

## Alcoholic Liver Disease

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This guideline has been approved by the American Association for the Study of Liver Diseases (AASLD) and the American College of Gastroenterology and represents the position of both associations.

### Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic (Medline search); (2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines<sup>1</sup>; (3) guideline policies, including the AASLD Policy on the development and use of Practice Guidelines and the American Gastroenterological Association Policy Statement on Guidelines<sup>2</sup>; and (4) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information. To more fully characterize the quality of evidence supporting recommendations, the Practice Guideline

Committee of the AASLD requires a Class (reflecting benefit versus risk) and Level (assessing strength or certainty) of Evidence to be assigned and reported with each recommendation (Table 1, adapted from the American College of Cardiology and the American Heart Association Practice Guidelines).<sup>3,4</sup>

### I. Prevalence and Natural History

Alcoholic liver disease (ALD) encompasses a spectrum of injury, ranging from simple steatosis to frank cirrhosis. It may well represent the oldest form of liver injury known to humankind. Evidence suggests that fermented beverages existed at least as early as the Neolithic period (circa 10,000 B.C.),<sup>5</sup> and liver disease related to it almost as long. Alcohol remains a major cause of liver disease worldwide. It is common for patients with ALD to share risk factors for simultaneous injury from other liver insults (e.g., coexisting nonalcoholic fatty liver disease, or chronic viral hepatitis). Many of the natural history studies of ALD, and even treatment trials, were performed before these other liver diseases were recognized, or specific testing was possible. Thus, the individual effect of alcohol in some of these studies may have been confounded by the presence of these additional injuries. Despite this limitation, the data regarding ALD are robust enough to draw conclusions about the pathophysiology of this disease. Possible factors that affect the development of liver injury include the dose, duration, and type of alcohol consumption; drinking patterns; sex; ethnicity; and associated risk factors including obesity, iron overload, concomitant infection with viral hepatitis, and genetic factors.

Geographic variability exists in the patterns of alcohol intake throughout the world.<sup>6</sup> Approximately two-thirds of adult Americans drink some alcohol.<sup>7</sup> The majority drink small or moderate amounts and do so without evidence of clinical disease.<sup>8-10</sup> A subgroup of drinkers, however, drink excessively, develop physical tolerance and withdrawal, and are diagnosed with alcohol dependence.<sup>11</sup> A second subset, alcohol abusers and problem drinkers, are those who engage in harmful use of alcohol, defined by the development of negative social and health consequences of drinking (e.g., unemployment, loss of family, organ damage, accidental injury, or death).<sup>12</sup> Fail-

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; AH, alcoholic hepatitis; ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUDIT, Alcohol Use Disorders Identification Test; GAHS, Glasgow Alcoholic Hepatitis Score; GGT, gamma glutamyl transpeptidase; MDF, Maddrey discriminant function; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; PTU, propylthiouracil; SAMe, S-adenosyl L-methionine; TNF, tumor necrosis factor.

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Received August 21, 2009; accepted August 21, 2009.

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Published online in Wiley InterScience ([www.interscience.wiley.com](http://www.interscience.wiley.com)).

DOI 10.1002/hep.23258

Potential conflict of interest: none of the authors received financial support/ editorial assistance to support the research and the preparation of the article for submission.

**Table 1. Grading System for Recommendations**

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation/procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence	Description
Level A	Data derived from multiple randomized clinical trials or meta-analyses.
Level B	Data derived from a single randomized trial, or nonrandomized studies.
Level C	Only consensus opinion of experts, case studies, or standard-of-care.

ure to recognize alcoholism remains a significant problem and impairs efforts at both the prevention and management of patients with ALD.<sup>13,14</sup> Although the exact prevalence is unknown, approximately 7.4% of adult Americans were estimated to meet DSM-IV criteria for the diagnosis of alcohol abuse and/or alcohol dependence in 1994<sup>15</sup>; more recent data suggest 4.65% meet criteria for alcohol abuse and 3.81% for alcohol dependence.<sup>16</sup> In 2003, 44% of all deaths from liver disease were attributed to alcohol.<sup>17</sup>

Population level mortality from alcoholic liver disease is related to per capita alcohol consumption obtained from national alcoholic beverage sales data. There are conflicting data regarding a possible lower risk of liver injury in wine drinkers.<sup>18,19</sup> One epidemiologic study has estimated that for every 1-liter increase in per capita alcohol consumption (independent of type of beverage), there was a 14% increase in cirrhosis in men and 8% increase in women.<sup>20</sup> These data must be considered in the context of the limitations of measuring alcohol use and defining alcoholic liver disease. The scientific literature has also used a variety of definitions of what constitutes a standard drink (Table 2). Most studies depend on interviews with patients or their families to quantify drinking patterns, a method that is subject to a number of biases, which may lead to invalid estimates of alcohol consumption.<sup>21</sup>

Although there are limitations of the available data, the World Health Organization's Global Alcohol database, which has been in existence since 1996, has been used to

estimate worldwide patterns of alcohol consumption and allow comparisons of alcohol related morbidity and mortality.<sup>22</sup> The burden of alcohol-related disease is highest in the developed world, where it may account for as much as 9.2% of all disability-adjusted life years. Even in developing regions of the world, however, alcohol accounts for a major portion of global disease burden, and is projected to take on increasing importance in those regions over time.<sup>22,23</sup>

## II. Disease Spectrum

The spectrum of alcohol-related liver injury varies from simple steatosis to cirrhosis. These are not necessarily distinct stages of evolution of disease, but rather, multiple stages that may be present simultaneously in a given individual.<sup>24,25</sup> These are often grouped into three histological stages of ALD: fatty liver or simple steatosis, alcoholic hepatitis, and chronic hepatitis with hepatic fibrosis or cirrhosis.<sup>26</sup> These latter stages may also be associated with a number of histologic changes (which have varying degrees of specificity for ALD), including the presence of Mallory's hyaline, megamitochondria, or perivenular and perisinusoidal fibrosis.<sup>24</sup>

Fatty liver develops in about 90% of individuals who drink more than 60 g/day of alcohol,<sup>27</sup> but may also occur in individuals who drink less.<sup>28</sup> Simple, uncomplicated fatty liver is usually asymptomatic and self limited, and may be completely reversible with abstinence after about 4-6 weeks.<sup>29</sup> However, several studies have suggested that progression to fibrosis and cirrhosis occurs in 5%-15% of patients despite abstinence.<sup>30,31</sup> In one study, continued alcohol use (>40 g/day) increased the risk of progression to cirrhosis to 30%, and fibrosis or cirrhosis to 37%.<sup>32</sup>

Fibrosis is believed to start in the perivenular area and is influenced by the amount of alcohol ingested.<sup>33,34</sup> Perivenular fibrosis and deposition of fibronectin occurs in 40%-60% of patients who ingest more than 40-80 g/daily for an average of 25 years. Perivenular sclerosis has

**Table 2. Quantity of Alcohol in a Standard Drink**

Region	Amount	Range
USA	12 g	9.3-13.2 g
Canada	13.6 g	13.6 g
UK	9.5 g	8-10 g
Europe	9.8 g	8.7-10.0 g
Australia and New Zealand	9.2 g	6.0-11.0 g
Japan	23.5 g	21.2-28.0 g

Adapted from Turner.<sup>263</sup> To standardize, many authorities recommend conversion to grams of alcohol consumed. To convert concentrations of alcohol, usually listed in volume percent (equivalent to the volume of solute/volume of solution  $\times$  100), the percentage of alcohol by volume (% vol/vol) is multiplied by the specific gravity of alcohol, 0.79 g/mL.<sup>264</sup>

been identified as a significant and independent risk factor for the progression of alcoholic liver injury to fibrosis or cirrhosis.<sup>33,35</sup> Progression of ALD culminates in the development of cirrhosis, which is usually micronodular, but may occasionally be mixed micronodular and macronodular.<sup>36</sup>

A subset of patients with ALD will develop severe alcoholic hepatitis (AH), which has a substantially worse short-term prognosis.<sup>37</sup> AH also represents a spectrum of disease, ranging from mild injury to severe, life-threatening injury, and often presents acutely against a background of chronic liver disease.<sup>38,39</sup> The true prevalence is unknown, but histologic studies of patients with ALD suggest that AH may be present in as many as 10%-35% of hospitalized alcoholic patients.<sup>40-42</sup> Typically, symptomatic patients present with advanced liver disease, with concomitant cirrhosis in more than 50%, and superimposed acute decompensation. Even patients with a relatively mild presentation, however, are at high risk of progressive liver injury, with cirrhosis developing in up to 50%.<sup>43,44</sup> The likelihood that AH will progress to permanent damage is increased among those who continue to abuse alcohol. Abstinence from alcohol in one small series did not guarantee complete recovery. Only 27% of abstaining patients had histologic normalization, whereas 18% progressed to cirrhosis, and the remaining patients had persistent AH when followed for up to 18 months.<sup>45</sup>

### III. Risk Factors

Unlike many other hepatotoxins, the likelihood of developing progressive alcohol-induced liver disease or cirrhosis is not completely dose-dependent, because it occurs in only a subset of patients. A number of risk factors have been identified that influence the risk of development and progression of liver disease.

