

Practice guidelines

Alcoholic Liver Disease: Proposed Recommendations for the American College of Gastroenterology

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PREAMBLE

Guidelines for clinical practice are intended to suggest preferable approaches to particular medical problems as established by interpretation and collation of scientifically valid research, derived from extensive review of published literature. When data are not available that will withstand objective scrutiny, a recommendation may be made based on a consensus of experts. Guidelines are intended to apply to the clinical situation for all physicians without regard to specialty. Guidelines are intended to be flexible, not necessarily indicating the only acceptable approach, and should be distinguished from standards of care that are inflexible and rarely violated. Given the wide range of choices in any health care problem, the physician should select the course best suited to the individual patient and the clinical situation presented.

These guidelines are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee. These guidelines are also approved by the governing boards of the American Gastroenterological Association and the American Association for the Study of Liver Disease. Expert opinion is solicited from the outset for the document. Guidelines are reviewed in depth by the Committee, with participation from experienced clinicians and others in related fields. The final recommendations are based on the data available at the time of the production of the document and may be updated with pertinent scientific developments at a later time.

Objective: The objective of this work was to develop practice guidelines for the management of alcoholic liver disease. **Method:** A computerized search using the Medline Data Base from 1966–July 1997 was performed with the search headings; alcohol, alcoholic hepatitis, alco-

holic liver disease, liver transplant, diagnosis, epidemiology, human, and English only. All randomized controlled trials, case-control studies, and meta-analyses were read in depth. A manual search was also done using references from each retrieved report, review articles, editorials, postgraduate course syllabi, and textbooks. In the subsequent review, evidence was evaluated using a hierarchical scale with randomized, controlled trials given the most importance. Abstracts presented at national meetings were included only when unique data were obtained from those studies. (Am J Gastroenterol 1998;93:2022–2036. © 1998 by Am. Coll. of Gastroenterology)

INTRODUCTION AND DEFINITION OF THE PROBLEM

Alcoholic liver disease (ALD) is a major health and economic problem in the western world. In 1994, the non-federal hospital charges for all forms of ALD in the United States were over 2.5 billion dollars (1). Of this amount, 1.6 billion was for alcoholic cirrhosis, a disease that is responsible for approximately 44% of the 26,000 deaths from cirrhosis in the United States (2). Recent data indicate that the 5-yr survival rate for alcoholic cirrhosis is between 23% and 50% (3, 4), which is significantly worse than that observed in nonalcoholic cirrhosis (3). In addition, a much discussed, poorly understood, and potentially fatal clinicopathological syndrome of alcoholic hepatitis develops in a minority of patients with ALD. Despite much effort, a consensus regarding specific therapy for ALD is lacking. Conventional therapy is based largely on abstinence as well as general supportive and symptomatic care. Unfortunately, hepatocellular damage may still progress despite these measures (5), and various specific therapies for improving both the short and long term morbidity and mortality of this disease have been proposed.

TABLE 1
Characteristics of Alcoholism

Characteristic	Clinical Feature
Tolerance	A state of adaptation in which increasing amounts of alcohol are needed to produce the desired effects
Physical dependence	A typical withdrawal syndrome appears upon interruption of drinking which is relieved by alcohol itself or other drugs in the alcohol/sedative group
Impaired Control	Total alcohol intake cannot invariably be regulated once drinking has begun at any drinking occasion
Craving	A dysphoria of abstinence that leads to relapse

Almost two thirds of all adult Americans drink some alcohol, the majority of whom drink light or moderate amounts and do so without problems (6). A subgroup are alcohol abusers (or problem drinkers) who experience negative consequences from drinking (such as unemployment, loss of family, or accidental injury/death). However, this group is not dependent on alcohol (7). Another group of drinkers are dependent on alcohol and have the disease of alcoholism, the characteristics of which are provided in Table 1. More formal diagnostic criteria of alcohol use disorders can be found in publications by the American Psychiatric Association (8) and the World Health Organization (9).

Failure to recognize alcoholism (10) as well as an incomplete understanding of the natural course and pathogenesis of alcoholic hepatic injury have made it difficult to develop and to deliver effective therapy. Another problem is the heterogeneity of the patient population with regard to disease severity and individual susceptibility to alcohol-related liver injury. It has been estimated (11), as shown in Figure 1, that although 90–100% of heavy drinkers show evidence of fatty liver, only 10–35% develop alcoholic hepatitis and 8–20% develop cirrhosis.

It is important to emphasize that the signs, symptoms, and severity of liver disease are variable among individuals with ALD and within its different histological stages. For example, the mortality rate in patients hospitalized for alcoholic hepatitis varies between 0 and 100%. In addition, relatively asymptomatic patients may have histologically advanced disease, whereas clinical decompensation carrying a poor prognosis may occur regardless of the histological stage of ALD. This information makes it important to identify those patients who are at risk for developing ALD as well as those who would benefit from specific interventional therapies.

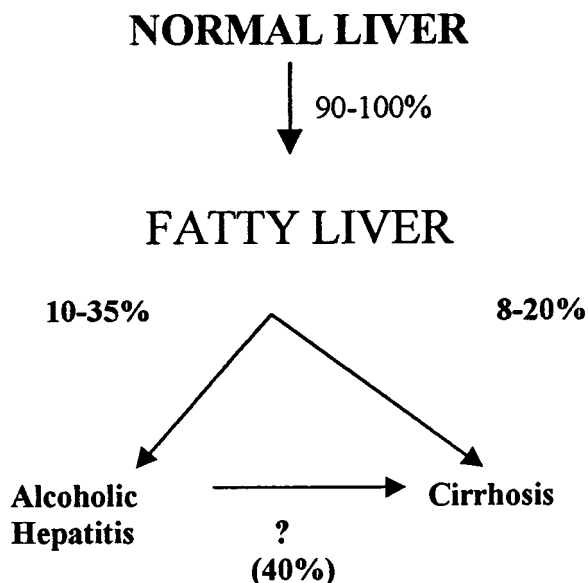


FIG. 1. Progression of alcoholic liver disease in heavy drinkers.

