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The Nutritional Management of Hepatic Encephalopathy in Patients With Cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus

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Nitrogen metabolism plays a major role in the development of hepatic encephalopathy (HE) in patients with cirrhosis. Modulation of this relationship is key to the management of HE, but is not the only nutritional issue that needs to be addressed. The assessment of nutritional status in patients with cirrhosis is problematic. In addition, there are significant sex-related differences in body composition and in the characteristics of tissue loss, which limit the usefulness of techniques based on measures of muscle mass and function in women. Techniques that combine subjective and objective variables provide reasonably accurate information and are recommended. Energy and nitrogen requirements in patients with HE are unlikely to differ substantially from those recommended in patients with cirrhosis *per se* viz. 35-45 kcal/g and 1.2-1.5g/kg protein daily. Small meals evenly distributed throughout the day and a late-night snack of complex carbohydrates will help minimize protein utilization. Compliance is, however, likely to be a problem. Diets rich in vegetables and dairy protein may be beneficial and are therefore recommended, but tolerance varies considerably in relation to the nature of the staple diet. Branched chain amino acid supplements may be of value in the occasional patient intolerant of dietary protein. Increasing dietary fiber may be of value, but the utility of probiotics is, as yet, unclear. Short-term multivitamin supplementation should be considered in patients admitted with decompensated cirrhosis. Hyponatremia may worsen HE; it should be prevented as far as possible and should always be corrected slowly. *Conclusion*: Effective management of these patients requires an integrated multidimensional approach. However, further research is needed to fill the gaps in the current evidence base to optimize the nutritional management of patients with cirrhosis and HE. (HEPATOLOGY 2013;58:325-336)

Malnutrition and hepatic encephalopathy (HE) are two of the most common complications of cirrhosis and both have detrimental effects on outcome.[1-4] Muscle tissue plays an important role in the removal of circulating ammonia[5]; thus, loss of skeletal mass may further confound neuropsychiatric status.[6] It follows that optimizing nutritional status, for example, by altering substrate

Abbreviations: BIA, bioelectric impedance analysis; BCAAs, branched chain amino acids; BMI, body mass index; CT, computerised tomography; D_{FFM}, density of FFM; DXA, dual X-ray absorptiometry; ESPEN, European Society for Enteral and Parenteral Nutrition; FFM, fat-free mass; HRQoL, health-related quality of life; HE, hepatic encephalopathy; HF_{FFM}, hydration fraction of FFM; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; LT, liver transplantation; MAMC, mid-arm muscle circumference; MRI, magnetic resonance imaging; REE, resting energy expenditure; RFH-GA, Royal Free Hospital Global Assessment; RFH-NPT, Royal Free Hospital Nutrition Prioritizing Tool; SGA, Subjective Global Assessment; WE, Wernicke's encephalopathy.

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availability, use of special substrates, or manipulation of metabolic regulation, could perhaps help prevent the development of HE and facilitate its management when present. However, any dietary manipulations designed to optimize patients' cognitive function can only be applied safely if the dietary requirements dictated by their "cirrhotic status" are also taken into account.[7-9] This situation is further confounded by the difficulties sometimes encountered in ensuring adequate and appropriate nutritional provision in patients with cirrhosis,[10] particularly in those who are cognitively impaired.

Thus, an expert panel was commissioned by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) at its 13th Symposium to debate and then develop a consensus document on nutritional issues in patients with cirrhosis and HE. Much of the information in this field is based on pragmatic clinical practice or on observational or open clinical trials, although several reviews[11-13] and some generic guidelines exist.[7-9] Each panel member was nevertheless asked to (1) identify and retrieve publications on an allocated aspect of the nutritional management of HE utilizing standard electronic database search techniques, manual searches of specialist journals, symposia, and conference proceedings, and cross-referencing of all identified publications, (2) review the evidence in relation to current practice, and (3) formulate recommendations. The evidence base for the recommendations was scored where possible (Table 1).[14] Unresolved or contentious issues that might be a focus for future trials were also identified.

The preliminary findings were presented, by panel members, at the 14th ISHEN Meeting in Val David, Montréal, Quebec, Canada, in September 2010. A draft document, which encapsulated the presentations and the subsequent discussion, was prepared and circulated for review and comment. Agreement was reached, where possible; where not, a pragmatic consensus was obtained.