The amount of alcohol ingested (independent of the form in which it is ingested) is the most important risk factor for the development of ALD.<sup>46</sup> The relationship between the quantity of alcohol ingested and the development of liver disease is not clearly linear.<sup>47,48</sup> However, a significant correlation exists between per capita consumption and the prevalence of cirrhosis.<sup>49</sup> The risk of developing cirrhosis increases with the ingestion of >60-80 g/day of alcohol for 10 years or longer in men, and >20 g/day in women.<sup>6,50</sup> Yet, even drinking at these levels, only 6%-41% develop cirrhosis.<sup>6,51</sup> In a population-based cohort study of almost 7000 subjects in two northern Italian communities, even among patients with very high daily alcohol intake (>120 g/day), only 13.5% developed ALD.<sup>50</sup> The risk of cirrhosis or noncirrhotic chronic liver disease increased with a total lifetime alcohol intake of more than 100 kg, or a daily intake >30 g/day.<sup>50</sup> The

odds of developing cirrhosis or lesser degrees of liver disease with a daily alcohol intake of >30 g/day were 13.7 and 23.6, respectively, when compared with nondrinkers.<sup>50</sup>

The type of alcohol consumed may influence the risk of developing liver disease. In a survey of more than 30,000 persons in Denmark, drinking beer or spirits was more likely to be associated with liver disease than drinking wine.<sup>18</sup>

Another factor that has been identified is the pattern of drinking. Drinking outside of meal times has been reported to increase the risk of ALD by 2.7-fold compared to those who consumed alcohol only at mealtimes.<sup>52</sup> Binge drinking, defined by some researchers as five drinks for men and four drinks for women in one sitting, has also been shown to increase the risk of ALD and all-cause mortality.<sup>53,54</sup>

Women have been found to be twice as sensitive to alcohol-mediated hepatotoxicity and may develop more severe ALD at lower doses and with shorter duration of alcohol consumption than men.<sup>55</sup> Several studies have shown differing blood alcohol levels in women versus men after consumption of equal amounts of alcohol.<sup>56</sup> This might be explained by differences in the relative amount of gastric alcohol dehydrogenase, a higher proportion of body fat in women, or changes in alcohol absorption with the menstrual cycle.<sup>57</sup> Based on epidemiological evidence of a threshold effect of alcohol, a suggested "safe" limit of alcohol intake had been 21 units per week in men and 14 units per week in women who have no other chronic liver disease<sup>58,59</sup> (where a unit is defined as the equivalent of 8 g of ethanol). However, other data suggest that a lower quantity may be toxic in women, implying a lower threshold of perhaps no more than 7 units per week.<sup>47</sup> A higher risk of liver injury may be associated with an individual's racial and ethnic heritage.<sup>60</sup> The rates of alcoholic cirrhosis are higher in African-American and Hispanic males compared to Caucasian males and the mortality rates are highest in Hispanic males.<sup>61</sup> These differences do not appear to be related to differences in amounts of alcohol consumed.<sup>62</sup>

The presence and extent of protein calorie malnutrition play an important role in determining the outcome of patients with ALD. Mortality increases in direct proportion to the extent of malnutrition, approaching 80% in patients with severe malnutrition (i.e., less than 50% of normal).<sup>63</sup> Micronutrient abnormalities, such as hepatic vitamin A depletion or depressed vitamin E levels, may also potentially aggravate liver disease.<sup>64</sup> Diets rich in polyunsaturated fats promote alcohol-induced liver disease in animals,<sup>65</sup> whereas diets high in saturated fats may



be protective. Obesity and excess body weight have been associated with an increased risk of ALD.<sup>66,67</sup>

In addition to environmental factors, genetic factors predispose to both alcoholism and ALD.<sup>68-70</sup> Children of alcoholics raised in adopted families had a significantly higher rate of alcohol dependence than did adopted children of nonalcoholics, who served as controls (18% versus 5%).<sup>71</sup> In population-based studies, monozygotic twins were approximately twice as likely to drink as dizygotic twins; among those who drank, monozygotic twins were more likely to have a similar frequency and quantity of alcohol consumption.<sup>72</sup> Moreover, monozygotic twins have a significantly higher prevalence of alcoholic cirrhosis than do dizygotic twins.<sup>73</sup>

Finally, polymorphisms of genes involved in the metabolism of alcohol (including alcohol dehydrogenase, acetaldehyde dehydrogenase and the cytochrome P450 system), and in those which regulate endotoxin-mediated release of cytokines have been associated with ALD.<sup>74,75</sup> However, to date, specific genetic abnormalities for susceptibility to alcohol abuse and the development of ALD have not yet been firmly established.

There is a clear synergistic relationship between chronic viral hepatitis and alcohol, resulting in more advanced liver disease jointly than separately. The combination of hepatitis C virus and alcohol predisposes to more advanced liver injury than alcohol alone,<sup>76,77</sup> with disease at a younger age, more severe histological features, and a decreased survival.<sup>78</sup> In a large cohort study of the effect of heavy alcohol abuse in patients with posttransfusion hepatitis C, the risk of cirrhosis was elevated 30-fold.<sup>79</sup> Although the precise toxic threshold for alcohol is not known, and may be lower and nonuniform among patients at risk, it seems prudent in light of these data to advise patients with hepatitis C to abstain from even moderate quantities of alcohol.

#### IV. Diagnosis

The diagnosis of ALD is based on a combination of features, including a history of significant alcohol intake, clinical evidence of liver disease, and supporting laboratory abnormalities.<sup>80</sup> Unfortunately, the ability to detect these is constrained by patient and physician factors, as well as diagnostic laboratory shortcomings. Denial of alcohol abuse and underreporting of alcohol intake are common in these patients.<sup>81,82</sup> Physicians underestimate alcohol-related problems and make specific recommendations even less frequently.<sup>83,84</sup> Both the physical findings and laboratory evidence for ALD may be nondiagnostic, especially in patients with mild ALD or early cirrhosis.<sup>85</sup> Therefore, the clinician must have a low threshold to raise the issue of possible ALD, and has to rely on indirect

evidence of alcohol abuse, such as questionnaires, information from family members, or laboratory tests to strengthen or confirm a clinical suspicion.<sup>86</sup>

##### A. Screening for Alcohol Abuse

Clinicians commonly fail to screen patients, and thus fail to recognize or treat alcoholism appropriately.<sup>87</sup> The clinical history which may suggest alcohol abuse or alcohol dependence includes the pattern, type, and amount of alcohol ingested, as well as evidence of social or psychological consequences of alcohol abuse. These may be suggested by other injuries or past trauma, such as frequent falls, lacerations, burns, fractures, or emergency department visits.<sup>88</sup> Biochemical tests have been considered to be less sensitive than questionnaires in screening for alcohol abuse,<sup>89,90</sup> but may be useful in identifying relapse.<sup>91,92</sup> Various questionnaires have been used to detect alcohol dependence or abuse, and include the CAGE, the MAST (Michigan Alcoholism Screening Test), and the Alcohol Use Disorders Identification Test (AUDIT).<sup>89,93</sup> The use of a structured interview, using instruments such as the Lifetime Drinking History, is often used as a gold standard for quantifying lifetime alcohol consumption.<sup>94</sup>

The CAGE questionnaire was originally developed to identify hospitalized inpatients with alcohol problems, and remains among the most widely used screening instruments. It has been faulted, however, on several measures: it focuses on the consequences of alcohol consumption rather than on the amount of actual drinking, and it refers to lifetime patterns of behavior, rather than short-term or recent changes. Its virtues, however, include its ease of implementation: it is short (four questions), simple (yes/no answers), and can be incorporated into the clinical history or is self-administered as a written document. As a result of its longevity, it has been tested in a wide range of populations.

One meta-analysis of its characteristics, using a cutoff of more than two positive responses, found an overall pooled sensitivity and specificity of 0.71 and 0.90, respectively.<sup>95</sup> The CAGE questionnaire is familiar to most physicians, and has been suggested for use in general screening<sup>96</sup> (Table 3). The AUDIT is a 10-item questionnaire developed by the World Health Organization to

**Table 3. The CAGE Questionnaire<sup>265</sup>**

1. Have you ever felt you should cut down on your drinking?
2. Have people annoyed you by criticizing your drinking?
3. Have you ever felt bad or guilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?