DIAGNOSIS OF ALCOHOLIC LIVER DISEASE

Recommendations

1. All patients should be screened for alcoholic liver disease. A thorough history of alcohol use should be obtained. The CAGE questionnaire is a useful screening method for alcohol abuse or dependency.
2. A detailed physical exam should be done, searching for signs of chronic liver disease and staging its severity.
3. A liver chemistry profile (including serum albumin, bilirubin and transaminases AST/ALT. A complete blood count and prothrombin time or INR should be obtained to support a clinical suspicion of alcoholic liver disease and to assess its severity. However, both laboratory abnormalities and physical findings may be minimal or absent even in patients with established alcoholic liver disease.
4. When evaluating a patient for alcoholic liver disease, the clinician must remember that the toxic daily threshold dose of 80 g of alcohol is not absolute. ALD may develop at much lower doses, especially in female patients and patients with hepatitis C infection.
5. It may be necessary to perform a liver biopsy in patients with suspected alcoholic liver disease when the diagnosis is unclear because of atypical features or possible concomitant disease.

The diagnosis of ALD is often made in the context of a history of significant alcohol intake, physical signs of liver

disease, and supporting laboratory data. However, denial of alcohol abuse is significant and histological abnormalities typically caused by alcohol may be seen in liver biopsies from patients who abstain from alcohol (12). In addition, both the physical findings and laboratory evidence for alcoholic liver disease may be absent or nonspecific, especially in patients with mild alcoholic liver disease or early cirrhosis. Therefore, the clinician may have to rely on indirect evidence of alcohol abuse, such as questionnaires, information from family members, or nonhepatic laboratory tests to suggest or strengthen a clinical suspicion of ALD (13).

The historical features that suggest alcohol abuse or alcohol dependence include the amount of alcohol ingested, the social and psychological consequences of alcohol abuse, the presence of other alcohol-related diseases, and past incidents of trauma (such as frequent falls, lacerations, burns, fractures, or emergency department visits) (14). Several tools have been used to screen different populations of patients for alcohol abuse, but the most commonly used is the CAGE questionnaire, which refers to lifetime occurrence of the following: Cutting down on drinking; Annoyance at others' concerns about drinking; feeling Guilty about drinking; and using alcohol as an Eye opener in the morning. Most authors use a CAGE cut score of 2 or more positive answers, as an indicator of alcohol dependency, which yields a sensitivity of 70–96% and specificity of 91–99% (15, 16). The predictive value will vary according to the prevalence of alcohol abuse in the population under scrutiny (higher in men and hospitalized patients) and it is therefore recommended that individual patient scores be interpreted based on their prior probability for alcohol abuse (15). The CAGE is easily administered by paramedical personnel or can be self-administered by the patient (17). A criticism of the CAGE questionnaire is that although it is reasonably sensitive and specific for those with a dependency syndrome, it may fail to identify those who ingest sufficient alcohol to be at risk for liver damage but do not yet suffer social or psychological consequences of alcohol ingestion, especially in patient subgroups who are at risk for alcohol-related organ damage at lower levels of alcohol ingestion, such as young or pregnant women (18). Despite the reservations of some authors (19, 20), CAGE is the preferred screening tool in patients because of its ease of administration and accuracy, particularly when alcoholic liver disease is suspected. After the CAGE questionnaire (21), a detailed alcohol history should be taken in all patients, especially when there is clinical suspicion for alcohol abuse and in those who are at risk for alcohol-related damage at lower levels of alcohol (22).

Physical examination

Patients with ALD may show a constellation of abnormalities on physical exam that may be related to portal hypertension (ascites, splenomegaly, abdominal wall collat-

TABLE 2
Typical Laboratory Abnormalities in ALD

Serum enzymes
AST >>> ALT
Both usually <300 IU/L
Alkaline phosphatase and γ -glutamyl transpeptidase
Both usually elevated to a variable degree
Metabolic alterations
Hyperglycemia
Hypertriglyceridemia
Hyperuricemia
Electrolyte abnormalities
low potassium, magnesium and phosphorus
Tests of liver function
Serum albumin, prothrombin time, and serum bilirubin usually normal until significant liver injury present
Hematological abnormalities
Mild anemia common (usually macrocytic)
platelets (normal to markedly decreased)
Elevated white blood cell count
Leukemoid reactions associated with alcoholic hepatitis

erals, and a venous hum), alcohol abuse and hepatic injury (cutaneous telangiectasias, palmar erythema, finger clubbing, Dupuytren's contractions, and peripheral neuropathy) and feminization (gynecomastia and hypogonadism). These and other aspects of the physical examination of patients with ALD have been discussed in great detail in recent reviews (23, 24). However, a number of specific issues need to be emphasized.

Although some of these findings are more commonly observed in ALD than in non-ALD (especially those symptoms associated with alcohol abuse and feminization (24–26), no single physical finding or constellation of findings is 100% specific or sensitive for ALD (23). Furthermore, there is significant interobserver variability among observers for most of these physical findings (27, 28), which is dependent on the experience of the examiner and the physical finding being sought. When present, certain findings on physical examination such as ascites, poor nutritional status, and cutaneous telangiectasias (29–31) indicate significant liver injury and poor prognosis. However, even in the absence of significant liver injury the physical findings associated with alcohol abuse may be present and then subsequently improve with abstinence (23). Physical examination of the liver, which may be normal in the presence of ALD, does not provide any accurate information regarding liver volume (23). Its major role remains to define the characteristics of the consistency of the liver's lower edge rather than to delineate disease etiology or liver volume (32).

Therefore, the physical exam is unable either to establish the diagnosis of ALD on its own or to delineate ALD from

non-ALD, and must be considered in the context of the patient's history and laboratory findings.

Laboratory data (Table 2)

Abnormalities typical of all forms of alcoholic liver injury include elevation of aspartate amino transferase (AST), which has a sensitivity of 50% and a specificity of 82% for alcohol consumption >50 g/day and alanine amino transferase (ALT), which is 35% sensitive and 86% specific for alcohol use >50 g/day (33). The most common pattern of enzyme elevation is AST > ALT with neither usually elevated greater than seven times the upper limit of normal (34) unless associated with acetaminophen toxicity (35). The diagnosis of ALD increases as the AST/ALT ratio increases (34). Elevation of gamma glutamyl transferase (GGT) is somewhat more sensitive at 69–73% with a specificity of 65–80% for excessive alcohol consumption (16, 33, 36). Serum albumin and prothrombin time will become abnormal as synthetic function of the liver declines with advancing liver disease (alcoholic hepatitis and alcoholic cirrhosis) or as the nutritional status of the patient worsens. However, it should be emphasized that no laboratory test is specific for ALD.

