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Nutrition Update in Hepatic Failure

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Malnutrition is common in patients with cirrhosis and is associated with decreased quality of life, increased complications, and increased morbidity post liver transplant. Advancements in the understanding of malnutrition and the limitations of traditional nutrition assessment have spurred the development of new methods of evaluating nutrition status that are particularly applicable to patients with cirrhosis. Nutrition therapy for patients with cirrhosis is also undergoing an evolution. Nutrition counseling should deemphasize non-essential dietary restriction, and instead focus on preventing, or reversing malnutrition and maintaining functional status and quality of life. Nutrition interventions may assist with symptom management and slow loss of muscle mass. However, there is a need for adequately designed research to investigate the effects of providing additional nutrition to cirrhotic patients with malnutrition on quality of life and other outcomes.

Incidence and Causes of Malnutrition

Malnutrition as a consequence of cirrhosis has been reported for more than 50 years. Although the incidence of malnutrition described has varied widely based on the severity of liver disease and the definition of malnutrition used, there is agreement that malnutrition occurs commonly in cirrhosis.[1-4] More than 60% of patients with end-stage liver disease are malnourished, and nearly all patients with decompensated liver disease that are transplant candidates have some element of malnutrition.[1-4]

Cirrhosis can be considered a form of "accelerated malnutrition."[4] Inadequate ability to store liver and muscle glycogen, combined with increased insulin resistance leads to rapid breakdown of muscle and fat stores after short periods without food in patients with cirrhosis.[4] Breakdown of muscle for fuel leads to severe muscle wasting (sarcopenia) which contributes to decreased strength, loss of functional status and may compromise quality of life.[5, 6] Patients with cirrhosis have alterations in serum biologic mediators such as leptin, tumor necrosis factor (TNF) and adiponectin that accelerate muscle wasting and also cause anorexia.[1]

Decreased food intake is the most obvious source of malnutrition in cirrhosis.[2,7] Patients with more severe disease have been reported to have a greater reduction in nutrition intake, compared to patients with less serious cirrhosis.[2,7] In addition to anorexia caused by alterations in cytokines and other circulating factors, patients with cirrhosis have an increased incidence of delayed gastric emptying and small bowel bacterial

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overgrowth that can affect food intake.[8,9] Ascites is a major source of anorexia and early satiety in patients with decompensated disease.[1,2,8] Patients with ascites frequently eat better in the hospital after paracentesis, but then experience a progressive decrease in food intake at home as the ascitic fluid re-accumulates. Food intake, nutrition status and body composition improve after resolution of ascites post transjugular intrahepatic portosystemic shunt (TIPS).[10]

Nutrition Assessment

Nutrition assessment in liver disease has traditionally relied on measurement of serum proteins such as albumin, prealbumin or transferrin. However, the best available evidence indicates that serum protein levels are not accurate measures of nutrition status.[11,12] Those serum proteins that were erroneously thought to reflect nutrition status are inverse acute phase reactants, which rapidly decrease in infection, injury or other physiologic stress, and then begin to increase as the stress resolves independent of changes in nutrition intake.[11,12] Serum proteins are also affected by a plethora of non-nutritional factors including synthetic function of the liver, hydration status, renal failure, corticosteroid administration (prealbumin) and iron status (transferrin).[11]

In many patient populations, weight loss is the most useful indicator of malnutrition. However, patients with decompensated cirrhosis who have ascites often gain weight even when oral intake is poor and advanced malnutrition is present. A modified body mass index (BMI) has been proposed for patients with cirrhosis, and to provide an index for underweight in patients with ascites.[1] A BMI < 18.5 kg/m^2 is usually considered underweight, but in patients with cirrhosis a BMI < 20 kg/m^2 was associated with increased mortality. A BMI < 23 kg/m^2 may indicate underweight in patients with mild ascites, while BMI < 25 kg/m^2 may be underweight for patients with severe or tense ascites.[1] Alternatively, adjustments to actual weight can be made based on the severity of ascites (see Table 1). Conversely, patients without cirrhosis may have substantial loss of muscle, but maintain, or even increase fat stores with no net change in body weight.