Scoring: Each response is scored as 0 or 1, with a higher score indicative of alcohol-related problems, and a total of 2 or more clinically significant.

**Table 4. AUDIT Questionnaire<sup>102</sup>**

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

To score the AUDIT questionnaire, sum the scores for each of the 10 questions. A total  $\geq 8$  for men up to age 60, or  $\geq 4$  for women, adolescents, or men over age 60 is considered a positive screening test.

avoid ethnic and cultural bias<sup>97</sup> and focuses on the identification of heavy drinkers. It has a higher sensitivity and specificity than shorter screening instruments (with sensitivity ranging from 51%-97%, and specificity of 78%-96% in primary care).<sup>98</sup> It has been suggested that it has three advantages over other screening tests: it may identify drinkers at risk who are not yet alcohol-dependent; it includes a measure of consumption; and lastly, it includes both current and lifetime drinking time spans. It is more likely to detect problem drinking before overt alcohol dependence or abuse might be diagnosed, and thus may be more robust and effective across a variety of populations.<sup>99-101</sup> One possible algorithm for clinicians suggests asking about quantity of alcohol consumed, and number of heavy drinking days in the preceding year (i.e.,  $\geq 5$  drinks/day for men or  $\geq 4$  drinks/day for women), as well as a version of the AUDIT questionnaire<sup>102</sup> (Table 4). An AUDIT score of  $\geq 8$ , or having had one or more heavy drinking days constitutes a positive screening test, and should prompt further evaluation to rule out an alcohol use disorder.<sup>102</sup>

Regardless of which screening instrument is selected, however, it is important for clinicians to incorporate screening into their general practice.<sup>98,103</sup> This may be especially important, because some data suggest that these screening instruments may improve the ability of physicians to predict long-term clinical outcomes, including hospitalization for alcohol-related diagnoses.<sup>104</sup>

A biomarker in longstanding use, gamma glutamyl transpeptidase (GGT), has been evaluated in a number of settings, including large population surveys.<sup>105,106</sup> Unfortunately, low sensitivity and specificity limit the usefulness of elevated GGT to diagnose alcohol abuse,<sup>107-109</sup> the levels of which may fluctuate with extensive liver injury.<sup>110</sup> Lower levels of GGT ( $<100$ ) or a total bilirubin/GGT ratio  $> 1$  have been described as a predictor of 1-year mortality in patients with alcoholic cirrhosis,<sup>110</sup> although this has not consistently added prognostic ability to other laboratory tests.<sup>111</sup> In combination with other biomarkers, however, GGT may add independent information in diagnosing alcohol abuse or problem drinking.<sup>112</sup> Macrocytosis is seen in individuals abusing alcohol

but this condition lacks sensitivity. A combination of raised GGT and mean corpuscular volume or changes in these values over time in hospitalized patients may improve the sensitivity for diagnosing alcohol abuse. Multiple other candidate biomarkers that may detect alcohol use or abuse objectively have been studied.<sup>113,114</sup> Carbohydrate-deficient transferrin has been the best studied, but has limited sensitivity and specificity.<sup>115</sup> Its test characteristics are also influenced by a number of other factors, including age, sex, body mass index, and other chronic liver diseases.<sup>116-118</sup> Despite enthusiasm about a possible quantitative, reliable assay of alcohol consumption or abuse, the lack of sensitivity and specificity prevent reliance on any single biomarker.<sup>119</sup>

### **B. Diagnosis of ALD**

The diagnosis of ALD is made by documentation of alcohol excess and evidence of liver disease.<sup>120</sup> No single laboratory marker definitively establishes alcohol to be the etiology of liver disease. Furthermore, alcohol may be one of a number of factors causing liver injury, and the specific contributory role of alcohol alone may be difficult to assess in a patient with multifactorial liver disease. A number of laboratory abnormalities, including elevated serum aminotransferases, have been reported in patients with alcoholic liver injury, and used to diagnose ALD.<sup>121</sup> Serum aspartate aminotransferase (AST) is typically elevated to a level of 2-6 times the upper limits of normal in severe alcoholic hepatitis. Levels of AST more than 500 IU/L or an alanine aminotransferase (ALT) > 200 IU/L are uncommonly seen with alcoholic hepatitis (other than alcoholic foamy degeneration, or concomitant acetaminophen overdose),<sup>122</sup> and should suggest another etiology. In about 70% of patients, the AST/ALT ratio is higher than 2, but this may be of greater value in patients without cirrhosis.<sup>123-125</sup> Ratios greater than 3 are highly suggestive of ALD.<sup>126</sup>

### **C. Physical Examination**

Physical exam findings in patients with ALD may range from normal to those suggestive of advanced cirrhosis. As in other forms of chronic liver disease, physical exam features generally have low sensitivity, even for the detection of advanced disease or cirrhosis, although they may have higher specificity.<sup>127</sup> It has been suggested, therefore, that the presence of these features may have some benefit in "ruling in" the presence of advanced disease.<sup>127</sup> Features specific for ALD are perhaps even more difficult to identify. Palpation of the liver may be normal in the presence of ALD, and does not provide accurate information regarding liver volume.<sup>128</sup> Certain physical exam findings have been associated with a higher likelihood of cirrhosis among alcoholics.<sup>129</sup> Although some of

the physical findings are more commonly observed in ALD (parotid enlargement, Dupuytren's contracture, and especially those signs associated with feminization) than in non-ALD, no single physical finding or constellation of findings is 100% specific or sensitive for ALD.<sup>130</sup> Some of the physical exam features may also carry some independent prognostic information, with the presence of specific features associated with an increased risk of mortality over 1 year. These include (with their associated relative risks): hepatic encephalopathy (4.0), presence of visible veins across the anterior abdominal wall (2.2), edema (2.9), ascites (4.0), spider nevi (3.3), and weakness (2.1).<sup>131</sup> Although this is somewhat helpful clinically, findings from the physical exam must be interpreted with caution, because there is considerable heterogeneity in the assessment of each of these features when different examiners are involved.<sup>132</sup> Several authors have reported the detection of an hepatic bruit in the setting of AH.<sup>133</sup> This has been used in some centers as a diagnostic criterion for AH.<sup>134</sup> However, the sensitivity, as well as the specificity of this finding is uncertain.<sup>135</sup> In one series of 280 consecutive hospitalized patients, only 4 of 240 (or 1.7%) with AH and cirrhosis had an audible bruit.<sup>136</sup> Caution about adopting this as a diagnostic criterion has therefore been advised.<sup>137</sup>

It is important for physicians caring for these patients to recognize that ALD does not exist in isolation, and that other organ dysfunction related to alcohol abuse may coexist with ALD, including cardiomyopathy,<sup>138,139</sup> skeletal muscle wasting,<sup>140</sup> pancreatic dysfunction, and alcoholic neurotoxicity.<sup>141</sup> Evidence of these must be sought during the clinical examination, so that appropriate treatment may be provided.<sup>142</sup>

### **D. Hepatic Imaging**

Imaging studies have been used to diagnose the presence of liver disease but do not have a role in establishing alcohol as the specific etiology of liver disease. However, the diagnosis of fatty change, established cirrhosis and hepatocellular carcinoma may be suggested by ultrasound, computed tomography scan, or magnetic resonance imaging (MRI) and confirmed by other laboratory investigations.<sup>143,144</sup> The major value of imaging studies is to exclude other causes of abnormal liver tests in a patient who abuses alcohol, such as obstructive biliary pathology, or infiltrative and neoplastic diseases of the liver.<sup>145</sup> MRI has been used as an adjunct to diagnose cirrhosis, and to distinguish end-stage liver disease related to viral hepatitis infection from ALD. Specific features that may be suggestive of alcoholic cirrhosis include a higher volume index of the caudate lobe, more frequent visualization of the right posterior hepatic notch, and smaller size of regenerative

nodules of the liver in patients with cirrhosis on the basis of ALD versus chronic viral hepatitis.<sup>146</sup> Although changes were identified on ultrasound and MRI, it is unclear whether these results are generalizable.<sup>146,147</sup>

### ***E. Liver Biopsy in ALD***

Although not essential in the management of ALD, a liver biopsy is useful in establishing the diagnosis.<sup>144</sup> As many as 20% of patients with a history of alcohol abuse have a secondary or coexisting etiology for liver disease.<sup>148</sup> In the absence of decompensated disease, clinical and biochemical indicators are poor markers of the severity of liver disease, and a biopsy is useful in establishing the stage and severity of liver disease.<sup>144,149</sup>

