Management of Patients with Moderate Alcoholic Liver Disease

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Alcohol consumption causes 3.8% mortality worldwide.[1] Because alcoholic liver disease (ALD) is a leading cause of preventable death, it is imperative to detect moderate ALD and arrest its progression.

For the purposes of this article, we define patients with moderate ALD as those who have recovered from severe alcoholic hepatitis, have early signs of ALD, or have very early compensated cirrhosis. Multiple grading systems are available for determining the severity and prognosis of ALD, and patients with moderate ALD generally have a Maddrey discriminant function score <32 or a Model for End-Stage Liver Disease score <21. Although they may not have immediately life-threatening problems, a great opportunity exists to improve their modifiable risk factors, address their underdiagnosed malnutrition, and consider whether they would benefit from pharmacotherapy (Fig. 1).

Many patients will be clinically evident with signs and symptoms of liver disease, whereas others will be asymptomatic at the time of diagnosis. Although not a prerequisite for the development of ALD, screening for alcohol abuse and/or dependency may detect an at-risk population of patients. The Alcohol Use Disorders Identification Test (AUDIT) can identify risky alcohol use (score ≥8 for men up to age 60 or ≥4 for women, adolescents, or men over age 60) and alcohol dependence (score ≥20).[1] Prior to complications of ALD, early ALD is clinically diagnosed in patients with a history of significant alcohol use combined with objective findings. Physical examination findings can be nonspecific, but most commonly hepatomegaly is present. Likewise, laboratory findings can be insensitive, but up to 80% of patients with ALD will have an aspartate aminotransferase/alanine aminotransferase ratio of >2.[2] Other indicative laboratory findings include leukocytosis, thrombocytopenia, prolongation of prothrombin time, and hypoalbuminemia.

Extrahepatic manifestations of more advanced ALD include spider angiomata, latent portosystemic encephalopathy, hepatopulmonary syndrome, hypertriglyceridemia, and electrolyte abnormalities such as hypokalemia and hypomagnesemia. A complete physical examination and basic laboratory evaluation to screen for these common derangements should be part of routine ALD care.

Lifestyle Modification

When managing a patient with ALD, steps should be taken to achieve alcohol cessation. Many studies have shown that patients who quit drinking have improved survival; moreover, even cutting back on alcohol consumption can lead to some improvement in liver disease.[3] Brief interventions, during which a patient has regular conversations with a nurse or physician focusing on feedback, responsibility, advice, empathy, and optimism, have been shown to reduce drinking.[4] Patients should be encouraged to consider behavioral programs such as Alcoholics Anonymous. Although it is difficult to obtain controlled outcome data for organizations whose members remain anonymous, the Alcoholics Anonymous 2007 self-reported membership survey reported that 33% of their members had been sober for more than 10 years, and the average sobriety of their members is more than 8 years.[5] For patients who continue to crave alcohol despite undergoing brief interventions and attending behavioral programs, pharmacologic adjuncts can be offered.

Trials examining the effectiveness of medical therapy for alcohol abuse have lacked consistent endpoints, and the results have not always been reproducible.[3] Naltrexone and baclofen both have shown benefit and failure in different clinical trials. Baclofen is the only drug for alcohol dependence currently under investigation that has good safety data

Abbreviations: ALD, alcoholic liver disease; MUST, Malnutrition Universal Screening Tool; SAMe, S-adenosylmethionine.

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Potential conflict of interest: Nothing to report.

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doi: 10.1002/cld.190

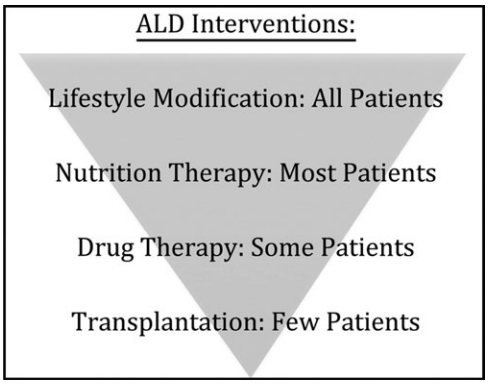

FIGURE 1. Interventions for moderate ALD patients lay on a continuum. All patients should control the modifiable risk factors of alcohol use, obesity, and smoking. Most patients will benefit from treatment for malnutrition. Some patients may need pharmacotherapy. The few patients who will be transplant candidates are those with severely decompensated ALD, which is not discussed here.

in patients with cirrhosis, making it a reasonable first-line choice in this patient population.[6] Naltrexone has a black box warning for hepatotoxicity and is contraindicated in acute hepatitis or hepatic failure. Topiramate is a relatively new therapy for alcohol abuse and has not yet been tested in a double-blind randomized trial with alcohol abstinence as an endpoint in patients with moderate ALD.[7]

The COMBINE Study showed that a multifaceted approach results in a higher number of days of abstinence from alcohol. Patients who met with a physician and also either took naltrexone or underwent combined behavioral intervention did better than those who only met with a physician and received a placebo.[8]

Cigarette smoking[9] and obesity[10] are both independent risk factors for fibrosis in ALD and must also be addressed. Although a patient may fit the definition of obesity (body mass index >30), they may still have concurrent nutritional deficiencies in macronutrients (e.g., protein) or micronutrients (e.g., zinc).