Several nonhepatic laboratory abnormalities may indirectly raise the possibility of alcoholic liver disease by indicating high alcohol consumption. As a diagnostic tool for alcohol abuse, the mean corpuscular volume (MCV) lacks sensitivity (27–52%) but is reasonably specific (85–91%) for alcohol use >50 g/day (16, 33, 36). Carbohydrate deficient transferrin (CDT) is 58–69% sensitive (33, 36) and 82–92% specific for current or recent alcohol use. In patients with alcohol intake >10 g/day there is a positive correlation between CDT and alcohol intake (33). When clinical suspicion is high, a positive test in the presence of denial of alcohol abuse may be helpful, particularly in young men ingesting >60 g of alcohol daily, when CDT is superior to GGT or MCV in detecting alcohol abuse (36, 37). However, CDT is not widely available to clinicians. In certain settings elevated blood alcohol levels themselves are strongly suggestive of alcoholism; especially levels >0.1 g% in a patient coming for a general examination. In addition, alcoholism is associated with a number of metabolic effects that normalize with abstinence, such as hypertriglyceridemia, hyperuricemia, and increased high-density lipoproteins.

Liver biopsy in alcoholic liver disease

Several reasons are cited to justify a liver biopsy in patients with ALD; namely, to confirm the diagnosis, exclude other unsuspected causes of liver disease, assess the extent of liver damage, define the prognosis, and aid in therapeutic decisions.

Liver biopsy is relatively safe, with an associated morbidity of 0.1–0.6% and a mortality of 0.01–0.03% (38–40). There is also relatively small interobserver variation in the histological interpretation of ALD with greater agreement in

samples containing more than 6 portal tracts (41). However, the practitioner is more adept at diagnosing ALD than other causes of liver disease on clinical grounds alone (42, 43), but it is more difficult to precisely define the type of liver disease in alcoholic patients (44). In a cohort of educated, middle to upper income, military personnel studied by Van Ness (42), the sensitivity and positive predictive value of a clinical diagnosis of ALD were 91% and 88%, respectively. The negative predictive value and the specificity were also excellent at 97% and 96%, respectively (42). In another well performed retrospective series, the prebiopsy diagnosis of ALD was 98% specific and 79% sensitive (45). The prebiopsy clinical diagnosis of ALD was confirmed in all but one patient. This study also found that 2% of patients with clinically suspected ALD alone had concomitant, unsuspected, nonalcoholic liver disease on biopsy, and only 4.6% of patients with a clinical suspicion of nonalcoholic liver disease had histological findings consistent with ALD alone on biopsy. Other data also suggest that a combination of clinical and laboratory data can make an accurate diagnosis of ALD (46, 47). In addition, laboratory indices (Prothrombin time, GGT, and apolipoprotein A1) predict the presence of cirrhosis on biopsy and may substitute when biopsy is not possible (48). On the other hand, data from Levin *et al.* (49) indicate that of 145 “alcoholic” patients, 28% had histological features of nonalcoholic liver disease and 20% of suspected cases of ALD were disproven by biopsy. Therefore, when the clinical diagnosis seems certain, the biopsy is usually confirmatory. Conversely, when there is an uncertain clinical diagnosis, a biopsy will frequently be useful (42, 49). However, many of the studies comparing the accuracy between the clinical diagnosis and liver biopsy for ALD were done before the recognition of hepatitis C. Some workers have ascribed some histological changes of chronic hepatitis to alcohol (38, 50), whereas in fact some of these patients had hepatitis C (51, 52).

Given that therapeutic options in most patients with ALD are limited to cessation of alcohol intake and nutritional supplementation, some investigators are willing to manage patients with some clinical uncertainty (53). The decision to biopsy depends on the strength of the clinical diagnosis and on the willingness of the clinician and the patient to work with a degree of uncertainty. In general, a biopsy should be performed to confirm the diagnosis, to exclude other or concomitant causes, and to define the prognosis. If the clinical and laboratory data are typical, however, biopsy is not mandatory. If the diagnosis is unclear, if there are atypical features, or if accurate prognosis is essential, a biopsy is indicated. This is especially true for those ALD patients with abnormal serum iron markers to rule out hemochromatosis (54). Some clinicians may also wish to establish the histological findings of perivenular fibrosis, giant mitochondria, or the type of fat accumulation (mixed macro/microvesicular) that prognosticates the development of cirrhosis (55, 56) and, in turn, survival. The clinician suspecting concomitant alcoholic liver disease and hepatitis C may

TABLE 3
Alcohol Content of Beverages

Type	% Ethanol (g/100 ml)	Dose (oz)	Ethanol (g)*	No. of Drinks/day Toxic Threshold	
				Initial† (Men/Women)	Revised‡ (Men/Women)
"Spirits"	43	1	10.3	7/5	4/1-2
Wine	12	4	11.5	7/5	4/1-2
Beer	4	12	11.5	7/5	4/1-2

* Calculations based on: a specific unit of alcohol \cong 0.80, 1 oz = 30 ml.

† Initial toxic threshold for men = 80 g; for women = 60 g.

‡ Revised toxic threshold for men = 40 g; for women = 10–20 g. These revised results were obtained from Ref. 73.

want to know which disease is histologically most prominent. Liver biopsy will help differentiate (57, 58), though there are only limited data on the outcome of these patients treated with antiviral therapy.

Patients with alcoholic hepatitis and a discriminant function >32 calculated from the equation $[(4.6 \times \text{prothrombin time above control in seconds}) + \text{serum bilirubin}]$ have a poor prognosis and will benefit from steroid treatment (59). Given the severity of illness combined with the potential side effects of steroid treatment, there is a strong case for liver biopsy in these patients to confirm the diagnosis of alcoholic hepatitis (60) before steroid treatment, although the probable benefit of this approach (i.e. performing a liver biopsy to confirm the diagnosis prior to steroid treatment) has not been confirmed by randomized trials. There is also evidence that certain liver biopsy findings predict response to steroids (61) or may identify a subgroup of patients with a milder form of disease (62). Biopsy in the setting of severe alcoholic hepatitis may be hazardous and is generally done by the transjugular route or plug technique (63, 64). If these latter biopsy techniques are not available, the need for a liver biopsy in this situation must be made on an individual case basis.