Physical examination to investigate possible muscle wasting in the extremities and temporal muscle should be part of routine nutrition assessment in patients with cirrhosis. Studies of body composition using ultrasound, bioimpedance or CT scan have identified severe muscle wasting as a common occurrence in cirrhosis, and the degree of sarcopenia may even be a prognostic indicator for some cirrhotic populations.[3,5,6,13] A new study identified that pre-transplant muscle mass was associated with post-transplant outcomes including duration of ICU stay and days of mechanical ventilation.[6] In men, muscle mass was a significant predictor of survival and ability to be discharged to home (rather than discharged to a transitional facility).[6] Further research is needed to define standards of muscle mass for different age and disease categories, and to standardize technology and techniques for measurement of muscle mass before routine use is indicated in the clinical setting.

Table 1. Estimated Fluid Weight Estimation in Ascites

Degree of Ascites	Estimated Ascitic Weight Masking Euvolemic Weight
• Mild Ascites	• 3 - 5 kg
• Moderate Ascites	• 7 - 9 kg
• Severe Ascites	• 14 - 15 kg

Research also indicates that changes in functional status may be one of the better indicators of alterations in nutrition status. Measurement of handgrip strength has been used as surrogate a marker for functional status in some studies.[3] Obviously, measurement of handgrip strength is not feasible in patients that are sedated, critically ill or have severely altered mental status. However, handgrip strength appears to be able to predict decline in nutrition status before other signs of clinical compromise are apparent.[14] When measurement of handgrip strength is not feasible, discussions with patients and the patient's family or caregivers about possible changes in a patient's functional status can provide insights into overall nutrition status.

Evaluation of recent oral intake remains one of the most valuable components of nutrition assessment in patients with cirrhosis. A reliable history that documents poor oral intake may be all that is needed to appreciate a patient's nutrition status. A more detailed interview can be helpful to assess diet quality, variety of intake and investigate the source of limitations to oral intake. Patients that are not meeting basic calorie and protein

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requirements are also likely not receiving sufficient vitamin and minerals (unless they consistently take vitamin/mineral supplements).[7] Nutrition deficiencies do not normally occur in isolation, and detection of any nutrition inadequacies should be a reminder to consider other possible vitamin and mineral deficiencies.

Nutrition Needs: Calories

Patients with cirrhosis do not have substantially greater total calorie requirements than other populations.[1,2] Adult patients that are bedbound or have minimal physical activity frequently require 25-30 kcals/kg, while patients with moderate physical activity may be maintained on 30-35 kcals/kg.[7] Patients with increased physical activity and those who need to gain weight may require in excess of 40 kcal/kg to maintain or improve nutrition status.[7,15] Adequate calorie intake is important to help prevent dietary or body protein from being used to meet energy needs. However, excessive calorie provision can cause or accelerate hepatic lipid accumulation, especially in critically ill patients. Patients with obesity, especially those with non-alcoholic fatty liver disease or insulin resistance, may benefit from slightly hypocaloric nutrition. Patients with severe malnutrition or those who have had an extended period of decreased oral intake should have reduced calorie provision for the first several days to minimize electrolyte changes associated with refeeding syndrome. Estimation of euvolemic weight in patients with ascites is helpful to avoid overfeeding (see Table 1).

There are a number of formulas to help estimate calorie expenditure, however, no data exists demonstrating improved outcomes from the use of any particular method. Considering the wide daily variability of calorie expenditure and intake, a time efficient method such as calories per kilogram, to prevent gross underfeeding or overfeeding is generally sufficient (see Table 2). Monitoring actual nutrition intake is far more important than the accuracy of the initial calorie goal.

Table 2. Calorie Requirements Per Kilogram

Factor	Calories per Kg
Refeeding Risk	15 – 20/kg euvolemic weight
Maintenance	25 – 30/kg euvolemic weight
Repletion	30 – 35/kg euvolemic weight