Panel members felt it appropriate to review the nutritional assessment of patients with cirrhosis. They also felt it important to emphasise that the general principles of nutritional management of patients with cirrhosis should be observed, and that any dietary changes that might benefit patients with HE should be applied within this context.[7,8]

For clarity, the various nutritional variables that might be subject to prescriptive change in patients with HE were dealt with individually, but change to individual dietary constituents should not be made in isolation, i.e., without due consideration of the diet as a whole.

Summary statements and recommendations are provided appropriately throughout, and the issues that require further research are clearly delineated (Tables 2-4). An overarching summary of recommendations is also provided (Table 5).

Nutritional Assessment

Accurate assessments of nutritional status are not easily obtained in patients with cirrhosis primarily because of the abnormalities in fluid homeostasis and compartmentalization,[15] protein metabolism,[16] and bone modeling and remineralization[17] that characterize this condition. This makes it difficult to identify those at risk for malnutrition and to evaluate the need for, and efficacy of, nutritional intervention.

Some objective assessment variables, such as percentage ideal body weight or plasma albumin, cannot be used in this patient population because of the potential confounding effects of fluid retention and the changes in protein metabolism.[4,18] Difficulties also arise in the use of objective techniques, for example, anthropometry, bioelectric impedance analysis (BIA), and dual-energy X-ray absorptiometry (DXA), which are based on a two-component model of body composition, that is, fat and fat-free mass (FFM). The validity of these techniques is critically dependent on assumptions relating to the density (D_{FFM}) and hydration fraction (HF_{FFM}) of FFM, which are violated in patients with cirrhosis.[19] In consequence, marked discrepancies are observed in the prevalence of malnutrition in patients with cirrhosis in relation to the assessment methods used.[19-23] Reported frequencies in studies employing multiple traditional assessment techniques range from 5.4% to 68.2%,[23] 5.0% to 74%,[22] and 19% to 99%.[21]

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Table 1. Criteria Used to Classify the Recommendations*

	Criteria
Strength of Recommendation	
Strong: 1	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient important outcomes, and costs.
Weak: 2	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost, or resource consumption.
Quality of Evidence	
High: A	Further research is unlikely to change confidence in the estimate of the clinical effect.
Moderate: B	Further research may change confidence in the estimate of the clinical effect.
Low: C	Further research is very likely to affect confidence on the estimate effect.

*Modified from Shekelle et al.[14]

Hand-grip dynamometry provides a functional assessment of muscle strength and, in patients with cirrhosis, is a sensitive and specific marker for depletion of body cell mass[21] and is positively correlated with total body protein stores.[24] Prevalence of malnutrition assessed using hand-grip strength is consistently higher than that obtained with other bed-side techniques.[20-24] In addition, hand-grip strength is significantly associated with health-related quality of life[22] and, in patients with well-compensated disease, predicts the development of the major complications of liver disease,[20] specifically HE.[22] However, although there is a significant relationship between hand-grip strength and nutritional status in men, with loss of strength having a detrimental effect for survival, no such relationship exits in women.[25]

Recent interest has focused on the use of imaging techniques, such as cross-sectional CT and magnetic resonance imaging (MRI), for assessing core skeletal muscle mass. In patients awaiting liver transplantation (LT), sarcopenia is independently associated with both waiting-list and posttransplant mortality.[26-29] However, although these assessments are objective and are not influenced by hepatic synthetic dysfunction or salt and water retention, they are invasive, costly, involve radiation, and cannot easily be repeated to monitor progress. In addition, little or no information is available on the relationships between central sarcopenia on imaging and (1) clinical or research methods for assessing nutritional status other than body mass index (BMI) and Subjective Global Assessment (SGA), which correlate poorly,[26] (2) more easily applicable measures of muscle mass, such as ultrasound, (3) functional measures of muscle strength, such as hand-grip dynamometry, or (4) health-related quality of life (HRQoL). In addition, the prevalence of sarcopenia is significantly higher in men than in women, and whereas its prevalence increases significantly with the severity of liver dysfunction in men, no such relationship exists in their female counterparts.[26] However, no interaction was observed between sarcopenia and sex in relation to waiting-list mortality, although the number of deaths was small, particularly among women.[26]