Risk factors

The quantity of alcohol ingested (independent from the form in which it is ingested) is the single most important risk factor for the development of ALD. A significant correlation exists between *per capita* consumption and the prevalence of cirrhosis (11, 65). Epidemiological data have shown a marked decrease in ALD with diminished alcohol ingestion during war rationing (66), prohibition (11, 67), and increased cost (11, 67, 68).

Based on epidemiology data, a threshold of 80 g of alcohol taken daily on average for 10–12 yr had been considered necessary for alcohol mediated injury to develop (11, 67). Disagreement exists, however, regarding whether the amount of alcohol ingested increases the risk of alcohol liver disease proportionally (69, 70).

It remains unclear why only a minority of individuals ingesting hazardous amounts of alcohol develop ALD (71). One factor appears to be gender. Women develop ALD

more quickly and at lower doses than men do. As compared with men, early data suggested the hazardous level to be 60 g daily (67). On a practical level, one unit of alcohol (1 ounce of "spirits", 1 12-oz beer, or one 4-oz glass of wine) contains 10–12 g of alcohol. Table 3 provides the alcohol content and toxic threshold for different types of alcohol. Since the majority of those individuals developing ALD ingested >35 units/wk (11, 66, 67), a "safe" limit of alcohol intake has been suggested to be 21 units/wk in men and 14 units/wk in women (72). However, more recent data from Copenhagen indicate that a lower number of weekly units may be toxic (73).

Dietary habits and nutritional status may also be important. The incidence of cirrhosis appears to be lower than expected in countries with high intakes of saturated fat (74), an epidemiologic finding that is supported by animal data (75, 76). Preliminary data from France (77) also suggest that obesity may be an independent risk factor for developing ALD. In addition to having a role in alcoholism (78, 79), genetics may also be involved in ALD (80). However, despite much investigation (80), the specific genetic abnormalities involved in this susceptibility have not been elucidated.

Finally, there is a strong association between hepatitis C and ALD. Unlike hepatitis B (81), hepatitis C (HCV) infection appears to be significantly involved in the development of advanced ALD. Serological surveys (82) have found an increased prevalence of HCV in patients with ALD as diagnosed by enzyme immunoassays (25–65%), by recombinant immunoblot assays (14–79%) and by HCV RNA tests (10–40%). There are several pieces of information that indicate that the combination of HCV plus alcohol predisposes to more advanced liver injury than alcohol alone. As compared to ALD patients without HCV infection, those ALD patients with HCV infection have more severe histological features (83), have decreased survival (81), and develop their disease at a younger age (84). The prevalence of HCV also increases proportionally as the liver injury becomes more severe (85–88) with the relative risk for developing cirrhosis estimated at 8.7 in those ALD patients with anti-HCV as compared with those ALD patients without HCV (89). In addition, the presence of HCV is reported to be the major risk factor for the development of hepatocellular cancer (HCC) in patients with alcoholic cirrhosis (90), with a 10-yr absolute cumulative occurrence risk of HCC being reported as high as 81% in anti-HCV-positive alcoholic cirrhotics as compared with 19% in anti-HCV-negative patients (91).

Although HCV infection appears to be an important factor contributing to the severity of ALD, HCV is present in the minority of noncirrhotic ALD patients (86–88) and HCV viremia (HCV RNA) should be confirmed if antibodies to HCV are present. It may also be necessary to perform a liver biopsy to separate HCV-induced liver disease from alcoholic-induced liver disease in an alcoholic patient with superimposed HCV infection. A liver biopsy should be

TABLE 4
Pharmacological Therapies Tested in Alcoholic Liver Disease

Therapeutic Agent	No. of Trials	No. of Patients	No. of Trials Favoring Therapy Significant	Trend
Long-term therapy in alcoholic liver disease				
PTU	1	310	1	0
Colchicine	1	45	1	0
Short term therapy in alcoholic hepatitis				
Corticosteroids	12	749	5	
Amino acid supplements	8	291	2	4
Insulin/glucagon (intravenous)	4 (+ 1 abstract)	307	1	2
PTU	2	105	0	1
Anabolic Steroids,				
Testosterone	2	140	0	0
Oxandrolone	2	173	1	1
Colchicine	1	72	0	0

performed in those patients who have biochemical findings suggestive of iron overload (total iron binding capacity-TIBC saturation >62% in male and >50% in female patients) to rule out hereditary hemochromatosis by calculating the hepatic iron index (92), especially because both HCV infection (93) and ALD (54, 94) can each individually cause biochemical abnormalities suggestive of hereditary hemochromatosis. With the recent discovery of HLA-H (the abnormal gene in the majority of patients with hemochromatosis (95), the measurement of this gene (when commercially available) also may be useful for evaluating abnormal biochemical tests (serum iron, TIBC, ferritin) that suggest iron overload in ALD (96).

Therapy of alcoholic liver disease

It is important that clinicians consider the continuous and ongoing long term management of ALD in addition to treatment of the acute symptomatic episodes of alcoholic hepatitis. The pharmacological therapies for ALD that have been studied in controlled trials are provided in Table 4.

LONG TERM MANAGEMENT

Recommendations

6. *The importance of abstinence needs to be continually emphasized in the long term management of alcoholic liver disease.*
7. *The patient with alcoholic liver disease should be kept well nourished, and nutritional supplements are indicated if dietary intake is insufficient. The routine use of specialized formulations are not indicated at the present time unless standard formulations cannot be tolerated at amounts necessary to achieve nutritional requirements. The patient should be encouraged to take a nighttime snack.*

8. *During hospitalizations for acute decompensation of alcoholic liver disease, aggressive nutritional therapy should be instituted to ensure that the patient's nutritional requirements are being provided. Nutritional supplementation (either enterally or parenterally) may be necessary to achieve this.*
9. *Complications of cirrhosis (such as portal hypertension, esophageal varices, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatocellular carcinoma) that arise in patients with alcoholic liver disease should be sought and treated as done for any other type of cirrhosis.*
10. *Patients with end stage alcoholic liver disease should be considered for liver transplantation. Six months of abstinence is usually required before transplant, but this length of time may be adjusted on an individual case basis. Candidates for liver transplantation should participate in alcohol counseling, and families of these patients should participate in family therapy. In addition to the standard evaluation before liver transplantation, alcoholic patients need to be evaluated for specific alcoholic-induced disease, comorbid disease (such as pancreatitis and cardiomyopathy), and the risk of recidivism.*