The histological features of alcohol-induced hepatic injury vary, depending on the extent and stage of injury. These may include steatosis (fatty change), lobular inflammation, periportal fibrosis, Mallory bodies, nuclear vacuolation, bile ductal proliferation, and fibrosis or cirrhosis.<sup>24</sup> These may coexist in the same biopsy, however, and are not individually pathognomonic of ALD. The clinical diagnosis of AH is made based on a typical presentation, with severe liver dysfunction in the context of excessive alcohol consumption, and the exclusion of other causes of acute and chronic liver disease. In the subset of patients with AH, a liver biopsy may demonstrate specific histologic features, including confluent parenchymal necrosis, steatosis, deposition of intrasinusoidal and pericentral collagen, ballooning degeneration, and lobular inflammation affecting the perivenular regions in the earliest stages.<sup>34</sup> The liver may be infiltrated with polymorphonuclear cells, typically clustered around cytoplasmic structures known as Mallory bodies,<sup>150</sup> which represent aggregated cytokeratin intermediate filaments and other proteins. In addition to confirming the diagnosis and staging the extent of disease, specific features on liver biopsy also convey prognostic importance. The severity of inflammation (i.e., degree of polymorphonuclear cell infiltration) and cholestatic changes correlate with increasingly poor prognosis, and may also predict response to corticosteroid treatment in severe AH.<sup>151,152</sup> Megamitochondria in alcoholic hepatitis may be associated with a milder form of AH, a lower incidence of cirrhosis and fewer complications with a good long-term survival.<sup>153</sup> AH is associated with perivenular and pericellular fibrosis which may be a harbinger of future cirrhosis, especially in patients who continue to abuse alcohol or those who are coinfecting with hepatitis C virus.<sup>33,154</sup> Mallory bodies, giant mitochondria, neutrophilic infiltration, and fibrosis may be seen in conditions other than ALD.<sup>155</sup>

Although a liver biopsy may not be practical in the management of all patients, it has been shown that phy-

sicians' clinical impression may correlate only moderately well with the histologic findings on liver biopsy. Studies that have included a liver biopsy in all patients with presumed AH have shown histologic confirmation in only 70%-80% of patients.<sup>156</sup> The incentive to make a definitive histologic diagnosis, however, is partly dependent on the possible risks of a biopsy, as well as the risks involved with particular treatments. If no treatment for ALD or AH is contemplated, based on noninvasive estimates of an individual patient's prognosis, it usually is not necessary to make a histologic diagnosis. Alternatively, if an investigational treatment or a therapy with associated risk is contemplated, the risk-benefit ratio involved in pursuing a liver biopsy may change.

#### ***Recommendation:***

***1. Clinicians should discuss alcohol use with patients, and any suspicion of possible abuse or excess should prompt use of a structured questionnaire and further evaluation (Class I, level C).***

***2. For patients with a history of alcohol abuse or excess and evidence of liver disease, further laboratory tests should be done to exclude other etiologies and to confirm the diagnosis (Class I, level C).***

***3. Patients with ALD and suggestive symptoms should be screened for evidence of other end-organ damage, as appropriate (Class I, level C).***

***4. For patients with a clinical diagnosis of severe AH for whom medical treatment is contemplated, or for those in whom reasonable uncertainty exists regarding the underlying diagnosis, a liver biopsy should be considered. This decision will depend on local expertise and ability in performing a liver biopsy in patients with coagulopathy, the patient's severity of illness, and the type of therapy under consideration (Class I, level C).***

## **V. Prognostic Factors**

### ***A. Prognosis in Alcoholic Hepatitis***

Decisions regarding treatment are critically dependent on the ability to estimate a given patient's prognosis. Many individual clinical and laboratory features, along with specific histologic features have also been tested as measures of disease prognosis. In AH, the Maddrey discriminant function (MDF), a disease-specific prognostic score, has been used to stratify a patient's severity of illness.<sup>157</sup> The initial formula was derived in the context of clinical trials of alcoholic hepatitis, and later modified to:  $MDF = 4.6 (\text{Patient's prothrombin time} - \text{control prothrombin time}) + \text{total bilirubin (mg/dL)}$ .<sup>158</sup> Patients with a score of greater than or equal to 32 were at the highest risk of dying, with a one month mortality as high as 30%-50%.<sup>151</sup> In particular, those with evidence of both



**Table 5. Prognostic Scoring Systems Used for Patients with Alcoholic Hepatitis**

Name	Derivation Set	Elements	Test Characteristics																								
1. Maddrey (modified) Discriminant Function (1989) <sup>158</sup>	n = 66	MDF = 4.6 (Patient's PT - control PT) + total bilirubin (mg/dL).	Poor prognosis if score $\geq$ 32																								
2. MELD score (2001) <sup>†160</sup>	n = 1179	MELD Score = 3.8 * log <sub>e</sub> (bilirubin in mg/dL) + 11.2 * log <sub>e</sub> (INR) + 9.6 * log <sub>e</sub> (creatinine mg/dL) + 6.4	Poor prognosis if >18																								
3. Glasgow Alcoholic Hepatitis score (2005) <sup>161</sup>	n = 241	Score*: <table border="1" style="margin-left: 20px;"> <thead> <tr> <th></th> <th>1</th> <th>2</th> <th>3</th> </tr> </thead> <tbody> <tr> <td>Age</td> <td>&lt;50</td> <td><math>\geq</math>50</td> <td>-</td> </tr> <tr> <td>WCC</td> <td>&lt;15</td> <td><math>\geq</math>15</td> <td>-</td> </tr> <tr> <td>Urea (mmol/L)</td> <td>&lt;5</td> <td><math>\geq</math>5</td> <td>-</td> </tr> <tr> <td>PT ratio</td> <td>&lt;1.5</td> <td>1.5-2.0</td> <td><math>\geq</math>2</td> </tr> <tr> <td>Bilirubin (mg/dL)</td> <td>&lt;7.3</td> <td>7.3-14.6</td> <td>&gt;14.6</td> </tr> </tbody> </table>		1	2	3	Age	<50	$\geq$ 50	-	WCC	<15	$\geq$ 15	-	Urea (mmol/L)	<5	$\geq$ 5	-	PT ratio	<1.5	1.5-2.0	$\geq$ 2	Bilirubin (mg/dL)	<7.3	7.3-14.6	>14.6	Poor prognosis if score > 8 (for score calculated on hospital day 1 or day 7)
	1	2	3																								
Age	<50	$\geq$ 50	-																								
WCC	<15	$\geq$ 15	-																								
Urea (mmol/L)	<5	$\geq$ 5	-																								
PT ratio	<1.5	1.5-2.0	$\geq$ 2																								
Bilirubin (mg/dL)	<7.3	7.3-14.6	>14.6																								

\*The GAH score is calculated by summing the points assigned for each of the 5 variables: age, white blood cell count, blood urea nitrogen, PT as a ratio of the patient to the control, and the bilirubin. This is done on hospital day 1 or on day 7.

†The MELD score has also been used to estimate 90-day mortality<sup>166</sup>; an online calculator is available: [www.mayoclinic.org/meld/mayomodel7.html](http://www.mayoclinic.org/meld/mayomodel7.html).

hepatic encephalopathy and an elevated MDF were at highest risk. Although relatively easy to use, and based on standard laboratory tests, several drawbacks to the use of the MDF have been noted. Although it is a continuous measure, its interpretation (using a threshold of 32) has converted it into an essentially categorical method of classification. Once patients have exceeded that threshold, their risk for dying is higher, but not specified. Dynamic models, which incorporate the changes in laboratory studies over time, have also been used to estimate the outcome in patients, including the change in bilirubin in the first week of hospitalization, which is significantly associated with outcome of patients with alcoholic hepatitis treated with prednisolone.<sup>159</sup>

Table 5 outlines some of the prognostic scoring systems used for patients with alcoholic hepatitis.

Other scoring systems have also been proposed to stratify patients, including the combined clinical and laboratory index of the University of Toronto,<sup>131</sup> the Beclere model,<sup>151</sup> the MELD (Model for End-Stage Liver Disease) score,<sup>160</sup> and the Glasgow Alcoholic Hepatitis Score (GAHS).<sup>161</sup> The diagnostic abilities of the latter two models have been tested against the MDF and other scoring systems for cirrhosis (such as the Child-Turcotte-Pugh score, or CTP) in terms of specific test characteristics, including sensitivity and specificity, at least in some populations.<sup>162,163</sup> Because of the inherent trade-offs involved in setting test thresholds, optimal cut points are not clearly established for each of these indices. Some investigators have suggested specific cutoffs for these indices, including an MDF  $\geq$ 32 or a MELD score > 11, that appear to be roughly equivalent in ability to detect patients with a poor prognosis, with similar sensitivity and specificity.<sup>162</sup> Others have suggested higher MELD cutoffs of 18,<sup>164</sup> 19,<sup>165</sup> or 21<sup>166</sup> (Table 6).