Table 2. Summary Statements and Recommendations Regarding Nutritional Assessment in Patients With Cirrhosis

Nutritional Assessment	
All patients should undergo baseline nutritional assessment as part of management planning; assessments should be repeated at regular intervals or as dictated by clinical condition.	1A
Accurate, validated tools for screening and assessing nutritional status have been developed, but are not universally available and are time-consuming to perform.	1B
Tools providing a reasonable compromise between simplicity and accuracy can be used in routine clinical practice for screening and monitoring.	1B
Issues Requiring Additional Research	
Identification/development of validated, universally accepted, and gender-independent tools for nutritional assessment in this patient population	

Table 3. Summary Statements and Recommendations Regarding Energy and Protein Provision in Patients With Cirrhosis and HE

Energy and Protein Requirements	
Optimal daily energy intake should be 35-40 kcal/kg ideal body weight.	1A
Optimal daily protein intake should be 1.2-1.5 g/kg ideal body weight.	1A
Small meals evenly distributed throughout the day and a late-night snack of complex carbohydrate will minimize protein utilization.	1A
Encourage ingestion of a diet rich in vegetable and dairy protein.	2B
BCAA supplementation might allow recommended nitrogen intakes to be attained/maintained in patients who are intolerant of dietary protein.	2B
Issues Requiring Additional Research	
Assessment of energy and protein requirements in patients with cirrhosis in relation to body weight and neuropsychiatric status	
Development of strategies to improve long-term compliance with dietary manipulation and the provision of supplements	
Defining optimal composition of late-evening snacks to maximize the pattern of substrate utilization	
Evaluation of the effects of late-evening snacks on clinically meaningful outcomes, such as HRQoL, development of complications, need for LT, and survival	
Defining management principles in obese individuals with cirrhosis to ensure a balance between the need to supply adequate energy intakes while facilitating weight loss, when appropriate	
Effects of isonitrogenous, isocaloric vegetable, and mixed protein diets on neuropsychiatric status in patients with HE	
Effect of supplements enriched with BCAA, but poor in aromatic amino acids, on neuropsychiatric performance in patients with HE already receiving standard therapy	

Table 4. Summary Statements and Recommendations Regarding Fiber and Micronutrient Provision in Patients With Cirrhosis and HE

Prebiotics	
Ingestion of diets containing 25-45 g of fiber daily should be encouraged.	2B
Micronutrients	
A 2-week course of a multivitamin preparation could be justified in patients with decompensated cirrhosis or those at risk for malnutrition. Clinically apparent vitamin deficiencies should be treated specifically.	2A
Hyponatremia should always be corrected slowly.	1A
Long-term treatment with manganese containing nutritional formulations should be avoided.	2B
Issues Requiring Additional Research	
Better definition of the neuropsychiatric, nutritional, and cost-effectiveness of dietary fiber supplements in patients with cirrhosis, particularly in comparison to standard treatment options	
Benefits and harms of probiotics in randomized trials with a low risk of systematic and random errors	
Comparative efficacy of various probiotics and optimal doses and duration of treatment	
Role of zinc in the pathogenesis of HE and the effects of supplementation	

These disparate findings in relation to gender are not surprising given that skeletal muscle function is known to correlate with muscle mass in men, but not in women,[30] and further that muscle mass is significantly better preserved in women with cirrhosis than in their male counterparts.[24,31] In consequence, hand-grip dynamometry and central sarcopenia are not reliable tools for assessing nutritional status, or as a measure of global health status, in women with cirrhosis.[24-26]

More accurate body-composition data can be obtained by use of multicomponent models that integrate measurements from a number of techniques, such as densitometry, isotopic dilution, DXA, and *in vivo* neutron activation analysis.[19,24,32] The prevalence of malnutrition is invariably higher when assessed using these composite techniques. However, the equipment and expertise necessary to undertake these assessments are not widely available.

