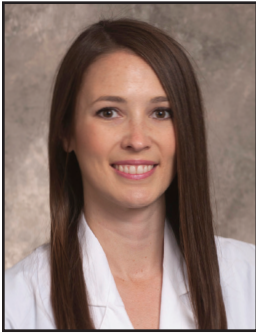


Carol Rees Parrish, M.S., R.D., Series Editor

## Food for Thought: Importance of Nutrition in Alcoholic Hepatitis



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As alcohol consumption increases worldwide, so does the prevalence of various clinical manifestations of alcohol-related liver disease. Acute alcoholic hepatitis (AAH) is the most severe form of alcoholic liver disease, yet many patients suffering from this syndrome are not diagnosed or are inadequately treated. Morbidity and mortality are high in patients with severe AAH. Unfortunately, available therapeutic regimens remain few and far between. Nutritional support is an essential component of treatment for AAH as malnutrition has been associated with poorer outcomes. The role of adjunctive nutritional support, including enteral feeding and specific supplemental micronutrients, needs to be better delineated as it relates to altering clinical outcomes. We review the nutritional aspects of patients with AAH and the effect implementation of various dietary interventions have on clinical outcomes of this frequently deadly condition.

### INTRODUCTION

**A**lcoholic liver disease (ALD) refers to a spectrum of diseases including asymptomatic steatosis, alcoholic steatohepatitis (ASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma. In its most severe form, AAH refers to decompensation of liver function on a background

of heavy alcohol use and chronic ALD. This syndrome is characterized by several clinical features including malaise, anorexia, jaundice, tender hepatomegaly, and features of the systemic inflammatory response syndrome (SIRS) such as fever, tachycardia, and leukocytosis. This syndrome increases catabolism by up to 60% energy expenditure with increasing nutritional requirements necessary to support this state.<sup>1,2</sup> Patients with ALD are prone to a wide range of nutritional issues including direct consequences such as protein/calorie malnutrition and deficiencies in many micronutrients; indirect consequences are often due to other environmental factors largely associated with lifestyle changes.

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## Therapeutic Approach

Goals of treatment are to reduce short-term morbidity and mortality by utilizing a combination of intensive supportive care and adjuvant pharmacological therapies. Abstinence from alcohol is the cornerstone of therapy that is integral to long-term survival. The currently accepted pharmacological standard of care in treatment of severe AH is glucocorticoid therapy, although the optimal duration of therapy remains unclear.<sup>3</sup> Several randomized control trials (RCTs) have demonstrated conflicting results regarding survival benefit. Glucocorticoids have been shown to improve short term mortality at 28 days, but long-term mortality benefits are unproven.<sup>4,5</sup> The efficacy of pentoxifylline for improving mortality is not supported.<sup>4</sup> Adequate intake of both calories and nutrients is an essential component of intensive supportive care<sup>6</sup> and has become an area of focus given the lack of other effective treatment modalities.

## Nutrition Support

Numerous factors contribute to poor overall nutritional status that is commonly observed in patients with AAH (Table 1). These long-standing observations are a major reason that nutrition support is viewed as an essential part of the standard care for AH. Not surprisingly, patients with malnutrition are at increased risk for impaired recovery from AAH.<sup>6</sup> Several studies have documented an association between protein-calorie malnutrition and higher short and long-term mortality rates in patients with severe AH.<sup>7,8</sup>

## Oral Nutrition

Multiple studies have shown that low daily caloric intake is associated with increased mortality in severe AH.<sup>9-12</sup> The degree of protein-calorie malnutrition is directly related to mortality with a rate that approaches 80% in those patients who are characterized as severely malnourished.<sup>9</sup> Patients with severe ALD often have reduced hepatic glycogen stores that result in hypoglycemia and accelerated catabolic breakdown of muscle to support gluconeogenesis.<sup>10</sup> Reducing the length of time without oral calories with an emphasis on eating breakfast and a bedtime snack, as well as avoiding prolonged fasting during hospitalization

**Table 1. Factors Affecting Nutritional Status in Patients with AAH**

- Poor intake
  - Anorexia
  - Nausea
  - Early satiety
    - Delayed gastric emptying
    - Gastric compression from ascites
      - NPO for procedures, etc.
      - Hospital food/restricted diets
- Prolonged small bowel transit
- Altered taste
- Hepatic encephalopathy
- Increased risk of Wernicke's Encephalopathy
- Mechanical ventilation
- Increased energy expenditure
- Alcohol withdrawal
- Insulin resistance
  - Increased postprandial glucose
  - Decreased postprandial ghrelin
- Impaired gut barrier function
  - Increased risk of small bowel bacterial overgrowth
  - Increased risk of infection
- Malabsorption

or for diagnostic testing (i.e., add D5 to IV fluids where possible), may reduce the adverse impact of reduced hepatic glycogen stores.<sup>11,12</sup>