Nutrition Therapy

Many patients with ALD are malnourished, and disease severity correlates with degree of malnutrition. Data from two VA Cooperative studies showed the importance of high caloric intake, as patients who consumed more calories had improved survival.[11]

While visceral proteins (albumin, prealbumin, and retinol binding protein) are the most common laboratory tests used to assess a patient's nutritional status, these results can be confounded by the underlying liver disease or superimposed infections. Evaluating clinical findings such as muscle wasting, edema, loss of subcutaneous fat, and glossitis/cheilosis are helpful in subjectively identifying protein energy malnutrition. Nutritional assessments of alcoholic patients can reveal adequate calorie intake. Indeed, in some studies, almost 50% of patients' energy intake was from alcohol alone, leading to deficient protein and micronutrient intake.[12] The most common vitamin deficiencies are folate, vitamin B_6, vitamin A, and thiamine. Mineral deficiencies include selenium, zinc, copper, and magnesium.[13] We advise that patients take a multivitamin and be supplemented with zinc sulfate 220 mg/day, as well as magnesium oxide 400 mg/day.

There are not adequate data to definitively determine ideal nutritional support. However, American College of Gastroenterology and American Association for the Study of Liver Diseases guidelines recommend 1.2-1.5 g/kg of protein and 35-45 kcal/kg of body weight in patients with ALD.[14] For a 175-pound patient, that is approximately 96-120 g/day of protein and 2,800-3,600 cal/day. These high numbers often come as a surprise to physicians and patients alike, but it should be stressed that ALD patients are often malnourished. Therefore, efforts should be made to gain lean body weight. A bedtime snack of 700 cal with 26 g of protein (e.g., a can of nutritional supplement) can prevent nocturnal amino acid breakdown for gluconeogenesis and improve the nitrogen balance. Evening meals improve nutritional status and cell immunity and may reduce hospital admissions.[15] Adherence to sodium restriction is vital in patients starting to retain fluid (peripheral edema, ascites), which is usually seen in more advanced disease. Table 1 provides a summary of nutritional recommendations for ALD patients.

Gut-derived endotoxin (lipopolysaccharide) plays a critical role in the pathogenesis of ALD. Improving the gut barrier function to prevent absorption of lipopolysaccharide is an active area of research. Fasting can impair gut barrier function. In a mouse model of ALD, unsaturated fat (corn oil/linoleic acid) worsened the gut barrier function and exacerbated ALD compared with diets rich in saturated fats.[16] Similarly, zinc deficiency impaired gut barrier function in an animal model of ALD. In summary, food intake helps maintain barrier function, and alterations in dietary fat and zinc may worsen alcohol-induced gut barrier dysfunction and endotoxemia.

Determining endpoints in nutritional support in ALD has not been studied adequately. In general, the more severe the ALD, the longer the patient will need to be replenished. Using the subjective global assessment---which is based on clinical findings such as muscle wasting, edema, loss of

TABLE 1: Nutritional Recommendations for ALD Patients

Evaluate for clinical signs of malnutrition in all ALD patients
Daily caloric intake: 35-40 kcal/kg
Daily protein intake: 1.2-1.5 g/kg
Evening snack of 700 cal and 26 g protein
Avoid unsaturated fats
Zinc sulfate 220 mg daily
Magnesium oxide 400 mg daily

TABLE 2: Medications and Complementary Therapy for ALD Patients

Pentoxifylline 400 mg 3 times daily (prescription)
Silybum marianum (milk thistle) 200 mg 2-3 times daily (complementary)
SAMe 400 mg 3-4 times daily (complementary)
Probiotics as directed (complementary)

subcutaneous fat, and glossitis/cheilosis---could help guide changes to nutritional support.[17] The Malnutrition Universal Screening Tool (MUST) has been used for alcoholic inpatients.[18] Although it has not been validated prospectively, the MUST score could be used to reassess a patient's nutritional status while on nutritional support. A MUST score of 2 or more would indicate that a patient is malnourished.

Drug Therapy

Despite the prevalence and morbidity of ALD, there is no US Food and Drug Administration–approved therapy for any form of ALD. In patients who show disease progression despite alcohol cessation and efforts to improve nutritional status, off-label drug therapy or complementary and alternative therapy may be considered (Table 2).

Pentoxifylline is a nonselective phosphodiesterase inhibitor that has been shown in clinical trials to improve mortality in alcoholic hepatitis, primarily through the prevention of hepatorenal syndrome.[3] Trials with pentoxifylline in patients with moderate ALD have not been performed. Because it has a very good safety profile, it may be used in patients with moderate ALD if they can tolerate the common side effect of nausea. Pentoxifylline is prescribed at a dose of 400 mg three times daily.

Basic evidence supports the use of *Silybum marianum* (milk thistle), and many of our patients are already taking this agent. Silybum has anti-inflammatory and antioxidative properties resulting in antifibrotic and immunomodulating effects.[19] It is safe to use in patients with liver disease and is widely used in Europe. A frequently used dose is 200 mg two to three times daily, but its efficacy has not been established in ALD.

S-adenosylmethionine (SAMe) is a major methylating agent that has important epigenetic and anti-inflammatory effects. In animal studies, SAMe is depleted in the early stages of ALD, leading to early fatty liver infiltration and mitochondrial damage. This damage can be reversed with SAMe supplementation.[20] SAMe is available at health food stores and is recommended at a dose of 400 mg three to four times daily.

Altered intestinal bacterial composition, impaired gut barrier function, and gut-associated endotoxemia are increasingly recognized as critical components of ALD. Probiotics are live microorganisms that, when consumed in adequate amounts, confer a health benefit to the host. There are many mechanisms by which probiotics enhance intestinal health and influence the gut-liver axis, including modulation of the intestinal microflora, modification of intestinal barrier function, and immunomodulation. Probiotics have been shown to have beneficial effects in multiple studies in experimental ALD, and their effects are now being evaluated in a multicenter trial in ALD that is sponsored by the National Institutes of Health.[21]

Conclusion

Moderate ALD should be considered an illness requiring medical attention for improved survival. To best help ALD patients, physicians can increase the likelihood of alcohol cessation though brief interventions, provide specific nutrition recommendations, and add medical therapy as needed.

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