Prognosis

A number of poor prognostic factors in ALD have been identified, which include the development of cirrhosis, ascites, portal hypertension (especially with esophageal variceal bleeding), hepatic encephalopathy, hepatorenal syndrome, coagulopathy, severe hyperbilirubinemia, and age (97). In contrast, alcoholic patients with fatty liver alone usually have nonprogressive disease that improves with abstinence (55, 98) unless associated with perivenular fibrosis, giant mitochondria, and a mixed macro/micro vesicular type of fat (55, 56). Hepatic inflammation and abstinence from alcohol appear to be the two most important prognostic factors and are indirectly related.

Hepatic inflammation

The presence of hepatic inflammation appears to be the single most important prognostic histological factor. In a study of 217 patients (140 cirrhotics and 77 noncirrhotics) with biopsy-proven ALD (99), the presence of alcoholic hepatitis indicated a poor prognosis. Patients with cirrhosis and hepatitis had increased 1- and 5-year mortality rates of 27% and 47%. This contrasts with cirrhotic patients without hepatitis, who had a survival rate similar to patients with no cirrhosis or hepatitis. These data have been indirectly confirmed by recent study (61), which found the presence of polymorphonuclear cells on liver biopsy to be a prognostic factor for both 1-month and 1-yr survival.

The decision to use antiviral therapy in those ALD pa-

tients with HCV infection is a difficult one and should be determined on an individual case basis. Because the limited data available (100, 101) indicate that active drinking will reduce the efficacy of interferon therapy for HCV infection, the potential use of interferon or other antiviral agents cannot generally be recommended at the present time for patients with ALD who continue to drink alcohol. However, the potential efficacy of antiviral therapy may be improved by abstinence and therefore the potential for HCV therapy may be a motivational factor (100).

Abstinence

Almost all authorities agree that abstinence from alcohol is the cornerstone in the long term management of patients with alcoholic liver disease (5, 102–104). However, it is difficult to confirm abstinence, and some authors have found that lack of abstinence did not affect survival in patients who ingested minimal amounts of alcohol or in patients who had not developed complications of liver disease (102, 105, 106). Despite these latter studies, the inability to demonstrate that certain subgroups of patients can benefit from abstinence is a moot issue, as it is unlikely that any benefit can be obtained from continued alcohol use in these patients. Consequently, abstinence should be emphasized early and continuously to optimize its beneficial effects.

Nutritional therapy

Protein calorie malnutrition is a common finding in ALD that is associated with major complications observed in cirrhosis (infection, encephalopathy, and ascites) and indicates a poor prognosis (107–110). However, only recently have data been presented that showed nutritional therapy to be efficacious.

In short term studies, Cabre *et al.* (111) and Kearns *et al.* (112) demonstrated that enteral feeding for 3–4 wk in hospitalized, severely malnourished or decompensated cirrhotic patients improved survival ($p < 0.065$), hepatic encephalopathy, liver function, and Child's score (which is a composite grading of severity based on abnormalities in albumin, bilirubin, prothrombin time, encephalopathy, and ascites) as compared with controls receiving a standard oral diet. In another short term study (113), nutritional support after liver transplantation produced better nitrogen balance, significantly shortened time spent in the intensive care unit, and quantitatively decreased hospital cost and length of stay.

In long term studies, Marchesini and coworkers (114) compared equinutrogenous amounts of dietary branched chain amino acids (BCAA) *versus* casein supplements (standardized for equal amounts of nitrogen) in patients with chronic hepatic encephalopathy for 3–6 months. BCAA significantly improved encephalopathy, nitrogen balance, and serum bilirubin compared with casein. Hirsch *et al.* (115) supplemented 34 g of protein and 1000 kilocalories to a regular diet in decompensated alcoholic cirrhotics and reduced hospitalizations for infections. These studies are

TABLE 5
Guidelines for Daily Dietary Feeding in ALD*

-
- Protein = 1.0–1.5 kg BW[†]
 - Total Calories = 1.2–1.4 × REE[‡] with a minimum of 30 kcal/kg BW
50–55% as carbohydrate (preferably as complex carbohydrates)
30–35% as fat; preferably high in unsaturated fat and with adequate essential fatty acids
 - Nutrition should be given enterally by voluntary oral intake and/or by small-bore feeding tube; PPN[§] is second choice; TPN[¶] is last choice.
 - Salt and water intake should be adjusted for patient's fluid volume and electrolyte status.
 - Liberal multivitamins and minerals.
 - Specialized BCAA^{||} enriched supplements not usually necessary
Most patients tolerate standard AA supplements
Reserve BCAA formulations for patients who cannot tolerate the necessary amount of standard AA (which maintain nitrogen balance) without precipitating encephalopathy
Avoid supplements providing only BCAA; they do not maintain nitrogen balance
- Conditionally essential AA as well as all essential AA are needed
Conditionally essential AA are those that normally can be synthesized from other precursors, but that cannot be synthesized in cirrhotic patients. These include choline, cystine, taurine, and tyrosine.
-

* = modified from reference 110.

† BW = body weight.

‡ REE = resting energy expenditure.

§ PPN = peripheral parenteral nutrition.

¶ TPN = total parenteral nutrition.

|| BCAA = branched chain amino acids.

AA = amino acids.

important because they emphasize the concept that patient selection and long term therapy (116) may be important factors for employing and demonstrating the benefits of nutritional therapy. Because standard nutritional supplements are effective and the cost of BCAA is high, the use of BCAA-enriched formulations should be restricted to patients who cannot tolerate nutritionally required amounts of standard formulations.

Changes in the dietary feeding patterns may also be beneficial. After an overnight fast, cirrhotics obtain >70% of nonprotein calories from fat as compared with 40% in normal volunteers (107). Therefore, patients with cirrhosis have early recruitment of alternative fuels and have metabolic profiles similar to those observed with prolonged fasting. Consequently it has been demonstrated that patients with cirrhosis should not be allowed to starve for extended periods of time and require frequent interval feedings emphasizing a night time snack (117, 118) and a morning feeding (119) that improve nitrogen balance.