Standard per oral dietary intake is often impaired in these patients for a multitude of reasons,<sup>13</sup> including delayed gastric emptying and prolonged small bowel transit times resulting in early satiety.<sup>14</sup> Furthermore, ascites can result in impaired gastric accommodation leading to postprandial discomfort.<sup>15</sup> In addition to the mental status changes that can be seen in hepatic encephalopathy (HE) limiting ability to eat, HE also contributes to impaired appetite, and in some more covert forms, leading to an overall malnourished

state. Finally, the use of lactulose (a non absorbable, but highly fermentable synthetic sugar) in treatment of encephalopathy can contribute to symptoms of bloating and discomfort, thus exacerbating impaired per oral intake.<sup>16</sup> Patients who develop HE are at risk of undernutrition and enteral access may be indicated.<sup>26,27</sup> Normal- to high-protein diets are safe and do not increase the risk of encephalopathy in alcoholic hepatitis.<sup>6</sup>

### Enteral Nutrition Support

In the most severe forms of AAH, patients may be intubated or obtunded to the point where conventional nutrition is not an option and enteral nutrition (EN) must be considered. Whether or not NG tubes should be recommended to provide EN remains controversial given potential feeding tube complications seen in some trials,<sup>17,21</sup> although the risk/benefit seems to weigh in favor of providing nutrition in these individuals.

Data suggest that the optimal nutrition goals for recovery are 1.5 g of protein/kg body weight and 30 – 40 kcal/kg of body weight per day and should be initiated as soon as impaired per oral intake is noted.<sup>18</sup> The American Society for Parenteral and Enteral Nutrition (ASPEN) suggest using an estimated euvolemic weight or usual weight for these calculations rather than actual weight in patients with cirrhosis and hepatic failure given complications of hypoalbuminemia, edema, intravascular depletion, and ascites that are often present in this patient population masking the patient's true weight.<sup>19</sup> EN is the preferred modality for providing nutrition in these patients unable to tolerate per oral intake based on expert consensus from ASPEN, and the American Gastroenterological Association.<sup>18,19</sup>

In a systematic review assessing effects of nutritional intervention for patients with AH or cirrhosis, analysis of 13 randomized controlled trials suggested that nutritional therapy may have beneficial effects on clinical outcomes and mortality yet, given the high risk of bias in all the studies included, the need for higher quality trials was again underscored.<sup>20</sup> Several RCTs have shown that EN was comparable with glucocorticoids in reducing 28-day mortality and more effective in reducing long-term mortality. Another study suggested that combining intensive EN via

nasogastric (NG) tube with glucocorticoids was not more effective than glucocorticoids alone, but the study was limited by lack of power and a higher than expected rate of NG tube complications in 7.4% of patients including aspiration pneumonia, poorly controlled hyperglycemia, and worsening HE. Premature feeding tube withdrawal was noted in 48.5% of patients predominantly due to intolerance and noncompliance.<sup>21</sup> Importantly, regardless of the study arm, nutritional intake was found to be an important determinant of mortality, with those patients consuming < 21.5 kcal/kg/day having lower survival. Another study investigated combining EN with corticosteroids revealed improved survival, suggesting a complementary mechanism with these two therapies. Of note, corticosteroids were tapered when serum bilirubin and prothrombin time decreased by 50%, suggesting that a more individualized approach to duration of steroid therapy is key.<sup>22</sup> The Lille model is useful to predict mortality rates in patients with severe alcoholic hepatitis treated with steroids and should be utilized to avoid extending therapy in those who are unlikely to respond, thereby reducing the risk of complications of glucocorticoid therapy.<sup>23</sup>

In general, EN is preferable to parenteral nutrition support because delivery of nutrition to the gut strengthens gut mucosal immunity and subsequently decreases endotoxemia that may play a role in the pathogenesis of alcoholic hepatitis; it is also a less expensive option with far fewer complications.<sup>24</sup> Those patients with hepatic encephalopathy should be treated with nonabsorbable disaccharides, such as lactulose; rifaximin can be added if this treatment is not effective after 24-48 hours.<sup>25</sup>

### Parenteral Nutrition Support

Many randomized control trials have been performed comparing parenteral nutrition (PN) to enteral feeding in hospitalized patients with AAH and ALD. PN was shown in one of these studies to decrease serum bilirubin more rapidly and improve nitrogen balance, one measure of improved nutritional status.<sup>28</sup> However, PN did not significantly improve mortality or hepatic encephalopathy and was associated with increased risk of line infections and other complications such as thrombophlebitis. Furthermore, a Cochrane

**Table 2. Summary Guidelines Based on Current Available Evidence**

- Abstinence from alcohol is the cornerstone of treatment for alcoholic hepatitis.
- Malnutrition is present in the vast majority of patients with AAH and restoration of adequate nutrition is a key component of treatment.
- Avoid restrictive hospital diets - make sure a patient is eating enough to warrant a dietary restriction
- In patients with early satiety, encourage more nutrient dense foods instead of salad, etc.
- Nutritional deficiencies are common and should be identified and repleted if present.
- Avoid periods of fasting to protect lean body mass in glycogen-poor individuals.
  - Add D5 to IV fluids when NPO for > 4 hours
  - Ensure snacks are provided, especially bedtime and morning after an overnight fast
  - Educate patient and family on why this is important
- Glucocorticoid therapy and enteral nutrition represent the best options for reducing short-term mortality in patients with severe AAH.
  - Ensure good glycemic control to maximize nutrient utilization and prevent catabolism from hyperglycemia
- Aim for diets with 1-1.5 g/kg protein and 30-40 kcal/kg body weight (after refeeding) for adequate recovery in AAH.
- In the setting of anorexia or altered mental status, or poor PO intake, a feeding tube should be considered for early enteral feeding.