Protein

Prior to the development of medications to treat hepatic encephalopathy, restricting dietary protein was often used in an attempt to control symptoms. However, there is no data in humans to support the use of dietary protein restriction in patients with cirrhosis. In one randomized study, patients receiving a protein restriction had significantly increased breakdown of body proteins with no advantage in treating encephalopathy, compared to patients receiving 1.2 gm protein/kg.[16] Three groups have reported that increasing protein to 1.2-1.5 gm/kg resulted in more rapid improvement in encephalopathy scores, compared to patients receiving reduced amounts of protein.[17-19] Considering that inadequate protein intake only results in muscle protein breakdown, it is not surprising that protein restriction has no clinical benefit. Unfortunately, there are no randomized studies that have investigated the ideal protein intake, or the upper limits of recommended intake in this population. There is sufficient evidence to support a protein intake of 1.2g/kg in most patients, with intakes up to 1.5 gm protein/kg in malnourished or acutely ill adults.[15]

There is extensive evidence that malnutrition is deleterious in cirrhosis. In view of the advantages of adequate protein intake on overall nutrition status and faster improvement of encephalopathy scores, plus the absence of any human data demonstrating a benefit of protein restriction, a protein intake below 1.0 gm/ kg should be discouraged in patients with cirrhosis. Our experience with those rare patients who have been described as protein intolerant is that symptoms have ultimately resolved upon discovery of an occult infection, GI bleeding, medication noncompliance or substance abuse. Unfortunately, there appears to be an "educational inertia" regarding the use of protein restriction in cirrhosis. Despite the lack of any evidence to support the use of protein restriction, and the data demonstrating the benefits of adequate protein, many textbooks and academic programs continue to propagate disproven notions of reduced protein intake in these patients.

Nutrition Intervention

Nutrition therapy for patients with hepatic failure should focus on preventing or reversing malnutrition. Maintaining adequate food intake, with frequent

Table 3. Suggested Nutrition Intervention in Cirrhosis

- Avoid extended periods of time without food
  - Consider adding D5 to IV fluids while NPO
- Provide frequent snacks and meals, especially at bedtime
  - See www.ginutrition.virginia.edu under patient education link for high calorie diet & high calorie snack suggestions
- Educate regarding the importance and encourage consistent evening snack
- Encourage high calorie oral liquid supplements
- Avoid unnecessary diet restrictions
  - Protein restriction is not indicated in patients receiving medications for encephalopathy
  - Tailor sodium restriction to absolute need
- Provide foods appropriate for dentition
- Optimize gastric emptying
  - Avoid excessive fiber
  - Control blood glucose
  - Avoid gut-slowing medications where possible
- Evaluate need for vitamin/mineral supplementation

feedings should be a priority. Caregivers can help identify and manage the "rate limiting" factors that impede nutrition intake. Small, frequent meals and oral liquid supplements may be helpful if patients experience fullness or early satiety. Medication adjustments may help if patients are fearful of eating due to frequent bowel movements related to disaccharide (lactulose) therapy for encephalopathy. Food should be appropriate for a patient's dentition, especially during a hospital admission.

Due to the inefficiency in storing glycogen and rapid oxidation of muscle protein between meals, every effort should be made to minimize time without nutrition.[1,2,4] Patients that require frequent hospitalizations often experience multiple interruptions in diet for altered mental status, procedures or diagnostic tests. Although the duration of each time period without food may be relatively brief, the cumulative effect of repeated bouts without nutrition can contribute to net loss of muscle and decreased functional status. In view of the limited capacity to enhance synthetic function and difficulties in rebuilding muscle mass, maximum efforts should be made to avoid catabolism where possible. If patients must remain npo, adding 5% dextrose to IV fluids will provide some short-term protein-sparing.

A late evening snack appears to be the single most effective intervention to help combat sarcopenia in patients with cirrhosis.[1,2,20] A snack containing both carbohydrate and protein prior to bedtime delays the onset of fat and muscle protein breakdown overnight.[20] A review of 15 studies of late evening snack in cirrhosis documents improvements in nitrogen balance and fat-free mass.[19] One substantial obstacle is the difficulty of convincing patients and families that frequent small meals and a late-evening snack containing both carbohydrate and protein are a vital part of care. Long-term studies of late evening snack document limited compliance after discharge.[20] It is not unexpected that advice regarding a peanut butter sandwich or cereal with milk may seem too mundane to be consistently followed. One study reported that when nutrition advice for patients with cirrhosis was reinforced during clinic visits by physicians and other members of the healthcare team, survival and quality of life were improved compared to nutrition counseling alone.[21]

Low sodium diets are routinely used to help manage ascites in patients with decompensated cirrhosis. There is limited research on the effectiveness or long term outcomes with different degrees of sodium restriction. One older study reported no significant advantage from sodium restriction,[22] but another study described faster resolution of ascites when a sodium restriction was added to diuretics.[23] In practice, a 2-3 gm sodium restriction is common, but the ideal level of sodium in the diet for management of ascites and optimized outcomes in cirrhosis has not been adequately studied. It is also conceivable that a strict sodium restriction alone can contribute to decreased food intake in some patients.