It now seems clear that long term, aggressive nutritional therapy is necessary and reasonable in these patients. General goals and practical points for nutritional therapy in chronic liver disease (Table 5) have been suggested recently (110, 120, 121), but three additional points need to be emphasized. First, nutritional assessment should be an ongoing process, but may be difficult. Recent guidelines discuss the methods and limitations of performing nutritional assessment in patients with ALD (121). Second, multiple

feedings emphasizing breakfast and a nighttime snack (117–119) with a regular oral diet at higher than usual dietary intakes (1.2–1.5 g/kg for protein and 35–40 kcal/kg for energy) appear to be indicated (120–123). Third, during intermittent acute illness or exacerbations of the underlying chronic liver disease, above normal protein and energy (1.5–2 g and 40–45 kilocalories per kg of body weight, respectively) improve protein calorie malnutrition (120, 121, 124).

Propylthiouracil (PTU)

The available human data (125–129) indicate that alcohol increases hepatic oxygen consumption, which decreases with abstinence and correlates with histologically advanced liver disease and hepatocellular necrosis. Because PTU decreases cellular metabolism and oxygen consumption, there is an adequate rationale for the use of PTU in patients with ALD.

There has been only one trial investigating the long term use of PTU in alcoholic liver disease (130). In a double blind, randomized, controlled trial involving 360 patients with ALD for 2 yr, PTU at a dose of 150 mg *b.i.d.* reduced the mortality rate from 25% in the placebo group to 13% in the PTU group. This beneficial effect was limited to those patients with severe disease. Furthermore, patients who continued moderate but not heavy alcohol consumption benefited most from PTU therapy.

Initially, there were statistical concerns regarding the validity of this study. However, these concerns have recently been addressed (131). Because PTU is not beneficial in heavy drinkers and hypermetabolism is not increased in totally abstinent alcoholics, the beneficial effect of PTU may be limited to only those patients who continue to drink moderate amounts of alcohol. Although at the present time the available data do not allow a recommendation for the widespread use of PTU outside of controlled clinical trials, its beneficial effects in the only controlled study published to date and the relative safety of this drug allow the clinician to consider its usage on a case by case basis.

Colchicine

Colchicine inhibits collagen production, enhances hepatic collagenase activity, and interferes with collagen's transcellular movement. Furthermore it may inhibit cytokine production, inflammation, and associated fibroblast proliferation. Because of these properties, long term colchicine use has been studied in one trial (132) of patients with cirrhosis (45% in whom alcohol was the etiology). In this double blind, randomized, placebo-controlled trial from Mexico City, 100 cirrhotic patients were followed for ≤ 14 yr. The median survival rate was improved from 3.5 yr in the placebo group to 11 yr in the colchicine group. Despite these encouraging results, these data do not justify the routine use of colchicine in ALD at the present time. Approximately 20% of the patients were lost to follow-up, patient compliance was not stated, and deaths related to liver failure did

not differ significantly between groups. Furthermore, this study did not provide insight into the effect of continued alcohol use and hepatic inflammation on the therapeutic effects of colchicine. Finally, the effect of colchicine was not observed until after 30 months of therapy. In another study, the effect of colchicine was shown to be of no benefit in alcoholic hepatitis (133). Based on these considerations, the efficacy of colchicine in ALD remains uncertain and must await further clinical trials.

Liver transplantation

Liver transplantation has evolved into an effective therapeutic modality for end stage ALD (134, 135) and now accounts for approximately 20% of the indications for liver transplantation in the United States (136). The clinical outcome of these patients after a liver transplant is excellent and comparable to that of patients transplanted for other diseases (136–143). When compared with a nontransplanted control group treated conservatively, 2-yr survival in a study of 169 alcoholic patients was 73% in the transplanted patients *versus* 67% in the matched and simulated control groups (144). Using the Beclere proportional hazards model (which includes bilirubin, albumin, patient age, and encephalopathy) for grading disease severity, patients with severe disease benefited the most, with a 2-yr survival of 64% *vs* 41% in the matched and 23% in a simulated control group. Patients with alcoholic cirrhosis who were at low or medium risk (graded by the Beclere model) did not benefit from transplant (144).

The quality of life of these patients after transplantation is also excellent. It compares favorably with that observed in patients transplanted for non-ALD and is similar to that expected in the general population (142). However, a recent study suggests that the quality of life may diminish slightly after 3 yr in these patients (143). A high rate of abstinence from alcohol has been observed in these patients after transplantation, with recidivism rates varying between 11% and 33% (137–141, 145–149). However, recent data suggest that recidivism rates may increase with longer follow-up (146), increasing from 15% at 1 yr to 31% at 3 yr posttransplant. Some studies have found that the rate of recidivism may be related to the duration of abstinence before liver transplantation (137, 138, 141, 147), but this remains controversial (142, 150). It should be emphasized that it is difficult to accurately diagnose alcohol consumption and that patients who have been transplanted for nonalcoholic liver disease have shown rates of alcohol use ranging from 24% to 46% (145, 147, 148). Therefore, some authors believe that “recidivism” after transplant should be defined as abusive drinking that occurs only in a subset of patients (142, 151), rather than the use of any alcohol at all (152). The Diagnostic Interview Schedule (DIS-IV-R), which is based on the Diagnostic and Statistical Manual of Mental Disorders Revised Fourth Edition (DSM-IV-R), is usually used to screen in detail for alcoholism and alcohol dependence before transplantation. At the present time, most centers

(135, 153) are accepting patients with alcoholic liver disease for liver transplantation, based on criteria that are similar to those for other forms of cirrhosis. Additionally, patients with ALD must be screened for alcohol related comorbid diseases (154), are required to actively participate in a rehabilitation program, and have a 6-month period of confirmed abstinence (although the use of any specific time period is controversial). Therefore, patients with acute alcoholic hepatitis are usually not considered for transplantation until they recover from the acute illness and can demonstrate rehabilitation and sustained abstinence.