review of 37 RCTs studying therapeutic effects of PN, EN, and nutritional supplements, found no significant difference in mortality. However, all but one of the included trials had a high risk of systematic error highlighting the need for better designed and higher powered randomized trials to prove efficacy of various nutritional therapies.<sup>29</sup> Given the known hepatic complications associated with PN including sepsis, coagulopathy, and death in addition to worsening of existing liver disease and steatohepatitis, this modality is not recommended as preferential therapy.<sup>30</sup>

### Supplements

In addition to a high prevalence of severe protein-calorie malnutrition in heavy alcohol users, numerous micronutrient deficiencies including zinc, folate, thiamine, pyridoxine, vitamins A, B12, D, and E, have been reported in patients with heavy alcohol use and ALD.<sup>31-33</sup> These nutritional deficiencies are not solely related to poor intake, but also to impaired absorption placing these

patients at risk of osteoporosis, myopathy, insulin resistance, and dyslipidemia, as well as increase the risk of developing alcohol-induced liver injury. Factors contributing to these deficiencies include:

- impaired hepatic production of carrier proteins;
- decreased bile acid synthesis and their small bowel delivery as a result of cholestasis leading to fat malabsorption.<sup>34</sup>

Zinc supplementation may attenuate alcohol-induced liver injury and prevent hepatic encephalopathy through several mechanisms including the improvement of intestinal barrier function, decreasing proinflammatory cytokines, oxidative stress, and endotoxemia, as well as offsetting hepatocyte apoptosis.<sup>35,36</sup> The recommended dose of zinc used for treatment of liver disease is usually 50 mg of elemental zinc (220 mg of zinc sulfate) taken once daily with a meal to decrease possible nausea. Of note, long term zinc supplementation can be associated with copper

deficiency due to competition at the brush border for absorption. The duration of supplementation requires further investigation.

### Obesity

Obesity and excess body weight have been associated with increased risk of development of ALD.<sup>37,38</sup> It is proposed by some experts that preexisting fatty liver due to obesity provides the necessary milieu to potentiate additional injury from alcohol,<sup>18</sup> thus explaining the increased risk of AH in these patients. Recent data has also shown that there is increased gut permeability in patients with obesity and hepatic steatosis, which likely plays a role in the development of alcoholic liver disease.<sup>39</sup>

### Microbiome

Newer research suggests that the intestinal dysbiosis induced by alcohol ingestion is integral to the development of alcohol-induced liver injury, further emphasizing the role of the gut-liver axis in disease development. The “leaky gut” phenomenon is supported by numerous human and animal studies, which suggest alcohol intake causes impaired intestinal barrier function allowing for bacterial transport across the intestinal basement membrane into systemic circulation.<sup>40-42</sup> One study using a murine model showed that acute on chronic alcohol ingestion led to alterations in gut microbiota.<sup>43</sup> Treatment with antibiotics prevented neutrophilic infiltration mimicking acute steatohepatitis in human patients, as well as reduced the expression of several proinflammatory markers and reduced steatosis.<sup>43</sup> Other human studies have shown a high level of endotoxemia associated with chronic alcohol use.<sup>44</sup> These observed changes in the gut microbiome have spurred investigations into possible interventions, which may normalize alcohol-induced intestinal dysbiosis. One study showed that rats consuming alcohol who were later fed with *Lactobacillus*-containing probiotics or prebiotic oats achieved similar microbiota compositions to the control mice.<sup>45</sup> Similar results have been seen in human studies,<sup>46,47</sup> suggesting that probiotics may improve clinical outcomes in patients with AH by reversing dysbiosis. Evidence also suggests that probiotics may prevent or decrease intestinal

hyperpermeability thus decreasing intestinal oxidative stress and proinflammatory cascade<sup>48-50</sup> which could potentially ameliorate development of alcoholic liver disease. Although probiotics are not considered a standard of care in the treatment of AAH, several RCT’s are underway to study potential benefits of probiotic therapy in patients with moderate AAH ([clinicaltrials.gov](http://clinicaltrials.gov)).

### CONCLUSION

Nutritional intake is an essential component in recovery from AAH. Protein-calorie malnutrition is associated with significantly higher short and long-term mortality. Existing data favor early initiation of EN during this critical illness, however, more robust data supporting provision of EN when per oral intake is inadequate is needed. The role of specific therapies, particularly zinc and probiotics, in addition to clear recommendations on optimizing nutritional supplementation in this patient population also needs further study. Table 2 provides suggested nutrition interventions for clinicians in patients with AAH based on available evidence. ■

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(continued on page 36)

(continued from page 34)

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