Several studies have also demonstrated the utility of repeat testing and calculation of these indices during the course of hospitalization, including MELD or MDF score at one week, and degree of change. A change of  $\geq$ 2 points in the MELD score in the first week has been shown to independently predict in-hospital mortality.<sup>164</sup> The GAHS was recently derived, and its test characteristics compared to the MDF and the MELD scores. Although it had an overall higher accuracy, it was substantially less sensitive for predicting one month and three month mortality compared to either the MDF or the MELD.<sup>161</sup> The degree of portal hypertension may be a sensitive marker for the severity of liver injury.<sup>167</sup> A recently proposed scoring system combines measurements of a marker of portal hypertension, asymmetric dimethylarginine and its stereoisomer, to predict outcomes.<sup>168</sup> This combined score has been compared to the CTP score, MELD, and MDF, and shown to have an overall sensitivity of 73% and specificity of 83%, which was at least as good as other scoring systems.<sup>168</sup> These results, however, require further validation.

As the goal of early detection of patients at highest risk of poor outcome requires maximization of the sensitivity of the test score, it would seem reasonable to use the MDF (with a cutoff of 32, and/or the presence of encephalopathy) to select patients for therapy.

#### ***Recommendation:***

***5. Patients presenting with a high clinical suspicion of alcoholic hepatitis should have their risk for poor outcome stratified using the Maddrey Discriminant Function, as well as other available clinical data. Evaluating a patient's condition over time with serial calculation of the MELD score is also justified (Class I, level B).***



**Table 6. Comparisons of Diagnostic Indices**

Author	Patient Population	Outcome	AUROC
Sheth <sup>162</sup>	N = 34 patients with alcoholic hepatitis hospitalized 1997-2000. 21% 30 day mortality	MELD > 11: Sensitivity 86% Specificity: 81% MDF ≥ 32: Sensitivity 86% Specificity 48%	MELD: 0.82 MDF: 0.86
Srikureja <sup>164</sup>	N = 202 AH patients admitted 1997-2002. 29 inpatient deaths	Admission MELD ≥ 18: Sensitivity 85% Specificity 84% Admission MDF ≥ 32: Sensitivity 83% Specificity 60% Admission CTP ≥ 12: Sensitivity 76% Specificity 80%	Admission MELD: 0.89 Admission CTP: 0.87 Admission DF: 0.81
Dunn <sup>166</sup>	N = 73 AH patients admitted 1995-2001. 16 deaths in 90 days. Outcome: 30 day mortality	Admission MELD > 21: Sensitivity 75% Specificity 75% MDF > 41: Sensitivity 75% Specificity 69	Admission MELD: 0.83 Admission MDF: 0.74
Soultati <sup>165</sup>	N = 34 patients admitted 2000-2005; 2 deaths/30 days, 5 deaths/90 days. Outcome: 30 day mortality	MELD ≥ 30.5: Sensitivity 1 Specificity 0.937 MDF ≥ 108.68: Sensitivity 1 Specificity 0.969	MELD: 0.969 MDF: 0.984

AUROC: area under the ROC curve, with optimal test results closest to 1

## VI. Therapy

Therapy of ALD is based on the stage of the disease and the specific goals of treatment.<sup>169,170</sup> Complications of cirrhosis, including evidence of hepatic failure (encephalopathy) as well as portal hypertension (ascites, variceal bleeding), are treated as in patients with non-ALD, with additional attention given to other organ dysfunction associated specifically with alcohol.<sup>170</sup>

### A. Abstinence

Abstinence is the most important therapeutic intervention for patients with ALD.<sup>171</sup> Abstinence has been shown to improve the outcome and histological features of hepatic injury, to reduce portal pressure and decrease progression to cirrhosis, and to improve survival at all stages in patients with ALD.<sup>171-174</sup> However, this may be less likely to occur in female patients.<sup>172,175,176</sup> This improvement can be relatively rapid, and in 66% of patients abstaining from alcohol, significant improvement was observed in 3 months.<sup>177</sup> Continued alcohol ingestion results in an increased risk of portal hypertensive bleeding, especially in patients who have previously bled, and worsens both short-term and long-term survival.<sup>178</sup>

Recidivism is a major risk in all patients at any time following abstinence.<sup>179,180</sup> Estimates vary, depending on

the time course of follow-up and the definition of recidivism (e.g., any alcohol consumption versus moderate to harmful drinking), but over the course of 1 year, relapse rates range from 67%-81%.<sup>181</sup> Therefore, several medications have been tried to help sustain abstinence. One of the first agents to be used, disulfiram, was approved by the U.S. Food and Drug Administration in 1983. However, a review of the published literature concluded that there was little evidence that disulfiram enhances abstinence,<sup>182</sup> and based on its poor tolerability, its use has been largely supplanted by newer agents. Naltrexone, which was approved in 1995 for the treatment of alcoholism, is a pure opioid antagonist and controls the craving for alcohol. However, it also has been shown to cause hepatocellular injury. A Cochrane systematic review of the use of naltrexone and nalmefene (another opioid antagonist) in 29 randomized clinical trials concluded that short-term treatment with naltrexone lowers the risk of relapse.<sup>183</sup> Acamprosate (acetylhomotaurine) is a novel drug with structural similarities to the inhibitory neurotransmitter gamma amino butyric acid (GABA), and is associated with a reduction in withdrawal symptoms.<sup>184</sup> In 15 controlled trials, acamprosate has been shown to reduce withdrawal symptoms, including alcohol craving, but its effects on survival are not yet known.<sup>185</sup> Its effect is more

pronounced in maintaining rather than inducing remission when used in combination with counseling and support. In detoxified alcoholics, it has been shown to decrease the rate of relapse, maintain abstinence, and decrease severity of relapse when it occurs. It has not been shown to have a significant impact on alcoholics who have not been detoxified or become abstinent. Whether it has any additional effect in combination with naltrexone is controversial. A recent large randomized controlled clinical trial did not suggest substantial benefit of acamprosate compared to naltrexone or to intensive counseling in maintaining abstinence.<sup>186</sup> There is a paucity of data about the use of these interventions in patients with advanced liver disease. One randomized clinical trial in patients with cirrhosis suggested benefit in achieving and maintaining abstinence with the use of baclofen, a  $\gamma$ -aminobutyric acid B receptor agonist.<sup>187</sup>

#### ***Recommendations:***

**6. In patients with evidence of alcohol-induced liver disease, strict abstinence must be recommended, because continued alcohol use is associated with disease progression (Class I, level B).**

**7. Naltrexone or acamprosate may be considered in combination with counseling to decrease the likelihood of relapse in patients with alcohol abuse/dependence in those who achieve abstinence (Class I, level A).**

### ***B. Therapy for Alcoholic Hepatitis***

The cornerstone of therapy of alcoholic hepatitis is abstinence, although even patients who become abstinent remain at increased risk of developing cirrhosis. However, the risk of cirrhosis is clearly higher in those who continue to drink,<sup>188,189</sup> particularly among women.<sup>175,190</sup> Although there are no clear dose–effect data, a threshold exists for the development of alcoholic hepatitis, with risk increasing with consumption beyond 40 g of alcohol per day.<sup>46,191</sup> Furthermore, after an episode of AH, there is no safe amount of alcohol consumption which can be recommended, as alcoholic hepatitis can persist or redevelop. There is a significant risk of recidivism in patients who attempt to cut back but not stop drinking altogether.<sup>192</sup> Complete abstinence is therefore a reasonable lifetime recommendation.

The need to consider therapy is less urgent in patients with alcoholic hepatitis who have a low risk of complications as defined by an MDF score of < 32, without hepatic encephalopathy, or a low MELD score (e.g., MELD < 18), or GAHS score of < 8. This is particularly true in those whose liver score improves during hospitalization, with a decrease in total bilirubin, as they will likely improve spontaneously with abstinence and supportive care

alone. For those with more severe disease and therefore a more dismal prognosis, however, medical treatment should be considered.