ALCOHOLIC HEPATITIS

Recommendations

11. *Corticosteroids should be used in patients with severe alcoholic hepatitis in whom the diagnosis is certain. Severity is defined as a discriminant function [$4.6 \times (\text{prothrombin time above control in seconds}) + \text{bilirubin}$] >32 and/or hepatic encephalopathy. The efficacy of steroids has not been adequately evaluated in patients with severe alcoholic hepatitis who also have concomitant pancreatitis, gastrointestinal bleeding, renal failure, and active infection.*
12. *Histological confirmation of alcoholic hepatitis optimizes the selection of those patients being considered for corticosteroid therapy. However, if the risk of performing liver biopsy is considered too great, the diagnosis can usually be made reliably by clinical and laboratory evaluation in the majority of patients.*
13. *Although amino acid supplementation has not been demonstrated to improve survival in hospitalized patients with alcoholic hepatitis, protein feeding is well tolerated in patients with alcoholic hepatitis, and pre-existing protein calorie malnutrition should be corrected and current nutritional needs supplied aggressively.*

Prognosis

The mortality rate of hospitalized patients with alcoholic hepatitis varies greatly. It is now generally agreed that patients with mild disease need not be treated beyond general supportive and symptomatic care. Patients with severe disease *in extremis* may be too ill to respond to any form of therapy. Therefore, it is important to identify patients who might benefit from aggressive intervention as well as to identify patients in whom the therapeutic benefit/risk ratio is unfavorable.

There have been three formulas that have been used to calculate the severity of alcoholic hepatitis: 1) the Child's-Pugh Class, which is usually used to stage the severity of cirrhosis (155); 2) the combined clinical laboratory index of the University of Toronto (156); and 3) the discriminant

function of prothrombin time and bilirubin (157). One analysis applied these three indexes to a Veteran's Administration cooperative alcoholic hepatitis study and evaluated their ability to predict 30-day mortality (158). All three correlated with survival, but the least complex prothrombin time/bilirubin discriminant function had the best correlation and the highest positive predictive value among the three. Furthermore, the prognostic value of the modified discriminant function has been prospectively confirmed and, at the present time, this discriminant function appears to be the most clinically helpful for therapeutic decisions when severity of illness determines treatment.

Therapeutic agents

As shown in Table 4, there have been a number of therapeutic agents that have undergone clinical testing for alcoholic hepatitis. Although all of these therapies will be discussed, only corticosteroids and supplemental amino acids have clearly shown benefit.

Corticosteroids

Corticosteroids have been the most extensively studied treatment modality, but their use in certain patient subsets remains controversial. There have been 12 randomized, controlled clinical trials; five of these trials showed that corticosteroids reduced mortality (159–163), whereas seven others showed no difference (164–170). In view of these conflicting results and the fact that disease severity varied among the different studies, three meta-analyses of these randomized trials were performed to determine whether corticosteroids affect short term mortality in alcoholic hepatitis. Two of the meta-analyses (59, 171) showed a beneficial effect of corticosteroids, whereas one (172) showed no difference. However, this latter meta-analysis, rather than excluding a treatment effect of corticosteroids, points out the inadequacies of the published studies in characterizing patients with severe disease who might respond to glucocorticoids. This latter point is emphasized by the fact that the three most recent studies (61, 162, 163), which stratified patients according to disease severity as defined by the prothrombin time and bilirubin discriminant function, all showed significant benefit in terms of 30-day hospital survival in patients with severe alcoholic hepatitis. In addition, the study by Mathurin *et al.* (61) showed that steroids improved the survival at 1 yr but not at 2 yr in these patients. In addition to the discriminant function criteria, one of the meta-analyses (59) identified that corticosteroids provided a protective efficacy of 27% in subjects with hepatic encephalopathy but had no protective efficacy in patients without hepatic encephalopathy. These observations were consistent across all trial groups. It should be emphasized that many of the studies excluded patients with active gastrointestinal bleeding, active infection, renal failure, and pancreatitis. Therefore, the efficacy of corticosteroids in severe alcoholic hepatitis with these complications has not been well studied.

These combined data provide a number of tangible sug-

gestions for the management of these patients. First, only patients with severe disease (as defined by the presence of hepatic encephalopathy or the prothrombin time/bilirubin discriminant function) should be treated with corticosteroids. Second, although such treatment reduces the mortality risk by 25%, there is still up to a 44% mortality in patients receiving corticosteroids. Therefore, other therapies or a combination of therapies need to be investigated. Third, approximately seven patients need to be treated to avoid one death. This latter point emphasizes the importance of careful selection to avoid the side effects of corticosteroids in the other six patients who will derive no clinical benefit from corticosteroids. In general, this means excluding patients with active infection and being certain of the diagnosis (liver biopsy may be necessary), as histologically confirmed alcoholic hepatitis correlates poorly with the clinical suggestion of alcoholic hepatitis (60, 61, 173). Up to 28% of patients with a clinical picture of alcoholic hepatitis do not have histological features of alcoholic hepatitis on liver biopsy. Fourth, based on pharmacological considerations (prednisone is converted to its active form, prednisolone, in the liver) rather than published data (174), prednisolone (40 mg daily \times 4 wk, followed by a taper) should be used in favor of prednisone.

Nutrition

The rationale for nutritional therapy has been discussed in the long term management section. In the largest and most definitive single trial to date, the VA cooperative study found a 100% prevalence of protein calorie malnutrition in patients with alcoholic hepatitis, the severity of which correlated with the degree of liver dysfunction (175). Furthermore, a composite analysis of protein calorie malnutrition correlated with both short and long term mortality, clinical severity of liver disease, and biochemical hepatic dysfunction. Improved nutritional status also correlated with greater food intake and improved survival. In addition, an uncontrolled trial (176) showed that enteral feeding in patients with alcoholic hepatitis improved intestinal absorption and function with resultant improved nitrogen balance.