Thus, tools such as anthropometry and BIA provide unreliable estimates of nutritional status when used singly,[19] while techniques based primarily on assessments of muscle mass and function have no predictive validity in women, and multicomponent models are not available for use in the clinical setting. Therefore, there is a need for a composite method of assessment that includes appropriate variables[4,18] and provides the reproducible, valid, and predictive data required to optimize nutritional management in this patient population.

The technique of SGA[33,34] utilizes clinical information and physical observation to determine nutritional status, but without recourse to objective measurements, such as anthropometry. However, this technique consistently underestimates the prevalence of malnutrition in this population, when compared with assessments made using objective measures, and it does not accurately predictive outcome.[20,21,23,32,35]

Ideally, therefore, a global schema should incorporate both subjective and objective variables. One such tool is the Royal Free Hospital-Global Assessment (RFH-GA)[36] (Fig. 1). In this schema, measurements of BMI, calculated using estimated dry body weight, and mid-arm muscle circumference (MAMC) are utilized, together with details of dietary intake, in a semistructured algorithmic construct. RFH-GA evaluations show excellent intra- and interobserver reproducibility and have been validated

Table 5. Nutritional Management of Patients With HE Based on Current Evidence and Consensus Opinion

	Patients With HE								
Nutritional Status	**Adequately Nourished**			**Moderately Malnourished/At Risk**			**Severely Malnourished**		
Body weight (estimated BMI*)	Normal/Overweight (20–30)	Obese (30–40)	Obese (>40)	Low/Overweight (18–30)	Obese (30–40)	Obese (>40)	Low/Overweight (18–30)	Obese (30–40)	Obese (>40)
Daily energy, kcal/kg†	35–40	25–35	20–25	35–40	25–35‡	20–25‡	35–40	25–35‡	20–25‡
Daily protein, g/kg†	1.2–1.5	1.0–1.5	1.0–1.5	1.2–1.5			1.2–1.5		
Meal patterns	Small frequent meals throughout the waking hours								
Late-evening snack	Encourage ingestion of 50 g of complex carbohydrate								
Dietary nitrogen source	Promote vegetable and dairy protein to level of tolerance			Promote high protein intake per patient preference to encourage intake					
Daily fiber§	Encourage ingestion of diets containing 25–45 g, especially in overweight patients								
Decompensated cirrhosis	Supplement as indicated								
HE incompletely/poorly controlled	Consider use of probiotics and/or BCAA supplements								

*Use estimated dry weight to calculate BMI in patients with fluid retention.

†Use ideal body weight for calculation of requirements.

‡Achieved by reducing the carbohydrate and fat content of the diet and increasing dietary fiber.

§Useful to aid weight loss, but care needed not to induce diarrhea in patients receiving lactulose.