**1. Nutrition Therapy.** The presence of significant protein calorie malnutrition is a common finding in alcoholics, as are deficiencies in a number of vitamins and trace minerals, including vitamin A, vitamin D, thiamine, folate, pyridoxine, and zinc.<sup>193</sup> In a Veterans Administration Cooperative study of 363 patients with alcoholic hepatitis, 100% of patients were found to have protein and/or combined protein calorie malnutrition, based on anthropometric and laboratory testing.<sup>194</sup> Moreover, the severity of malnutrition correlated with disease severity and outcomes.<sup>194</sup>

This early finding was the motivation for a number of clinical trials of anabolic steroids, nutritional supplementation, or aggressive enteral feeding. Several of these studies showed improvement in biochemical markers of liver function or nutritional parameters, but were unable to demonstrate an improvement in short-term survival.<sup>195</sup> At least in some trials, however, subgroups of patients who achieved nutritional goals and positive nitrogen balance had improved survival compared to those who did not.<sup>196</sup> As an example, in one study the mortality rate was 3.3% in the 30 patients in whom positive nitrogen balance was achieved, but 58% in patients who remained in negative nitrogen balance.<sup>196</sup>

A recent study of nutritional therapy compared the outcomes of 35 patients randomized to 1 month of enteral tube feeding of 2000 kcal/day versus 40 mg of prednisone/day.<sup>197</sup> No difference in mortality was noted, but the time course of deaths was different, with the patients randomized to enteral feeding dying at a median of 7 days, versus 23 days in the steroid treated group. Patients treated with nutritional support who survived past the first month seemed to have a decreased mortality compared to the steroid-treated patients (8% versus 37%).<sup>197</sup> Although technically a negative study, the similar overall mortality rate in the treatment groups suggests a role for nutritional intervention,<sup>198</sup> particularly in light of the relatively benign risk:benefit ratio. Based on these data, other societies have recommended oral or parenteral supplements for patients with AH at risk of undernutrition.<sup>199</sup>

**2. Steroids.** The most extensively studied intervention in alcoholic hepatitis is the use of steroids, based on 13 clinical trials that date back almost 40 years (Table 7).

Most of these trials were small, and therefore had only limited statistical power to detect even moderate treatment effects; five suggested an improvement in outcome, with decreased short term mortality in steroid-treated pa-

**Table 7. Clinical Trials of Steroids in Patients with Alcoholic Hepatitis.**

Author	Date	No. of Patients	Intervention	Deaths: placebo	Deaths: steroid
Porter <sup>266</sup>	1971	20	Prednisolone: 40 mg IV × 10 days, then tapered: 4 mg/day × 1 week, 2 mg/day × 11 days, then 2 mg every 3rd day × 15 days	7/9	6/11
Helman <sup>267</sup>	1971	37	Prednisolone: 40 mg/day × 4 weeks, then tapered over 2 weeks	6/17	1/20
Campra <sup>268</sup>	1973	45	Prednisone: 0.5 mg/kg × 3 weeks, then 0.25 mg/kg × 3 weeks	9/25	7/29
Blitzer <sup>269</sup>	1977	33	Prednisolone: 40 mg/day × 14 days, then 20 mg/day × 4 days; 10 mg/day × 4 days; 5 mg/day × 4 days	5/16	6/12
Lesesne <sup>270</sup>	1978	14	Prednisolone: 40 mg/day × 30 days, then tapered over 2 weeks	7/7	2/7
Shumaker <sup>271</sup>	1978	27	Prednisolone: 80 mg/day × 4-7 days, then tapered off over 4 weeks	7/15	6/12
Maddrey <sup>157</sup>	1978	55	Prednisolone: 40 mg/day × 30 days	6/31	1/24
Depew <sup>272</sup>	1980	28	Prednisolone: 40 mg/day × 28 days, then tapered over 14 days	7/13	8/15
Theodossi <sup>273</sup>	1982	55	Prednisolone: 1 g × 3 days	16/28	17/27
Mendenhall <sup>274</sup>	1984	178	Prednisolone: 60 mg × 4 days; 40 mg/day × 4 days; 30 mg/day × 4 days; 20 mg/day × 4 days; 10 mg/day × 7 days; 5 mg/day × 7 days	50/88	55/90
Bories <sup>275</sup>	1987	45	Prednisolone: 40 mg/day × 30 days	2/21	1/24
Carithers <sup>158</sup>	1989	66	Prednisolone: 32 mg/day × 28 days, then 16 mg/day × 7 days, then 8 mg/day × 7 days	11/31	2/35
Ramond <sup>276</sup>	1992	61	Prednisolone: 40 mg/day × 28 days	16/29	4/32

tients compared to placebo-treated patients, whereas eight showed no effect. It is important to note, however, that these trials used varying inclusion and exclusion criteria, dosing, and were done in a variety of patient populations. Three meta-analyses have analyzed data from these trials and showed an improvement in survival in treated patients<sup>200-202</sup>; one meta-regression, however, using different statistical weighting of the varying trials, was unable to show any difference.<sup>203</sup> The most recent meta-analysis of these data did not show a statistically significant effect of steroids on mortality among all patients treated, although it did demonstrate an effect of steroids in the subgroup of patients with hepatic encephalopathy and/or a MDF score  $\geq 32$ .<sup>204</sup> The presence of substantial statistical heterogeneity in this subgroup of studies prevented the authors from reporting an overall beneficial effect. The implication of this finding is unclear, as statistical heterogeneity among subgroups is a function of both clinical differences and/or methodologic differences among studies, and these analyses may be reflect bias or confounding.<sup>205</sup> One potential approach to resolve this is the use of individual patient data across clinical trials, which represents the "gold standard" approach to meta-analysis.<sup>206</sup> Although it is impractical to retrieve and combine primary data from all the clinical trials in this field, where large variation in studies over time exists, this approach was pursued with the use of a combined dataset, using pooled primary data from three placebo controlled

trials in patients with comparable measures of disease severity (i.e., an MDF  $\geq 32$ ). The result showed a significant increase in short-term survival among treated patients compared to control patients: 84.6% versus 65%.<sup>207</sup> This represents a modest absolute reduction in risk, but a 30% relative risk reduction, and translates into a number needed to treat of 5, i.e., five patients need to be treated to avert one death. This last meta-analysis also excluded a recent trial comparing steroids to a combination of antioxidants, which showed a similar protective effect of corticosteroids among treated patients.<sup>208</sup> Although it is possible that antioxidants themselves may be detrimental,<sup>209</sup> the doses used seem unlikely to account for the differences in survival, and the consistency of the data suggest a protective effect of steroids.

Although the doses and durations of steroid treatment used in the clinical trials were variable, the best available evidence suggests a dose of prednisolone (40 mg/day for 4 weeks then tapered over 2-4 weeks, or stopped, depending on the clinical situation) should be used in favor of prednisone.<sup>210</sup> It is important to recognize that the efficacy of steroids has not been evaluated in patients with severe alcoholic hepatitis and concomitant pancreatitis, gastrointestinal bleeding, renal failure, or active infection, which were exclusion criteria in many of the early studies of alcoholic hepatitis.

An important issue in all studies of medical therapy, and one that has been recognized for some time in this

literature, is the possibility that these therapies may not be effective at an advanced stage of disease. Just as there is a threshold for the use of steroids (i.e., identifying patients at high risk of mortality defined by a MDF score  $\geq 32$ ), there may also be a ceiling beyond which medical therapies aimed at decreasing the inflammatory cascade may cause more harm than benefit. One study examined this issue, and suggested that patients with a MDF  $> 54$  were at a higher mortality risk from use of steroids than from not being treated.<sup>211</sup> This cutoff, however, needs to be confirmed.

One recently derived model used six variables to predict 6-month mortality in patients who were universally treated with steroids (including age, renal insufficiency (serum creatinine  $> 1.3$  or creatinine clearance  $< 40$ ), albumin, prothrombin time, bilirubin, and change in bilirubin over 1 week), and showed an improved prognostic ability compared to MDF or GAHS scores.<sup>212</sup> This model, available on the internet ([www.lillemodel.com](http://www.lillemodel.com)) may allow identification of patients who remain at high risk to be treated with other interventions.

**3. Anticytokine Therapy.** A wealth of evidence suggests that dysregulated cytokines, including tumor necrosis factor alpha (TNF $\alpha$ ) and a host of downstream cytokines play a pivotal role in the pathophysiology of AH. Thus, several agents have been studied that impact the immunologic milieu, targeting specific cytokines, and TNF $\alpha$  in particular.

Among the first agents to be studied was pentoxifylline, an oral phosphodiesterase inhibitor which also inhibits the production of TNF $\alpha$ , among other cytokines. A randomized placebo controlled clinical trial tested pentoxifylline in 101 patients with clinical evidence of severe AH.<sup>213</sup> The in-hospital mortality in the treated patients was 40% lower than in the placebo arm, with the bulk of the reduction related to a substantially lower likelihood of developing hepatorenal syndrome (HRS). HRS was responsible for 50% of the 12 deaths in the treatment arm, compared to 91.7% of the 24 deaths in the placebo group.