There have been eight published controlled trials on the use of standard intravenous amino acid formulations as primary therapy for alcoholic hepatitis (177–184). The results are conflicting (110), but six of the eight studies (177–182), showed improvement in histology and/or liver function. Two of the studies concluded that supplemental amino acids were of no benefit (183, 184). However, in contrast to the first published article using this therapy (182), improvement in survival has not been clearly established. The aggregate mortality of the combined studies showed a 17% mortality in the controlled groups and a 9.6% mortality in the treatment groups. This is not significantly different, but sample size considerations cannot reliably exclude a type II statistical error. The need for larger prospective studies has also been emphasized (185, 186). Furthermore, in one of the negative studies, there was a pro-

portion of patients with inactive cirrhosis (183) rather than alcoholic hepatitis, and nutritional supplementation was not always achieved in the treatment groups. In the other negative study, the mortality was 3.3% in 30 patients in whom positive nitrogen balance was achieved, but 58% in those who remained in negative nitrogen balance (184). These combined data indicate that protein feeding is well tolerated and that there is no reason to routinely restrict protein in patients with alcoholic hepatitis. Furthermore, the benefit of achieving positive nitrogen balance as well as improving liver function emphasizes the fact that nutritional support is helpful, but which type of support is most cost-effective still remains in question. If encephalopathy should worsen with protein feeding, branched chain amino acids may be indicated, as they are better tolerated in patients with protein intolerance (187, 188). The general nutritional axiom that enteral feeding is preferred over intravenous feeding also pertains to patients with ALD.

Other manipulations have also been attempted to improve nutritional status. In a VA cooperative study, 30 days of oxandrolone therapy was compared with prednisolone or placebo in patients with moderate or severe alcoholic hepatitis (164). Although short term survival did not differ between the groups, when dietary intake was analyzed retrospectively, oxandrolone had a beneficial effect on long term survival, but only in patients who ingested significant calories (189). However, because of its potential hepatotoxicity and nonuniform efficacy in these patients, the use of oxandrolone cannot be recommended until more data are available.

Hepatic regeneration therapy

The importance of hormonal control on hepatic regeneration has been extensively studied and scientifically confirmed in animal experiments (190). There have been five published trials: four papers (191–194) and an abstract (195) in this area. Three trials reported significant differences or a trend for improved survival (191, 192, 195) in favor of insulin and glucagon therapy, whereas two (193, 194) showed no benefit with 3 wk of treatment using daily 12-h infusions of insulin and glucagon. The combined aggregate mortality for these trials was 25.2% in the treatment group and 37.5% in the placebo group. This apparent lack of efficacy and the two hypoglycemic deaths have diminished enthusiasm for this approach.

The only other regenerative agent used in a clinical trial has been malotilate, which has been shown in animal experiments to be protective against ethanol-inhibited hepatocyte regeneration (196). Using this agent, a multicenter European trial showed that malotilate improved survival in a non-dose-dependent fashion (197). These initial results, as well as the fact that stimulation of liver regeneration should be beneficial, warrants further studies in this area. However, alterations at the receptor level on hepatocytes may be a major limiting factor for the use of growth factors, and the beneficial affects of insulin may be best observed in

combination with amino acids (198) or other agents (192). At the present time, these therapies should be limited to controlled trials.

Propylthiouracil (PTU)

The rationale for the use of PTU in ALD has already been discussed. There have been only two randomized, controlled, double blind studies investigating short term PTU and alcoholic hepatitis (199, 200). In a study from the University of Toronto (199), PTU (at a dose of 75 mg every 6 hr for up to 6 wk) produced a more rapid rate of normalization of the composite clinical laboratory index in patients with biopsy-proven alcoholic hepatitis. However, no difference in mortality was observed between the placebo and PTU groups. The benefit of PTU therapy was observed only in the alcoholic hepatitis patients and not in those patients with either fatty liver or cirrhosis without inflammation. In the other trial from the University of Southern California, PTU had no significant effect regarding mortality or laboratory tests in patients with severe alcoholic hepatitis (200). The reason for the disparity in the results between the two studies is unclear. However, the fact that hepatic oxygen consumption remains elevated for a relatively short period of time (10–14 days) after abstinence may have therapeutic implications, as the negative trial from the University of Southern California instituted the PTU therapy at a later time after hospitalization as compared with the University of Toronto study. In addition, neither study categorized the patients into those with normal or decreased T₃ levels; a factor that has shown to influence the response to PTU (201). Until further information is obtained, PTU should be considered as an experimental drug for alcoholic hepatitis and not be used routinely at this time.

Follow-up of alcoholic hepatitis

In a small series from Atlanta (202), serial biopsies were performed in 61 patients with alcoholic hepatitis but without fibrosis on liver biopsy. If alcohol use continued, 38% of patients progressed to cirrhosis, with alcoholic hepatitis persisting in the remainder. No nonabstinent patient normalized their histology. However, abstinence from alcohol did not guarantee complete recovery. Only 27% of abstaining patients had histological normalization, whereas 18% progressed to cirrhosis. The remaining abstainers had persistent alcoholic hepatitis when followed for up to 14 months. These findings indicate that the histological lesion of alcoholic hepatitis resolves slowly and in a fashion that is related to, but not totally dependent on, continued alcohol consumption.

SUMMARY AND CONCLUSIONS

ALD is a common illness that develops only in a subgroup of persons who chronically use or abuse alcohol. The hepatotoxic dose of alcohol is nonuniform and is dependent on incompletely understood risk factors that include gender,

hepatitis C, malnutrition, and possibly genetic inheritance. These factors, in addition to a variable natural history and vaguely defined epidemiology and pathophysiology, can make ALD difficult to diagnose and frustrating to manage.

The management of the complications of chronic liver disease (ascites, portal hypertension-associated bleeding, encephalopathy, and hepatocellular complications) is similar in alcoholic and nonalcoholic liver disease. However, abstinence remains the cornerstone of therapy for ALD. There is also consensus for the use of corticosteroids in severe alcoholic hepatitis, for maintaining good nutritional status in all forms of ALD, and for liver transplantation in carefully selected patients with ALD. No other therapies can be recommended at the present time, although many potentially effective treatments are being investigated currently.

Because of the paucity of effective therapies, the persistently high *per capita* consumption of alcohol, and the inability of affected individuals to abstain, ALD will remain a highly prevalent and costly form of chronic liver disease.

Understanding the pathophysiology of ALD and the interactive role of other cofactors in causing hepatotoxicity needs to remain a major focus of alcohol research. Other unresolved issues important for managing ALD must also be addressed. These include cost-effectiveness (203), resource use (204), certain ethical considerations (205), and social bias (206). The current guidelines hopefully will provide a useful framework for clinicians until these issues are resolved and more effective therapies are forthcoming.

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