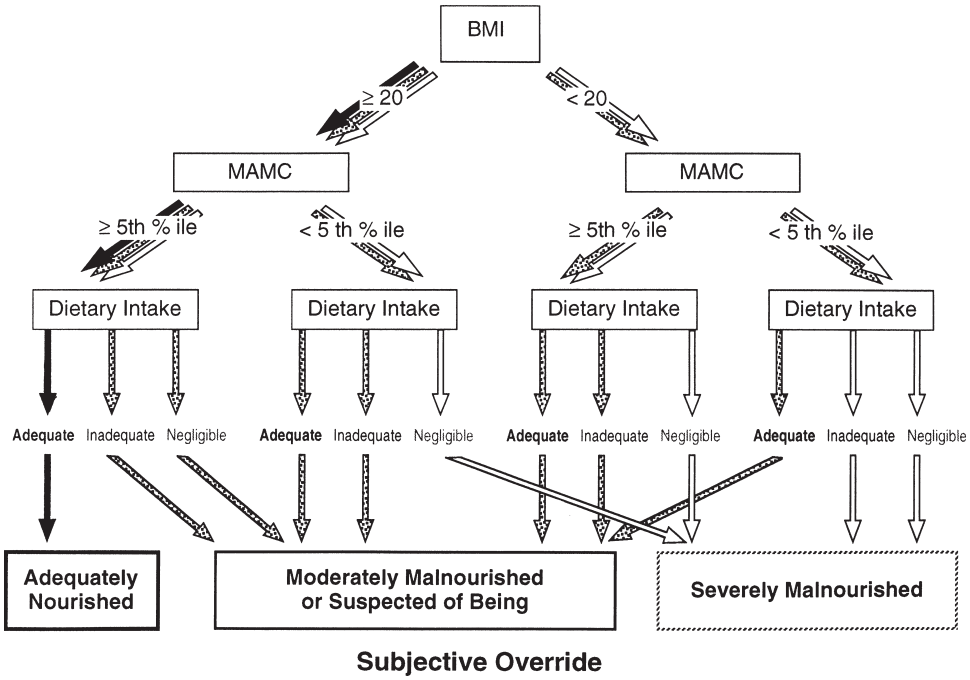

Fig. 1. RFH-GA schema for determining nutritional status in patients with cirrhosis.[36] Patients are categorized in relation to their BMI, MAMC, and dietary intake into one of three categories: adequately nourished, moderately malnourished (or suspected to be), and severely malnourished. A subjective override, based on factors such as profound recent weight loss or recent significant improvements in appetite and dietary intake, can be used to modify the classification by one category only.

against a multicomponent model of body composition.[19] However, skilled staff are needed to carry out the assessments, which can take up to 1 hour to complete. Therefore, simpler and less time-consuming techniques are needed for routine nutritional screening, but these should be validated and fit for purpose.

The Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) has recently been developed (Fig. 2). This schema takes less than 3 minutes to complete and can be used by nonspecialist staff. It has excellent intra- and interobserver reproducibility and significant external validity against the RFH-GA; it has also been validated in a UK multicenter trial.[37] However, further, more extensive validation is needed.

Many gastroenterology and hepatology units have developed and adapted their own schemas for nutritional screening. Use of these tools should not be discouraged, particularly for monitoring patients over time where they act as their own controls. However, there are advantages in utilizing validated "universal" techniques, not least to allow comparisons across units and to facilitate the undertaking of multicenter treatment trials. However, one of the key issues that must be addressed when validating any new or proposed technique is the confounding effects of the relative conservation of protein stores in women with cirrhosis, irrespective of disease severity or etiology (Table 2).

Energy and Protein Requirements

Resting energy expenditure (REE) is increased in patients with cirrhosis relative to their lean body mass.[38,39] In these individuals, utilization of macronutrients is affected by postreceptor impairment of glucose utilization resulting from reductions in hepatic glycogen synthesis and storage.[40,41] As a consequence, they produce a response to fasting akin to that observed in starved healthy individuals, namely, an early, excessive activation of lipolysis, with utilization of fat stores, and a switch from glycogenolysis to gluconeogenesis.[42,43] Gluconeogenesis is an energy-expensive procedure and this switch is generally considered to explain the observed increase in REE in these patients.

This observed increase in energy expenditure will need to be offset by a proportionate increase in energy intake. The European Society for Enteral and Parenteral Nutrition (ESPEN) guidelines suggest daily energy intakes of 35-40 kcal/kg body weight,[8] although it is unclear whether actual, ideal, or "dry" body weight should be used for the calculation and this was debated by the panel. Use of actual body

