of standard drinks in:
  - a mixed drink = 1 or more*
  - a pint (16 oz.) = 11
  - a fifth (25 oz.) = 17
  - 1.75 L (59 oz.) = 39

US: United States; oz.: ounces.

* It can be difficult to estimate the number of standard drinks in a single mixed drink made with hard liquor. Depending on factors such as the type of spirits and the recipe, a mixed drink can contain from 1 to 3 or more standard drinks.

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Contributor Disclosures

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