Hospitalized patients with minimal oral intake

generally do not require any diet restrictions. Regular diets in most hospitals provide a 3-4gm sodium restriction if 100% of all foods are consumed. Adding a diet restriction to any patient who is eating < 50% of their hospital meals is redundant. The education of patients and families about the sodium content of foods is much more important prior to hospital discharge where fast foods, frozen meals and canned meats and meals can provide excessive sodium.

Oral Liquid Nutrition Supplements

Liquid oral nutrition supplements can be useful adjuncts to increase calorie, protein and vitamin-mineral intake in selected patients. Patients that have early satiety or otherwise have difficulty with eating full meals can often meet needs with oral liquid supplements. Two meta-analysis have evaluated studies of oral supplements in patients with cirrhosis.[24,25] One meta-analysis reported reduced occurrence of ascites and infections with improved resolution of hepatic encephalopathy.[24] The other meta-analysis reported significantly decreased mortality with oral nutrition supplements in patients with cirrhosis.[25] Although long term compliance and cost may limit the effectiveness of oral supplements for some patients, overall, they can be an effective component of nutrition therapy for many patients with cirrhosis. See Table 3 for a summary of suggested nutrition interventions.

Branched Chain Amino Acids (BCAA)

Serum levels of the branched chain amino acids (leucine, isoleucine and valine) are decreased in cirrhosis. Research with parenteral BCAA infusions reported improvements in symptoms of encephalopathy.[1,2] However, research with enteral BCAA feedings and supplements have produced mixed results. Most studies that have described beneficial effects of BCAA supplements generally did not provide isocaloric and isonitrogenous control supplements.[26] Furthermore, many patients in past studies were inappropriately maintained on reduced protein diets at baseline, and supplementing *any* additional amino acids or feedings to help reverse protein malnutrition and support hepatic synthetic function may be of benefit. BCAA products are significantly more expensive than conventional foods or nutrition supplements; palatability and compliance are also limiting factors. A well controlled study of BCAA supplements did not report any significant improvement in overall patient outcomes.[27] Nonetheless, those patients who remained compliant with long term BCAA supplements had decreased frequency of hospitalizations compared to patients that received protein supplements.[27] The effects of BCAA supplements on encephalopathy appear modest and there is insufficient data to know if BCAA supplements would provide benefits above and beyond those patients receiving full nutrition (frequent feedings with a bedtime snack).

Glutamine

One amino acid that *should not* be supplemented in increased amounts in patients with cirrhosis is glutamine. Glutamine is metabolized to glutamate and ammonia, and supplemental glutamine can cause an exacerbation of hepatic encephalopathy. Oral glutamine supplements used as a "challenge" to help diagnose patients suspected to have minimal hepatic encephalopathy, acutely increased serum ammonia and overt encephalopathy symptoms.[28]

Vitamin and Mineral Supplementation

Patients with cirrhosis are at risk for multiple nutrient deficiencies.[1,2,7] A multi-vitamin with minerals can be useful for patients that are not meeting micronutrient needs. However, supplements that contain iron and copper should be avoided until hemochromatosis and Wilson's disease as a cause of cirrhosis have been ruled out.

Patients with cholestatic disease or a biliary disorder such as primary sclerosing cholangitis or primary biliary cirrhosis, are at increased risk for fat-soluble vitamin deficiencies.[1,2] Vitamins A, E and D should be monitored and provided at increased doses if deficiencies occur. Due to the risk of hepatic toxicity and long-bone fractures with increased vitamin A supplementation, serum levels should be checked before high-dose supplementation is initiated. In those patients with severe cirrhosis, it is unclear whether vitamin A stores can be mobilized from the liver as alterations in serum proteins make serum vitamin A results difficult to interpret.