Other specific inhibitors of TNF that have been studied include infliximab, a monoclonal chimeric anti-TNF antibody, and etanercept, a fusion protein containing the ligand-binding portion of the human TNF receptor fused to the Fc portion of human immunoglobulin G1.<sup>214</sup> In the first clinical trial of infliximab, 20 patients with biopsy proven alcoholic hepatitis and an MDF score between 32 and 55 (based on the original Maddrey score, which demonstrated an increased mortality at a score  $> 93$ ) were randomized to either 5 mg/kg of infliximab plus 40 mg/day of prednisone ( $n = 11$ ) or to prednisone alone.<sup>215</sup> No substantial difference in overall mortality was found, but

substantial decreases in other prognostic markers, including cytokine levels and MDF scores were seen in patients treated with combination therapy. Another trial, performed at 19 centers in France, randomized 36 patients with biopsy proven alcoholic hepatitis and an MDF  $\geq 32$  to prednisolone (40 mg/day for 4 weeks), versus prednisolone along with infliximab (10 mg/kg, given at study entry, and again at 2 weeks and 4 weeks after entry).<sup>216</sup> The trial was stopped prematurely after seven deaths had occurred in the infliximab group, compared with three in the prednisolone arm. Four of the seven deaths in the infliximab arm were related to infectious etiologies, compared to one in the prednisolone group. The design, and in particular, the dose of infliximab chosen in the study, has been criticized as predisposing to these infections.<sup>217</sup> The utility of etanercept (given six times over 3 weeks) was tested in 48 patients with moderate to severe alcoholic hepatitis (MELD score  $> 15$ ); unfortunately, no significant difference in 1-month mortality was seen in the treated patients compared to patients given placebo, and an increased mortality was seen at 6 months.<sup>218</sup>

Although a strong rationale remains for the use of anti-TNF therapy in alcoholic hepatitis, there is also a theoretical basis for minimizing TNF inhibition, because it plays a role in liver regeneration as well as apoptosis.<sup>219</sup> Thus, in light of the poor clinical outcomes observed in the largest of the infliximab trials and the etanercept study, the use of these parenteral TNF inhibitors should be confined to clinical trials, and recommendations regarding specific therapy will need to await the results of these trials. There are no substantive clinical data comparing the use of steroids or nutrition to specific anti-TNF therapies.

**4. Combination Therapy.** Although it is assumed that each of these different treatments may operate via independent mechanisms, there are only minimal data regarding the comparative benefit of sequential therapies or combined approaches. One study tested the use of pentoxifylline in 29 patients with severe AH (MDF  $> 32$ ) who did not respond to steroids based on a drop in bilirubin level after 1 week of prednisolone treatment. Compared to previously treated patients (who were continued on steroids despite lack of bilirubin response), there was no improvement in 2-month survival, thus arguing against a two-step strategy with an early switch to pentoxifylline.<sup>220</sup> Several older studies had examined the role of anabolic steroids with nutritional interventions (based on the presumption that both interventions acted via a similar mechanism, i.e., correction of protein calorie malnutrition).<sup>221</sup> One pilot study evaluated the role of steroids in combination with enteral nutrition in 13 patients with severe AH, and found an overall mortality of 15%—pos-



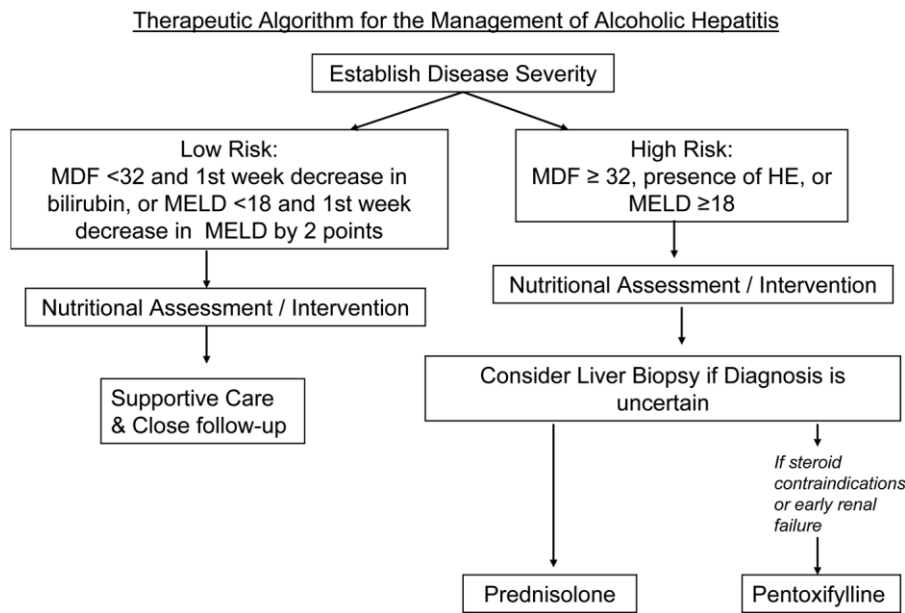


Fig. 1. Proposed algorithm for alcoholic hepatitis.

sibly an improvement from expected.<sup>222</sup> With the advent of new therapies, it is necessary to reconsider the risk-benefit ratio of medical treatment. It has been suggested that it may be possible to use less toxic therapies at a lower threshold of disease severity.<sup>223</sup> However, the exact role of these new therapies, and the threshold for their use, is still undefined.

**5. Other Treatments.** Many other therapeutic interventions have been studied in alcoholic hepatitis, but have not been able to show convincing benefit, including trials of antioxidants (vitamin E, silymarin, combination antioxidants), antifibrotics (colchicine), antithyroid drugs (propylthiouracil [PTU]), promoters of hepatic regeneration (insulin and glucagons), anabolic steroids (oxandrolone and testosterone), as well as calcium channel blockers (amlodipine), polyunsaturated lecithin, and a number of complementary and alternative medicines (reviewed in O'Shea and McCullough<sup>224</sup>). In addition to medical treatment directed at the underlying pathophysiologic abnormalities, several studies have tested other aggressive interventions in patients with AH, such as a molecular adsorbent recirculating system.<sup>225</sup> Although the results of early studies were optimistic, with better than predicted outcomes in treated patients, a further case series was less promising.<sup>226</sup> Case reports have also described the outcome of patients with severe AH treated with leukocytapheresis after failing to improve substantially on steroids.<sup>227,228</sup> These reports are promising, but recommendations regarding their appropriate use must await results of comparative studies of outcomes in these patients.

A proposed treatment algorithm for alcoholic hepatitis is shown in Fig. 1.

**Recommendations:**

**8. All patients with alcoholic hepatitis should be counseled to completely abstain from alcohol (Class I, level B).**

**9. All patients with alcoholic hepatitis or advanced ALD should be assessed for nutritional deficiencies (protein-calorie malnutrition), as well as vitamin and mineral deficiencies. Those with severe disease should be treated aggressively with enteral nutritional therapy (Class I, level B).**

**10. Patients with mild-moderate alcoholic hepatitis—defined as a Maddrey score of <32, without hepatic encephalopathy, and with improvement in serum bilirubin or decline in the MDF during the first week of hospitalization—should be monitored closely, but will likely not require nor benefit from specific medical interventions other than nutritional support and abstinence (Class III, level A).**

**11. Patients with severe disease (MDF score of ≥32, with or without hepatic encephalopathy) and lacking contraindications to steroid use should be considered for a four week course of prednisolone (40 mg/day for 28 days, typically followed by discontinuation or a 2-week taper) (Class I, level A).**

**12. Patients with severe disease (i.e., a MDF ≥ 32) could be considered for pentoxifylline therapy (400 mg orally 3 times daily for 4 weeks), especially if there are contraindications to steroid therapy (Class I, level B).**

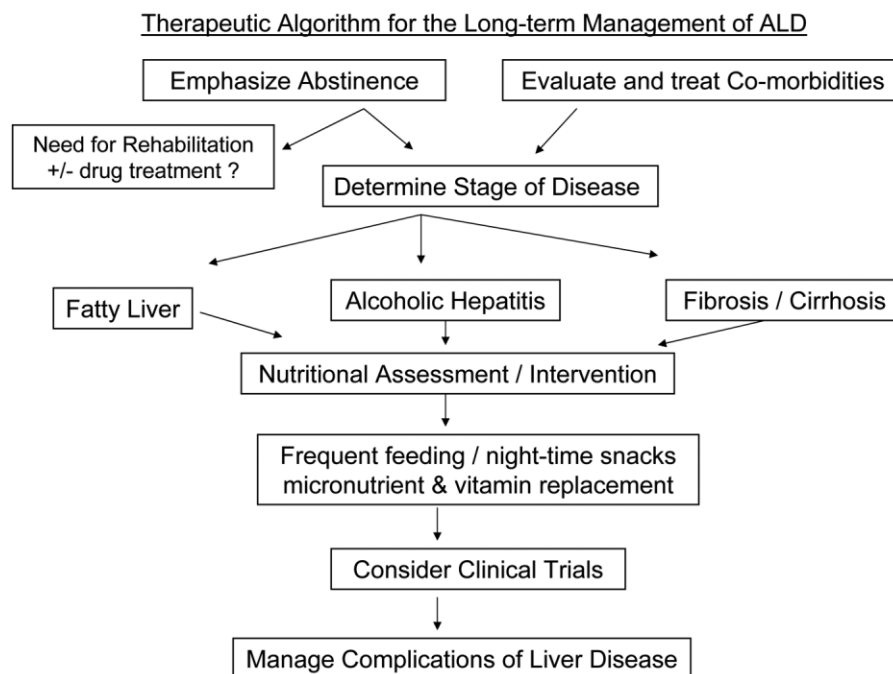


Fig. 2. Proposed therapeutic algorithm for the long-term management of alcoholic liver disease.

## VII. Long-Term Management of ALD

A proposed algorithm for the management of ALD is shown in Fig. 2.

### 1. Nutritional Therapy

Protein calorie malnutrition is common in ALD, is associated with an increased rate of major complications of cirrhosis (infection, encephalopathy, and ascites), and indicates a poor prognosis.<sup>194</sup>

A total of 13 studies (seven randomized and six open-label studies) have examined the effect of oral or enteral nutritional supplementation in patients with alcoholic cirrhosis, with interventions that ranged from 3 days to 12 months (reviewed in Stickel et al.<sup>229</sup>). Most of these studies are limited by small sample sizes and short durations of therapy. In one study, enteral feeding for 3-4 weeks in 35 hospitalized, severely malnourished or decompensated patients with alcoholic cirrhosis seemed to improve survival ( $P < 0.065$ ), hepatic encephalopathy, liver tests and Child-Pugh score, as compared with controls receiving a standard oral diet.<sup>197</sup> In longer-term studies, equinutritious amounts of dietary branched chain amino acids (BCAA) were compared with casein supplements for 3-6 months in patients with chronic hepatic encephalopathy,<sup>230</sup> and shown to improve encephalopathy, nitrogen balance and serum bilirubin compared with casein. Supplemental protein and 1000 kcal in decompensated patients with alcoholic cirrhosis have also been shown to

reduce hospitalizations for infections over a 1-year period.<sup>231</sup>

Long-term aggressive nutritional therapy by the enteral or oral route in patients with alcoholic cirrhosis is supported by studies that have shown improved nutritional status.<sup>232,233</sup> Although controversial, this may possibly prevent complications of cirrhosis.<sup>195,234</sup> Multiple feedings, emphasizing breakfast and a nighttime snack, 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) seem beneficial.<sup>235,236</sup> Finally, during intermittent acute illness or exacerbations of the underlying chronic liver disease, above normal protein intake (1.5 g/kg body weight), and kilocalorie intake (40 kcal/kg) improves protein calorie malnutrition,<sup>234</sup> and should be considered in the treatment of these patients.

#### **Recommendation:**

**13. Patients with alcoholic cirrhosis should receive frequent interval feedings, emphasizing a night time snack and morning feeding, to improve nitrogen balance (Class I, level A).**

### 2. Medical Therapies

A number of other agents have been tested in patients with ALD. These include PTU, which was thought to decrease the hypermetabolic state induced by alcohol.<sup>237,238</sup> A Cochrane review of 6 randomized controlled trials of PTU in alcoholic liver disease, with a total of 710 patients administered either PTU or placebo did not

show any benefit of PTU over placebo on the total or liver related mortality, complications of liver disease or liver histology in patients with alcoholic liver disease.<sup>239</sup> A possible benefit of supplementation with S-adenosyl L-methionine (S-AMe), a precursor to glutathione, has also been studied extensively.<sup>240</sup> One trial demonstrated a statistically significant improvement in survival in patients with Childs A and B cirrhosis randomized to S-AMe compared to placebo.<sup>241</sup> Despite a strong theoretical rationale, and a number of supportive clinical trials,<sup>240,242</sup> a Cochrane review of published data, based on nine randomized controlled trials with 434 patients in different stages of ALD, did not demonstrate any significant benefit of S-AMe on total mortality, liver related mortality, complications or liver transplantation in patients with ALD.<sup>243</sup>

Colchicine, which has both anti-inflammatory and antifibrotic properties, has also been tested in alcoholic cirrhosis after several small clinical trials, had suggested improvement in fibrosis on serial liver biopsies in treated patients.<sup>244,245</sup> However, a systematic meta analysis by the Cochrane group of 15 randomized trials with 1714 patients (including patients with alcoholic fibrosis, alcoholic hepatitis, and/or alcoholic cirrhosis as well as patients with viral induced or cryptogenic fibrosis and/or cirrhosis)<sup>246</sup> showed no benefit of treatment on overall mortality, liver related mortality, liver tests or histology. In addition, there was an increased risk of adverse effects related to colchicine therapy.

Emerging data suggest a role for TNF- $\alpha$  mediated apoptosis in alcoholic hepatitis and, therapy targeting this cytokine to inhibit apoptosis may be effective.<sup>247</sup> Thalidomide, misoprostol, adiponectin and probiotics have been shown in preliminary reports to have anticytokine properties.<sup>248-251</sup> Although promising, these treatments can not be considered as standard treatment for ALD and AH until further evidence of efficacy has been obtained.

### 3. Complementary and Alternative Medicine Treatment Options

Various alternative treatment options have been tested in the therapy of ALD. Silymarin, the presumed active ingredient in milk thistle, is postulated to protect patients from ALD on the basis of its antioxidant properties. Six published trials of the use of silymarin in patients with ALD<sup>252</sup> have tested its effects on normalizing liver tests and improving liver histology. One study suggested a possible survival benefit compared to placebo.<sup>253</sup> However, a Cochrane systematic review and meta analysis of the 13 published studies of silymarin in ALD and other liver diseases determined that the overall methodological quality of the studies was low. Based on the few high quality trials, it was concluded that milk thistle does not signifi-

cantly influence the course of patients with alcoholic liver disease.<sup>254</sup>

#### **Recommendations:**

**14. PTU and colchicine should not be used in the treatment of patients with ALD; S-AMe should be used only in clinical trials (Class III, level A).**

**15. The use of complementary or alternative medicines in the treatment of either acute or chronic alcohol-related liver disease has shown no convincing benefit and should not be used out of the context of clinical trial (Class III, level A).**

## VIII. Liver Transplantation for ALD

ALD is the second most common indication for liver transplantation (LT) for chronic liver disease in the Western world.<sup>255</sup> Despite this, it is estimated that as many as 95% of patients with end-stage liver disease related to alcohol are never formally evaluated for candidacy for liver transplantation.<sup>256</sup> This is attributed to perceptions that ALD is self-induced, the possibility of recidivism or noncompliance, and the shortage of organs.<sup>179</sup>

A 6-month period of abstinence has been recommended as a minimal listing criterion.<sup>257</sup> This time period allows chemical dependency issues to be addressed; in patients with recent alcohol consumption, it may also allow sufficient clinical improvement to make LT unnecessary. This requirement for a fixed abstinence period has not been shown to accurately predict future drinking by alcoholic candidates for LT.<sup>258</sup> Despite some data suggesting that patients with ALD were more ill at the time of LT, and likely to have prolonged intensive care unit stays and increased blood product requirements,<sup>259</sup> overall survival rates are generally similar between alcohol-related and non-alcohol-related LT recipients.<sup>260</sup>

Patients who underwent LT for alcoholic liver disease are highly likely to drink after transplantation.<sup>260</sup> It has been suggested that the consequences of alcohol use are minimal for many recipients, because the amounts consumed are small and infrequent, but there are little reliable data to support this contention. Rates of recidivism between 11%-49% (defined as any alcohol consumption after transplantation) at 3-5 years after LT have been reported.<sup>179,261</sup> In general, however, only a small fraction of those who undergo liver transplantation for ALD revert to heavy alcohol use or abuse.<sup>256</sup> Poor follow-up and non-compliance with therapy are observed in only a minority of patients, and graft rejection rates are similar for patients with ALD compared to those without ALD.<sup>255,260</sup>

An important issue that is still unresolved is the role of LT in patients with alcoholic hepatitis, who are generally excluded from transplant.<sup>257</sup> In one study using retrospective histological analysis of the explanted liver, super-

imposed alcoholic hepatitis did not worsen the outcome after LT.<sup>262</sup> The availability of living donor transplantation and extended criteria donor liver transplantation are likely to heighten the debate on this issue.

**Recommendation:**

**16. Appropriate patients with end-stage liver disease secondary to alcoholic cirrhosis should be considered for liver transplantation, just as other patients with decompensated liver disease, after careful evaluation of medical and psychosocial candidacy. In addition, this evaluation should include a formal assessment of the likelihood of long-term abstinence (Class I, Level B).**

*Acknowledgment:* This guideline was produced in collaboration with the Practice Guidelines Committee of the American Association for the Study of Liver Diseases and the Practice Parameters Committee of the American College of Gastroenterology. These committees provided extensive peer review of the manuscript.

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