Patients with cirrhosis are at risk for osteopenia, osteoporosis and fractures.[29] Vitamin D should be monitored and replaced in all patients with liver disease.

Zinc is an essential cofactor for enzymes in the urea cycle and throughout the body. Patients with cirrhosis are particularly susceptible to zinc deficiency

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due to increased losses from diuretics, increased stool output, decreased food intake, or if patients have been told to limit meat.[30, 31] Treating a zinc deficiency is advisable, but routine zinc supplementation in patients with decompensated cirrhosis did not improve encephalopathy.[31] Long term zinc supplementation should be avoided due to the risk of inducing a deficiency of other trace minerals that compete with zinc for absorption. Some populations may be at increased risk for urinary tract infections with chronic zinc supplementation.[32] Serum levels of zinc are unreliable as serum levels are decreased in conditions of stress, injury or infection and hypoalbuminemia. One clinical approach if a zinc deficiency is suspected is to provide 25 - 50 mg of elemental zinc/day for a limited time (2-3 weeks) and then discontinue the supplement.

Nutrition Support

Enteral Nutrition (EN)

Placement of a feeding tube to provide EN is indicated when patients with cirrhosis are unable to meet nutrition needs with oral intake alone. Considering the difficulties with maintaining and restoring nutrition status in patients with cirrhosis, patients should not be permitted to go extended periods without adequate nutrition. Small bore nasogastric (NG) placement is feasible in most patients, even those with recent GI bleeding.[33]

Patients with altered mental status are at risk for frequent displacement of NG feeding tubes. Securing the feeding tube with a nasal bridle (http://www.amtinnovation.com/bridle.html) has been shown to help maintain NG placement and increase nutrition delivery.[34] Careful patient selection for placement of a nasal bridle and feeding tube is essential because patients with cirrhosis may be at higher risk for bleeding. Placement of mitts and/or temporary restraints in addition to a nasal bridle may be required to safely maintain NG access in some patients. Multidisciplinary engagement and a dedication to maintain nutrition as a basic component of care for patients with cirrhosis is often required for successful EN. Standard calorie-dense, polymeric EN formulas are tolerated by most patients.

Placement of long-term percutaneous enteral feeding access is associated with significantly increased complications in patients with cirrhosis, and is generally considered contraindicated in patients with ascites.[35] Social embarrassment and discomfort generally limit the ability to maintain NG access in the outpatient setting for any duration.

There is a need for additional research to examine the role of EN in patient outcomes for patients with cirrhosis.[24, 25] EN provided to patients with advanced cirrhosis with jaundice for 4 weeks did not improve mortality at one year, but the potential role of EN for patients with less advanced disease has not been adequately studied.[36]

Parenteral Nutrition (PN)

The indications for PN in patients with hepatic failure are similar to any other disease process; yet it also increases the risk for infectious complications and is more expensive, compared to EN.[37] PN also requires a greater fluid volume, compared to calorie-dense EN.

PN that provides lipid emulsion > 1 gm/kg in adults is associated with increased incidence of hepatic compromise.[38] However, increased carbohydrate loads that would be necessary for patients receiving very low fat PN have also been implicated in hepatic compromise.[38] PN that provides fat, calories and protein similar to a healthy diet and EN formulas, without an excessive amount of any single nutrient, may be the best approach until further data is available. Lipid emulsions made from fish oils have demonstrated potential to prevent or even reverse PN-associated liver disease in neonates and pediatric patients.[39] However, there is limited data to know if fish-oil containing lipid emulsions are effective in adults with PN-induced liver disease.

CONCLUSIONS

Malnutrition is a serious problem in cirrhosis that leads to muscle wasting, compromised quality of life and increased complications. Successfully combating malnutrition requires the efforts of the entire healthcare team to educate patients and families that frequent feedings and an evening snack are an important part of their care. Education efforts must also include "mythbusting" the outdated, mistaken and potentially deleterious notions about restricting protein intake in patients with cirrhosis. Enteral nutrition support is useful for hospitalized patients to help minimize the cumulative nutrition deficit that frequently occurs in patients with cirrhosis. However, further research is

required to understand if there are outcome advantages of longer periods of nutrition support in malnourished patients with cirrhosis, especially those preparing for transplant. ■

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