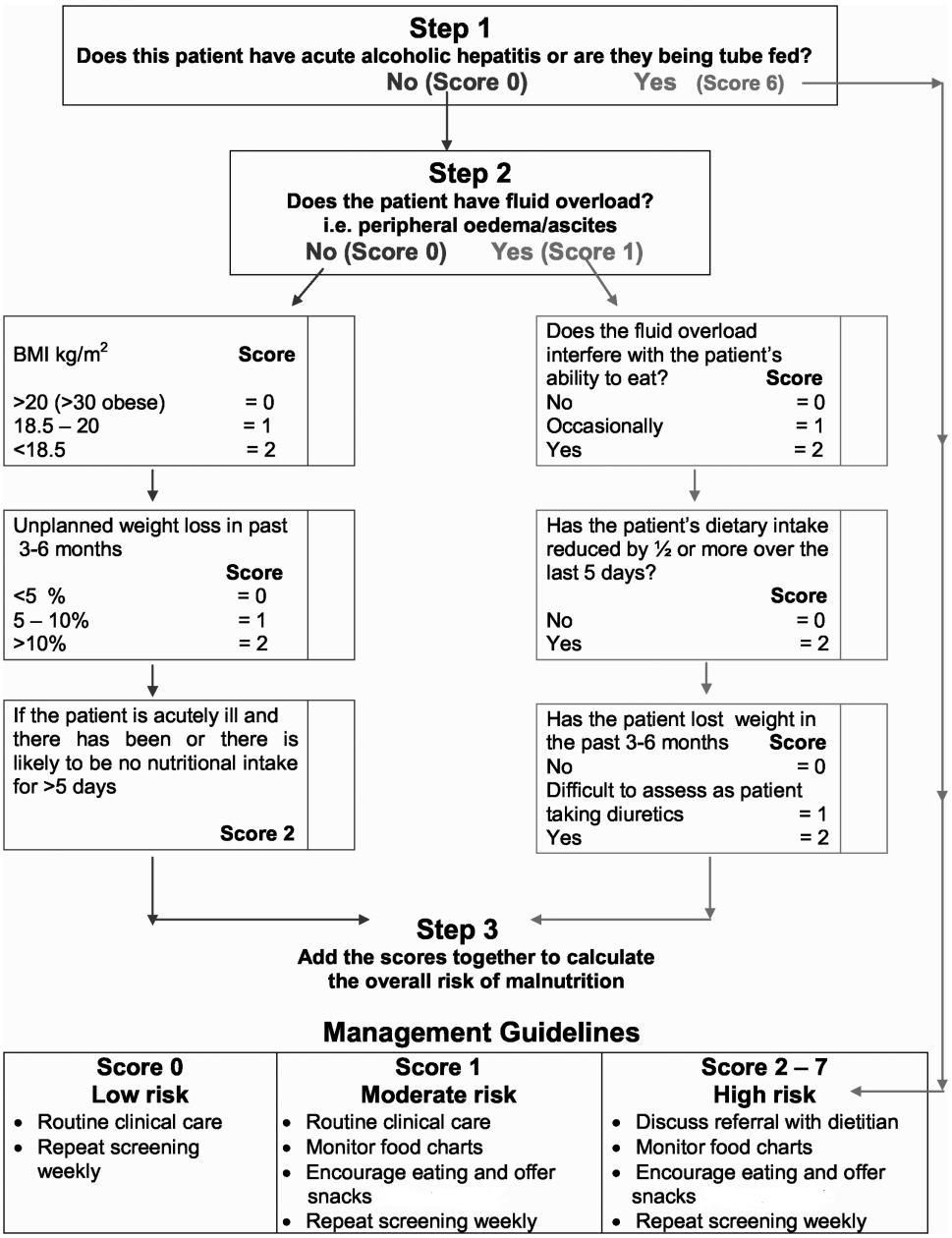

Fig. 2. RFH-NPT schema for determining nutritional risk in patients with cirrhosis.[37] Nutritional risk is assessed on the summate scores allocated to the assessed variables. Management guidelines are provided based on the assessed nutritional risk.

weight or errors in estimating dry weight may lead to erroneous values deviating to the extremes, so using ideal body weight may be the safest approach. Although no specific studies have been undertaken to date to define energy requirements in patients with cirrhosis and HE, there is good evidence from studies, in which a significant proportion of the included patients were neuropsychiatrically impaired, that energy requirements in these patients do not differ substantially from those in patients with cirrhosis *per se*.[44,45]

Reliance on gluconeogenesis to maintain splanchnic glucose output results in utilization of amino acids derived from proteolysis.[42,43] This, in turn, results in additional loss of amino acids and an increase in protein requirements and ammonia production.[46-48] The ESPEN guidelines recommend daily intakes of 1.2-1.5 g protein/kg body weight to maintain nitrogen balance[8]; requirements are best related to a measure of ideal body weight.

Dietary protein restriction should be avoided in this patient population, except perhaps for very short periods in patients with gastrointestinal (GI) bleeding while they are being stabilized. There is currently ample evidence that patients with HE tolerate normoproteinemic diets

and benefit from them.[49] Nevertheless, surveys undertaken in the UK, Australia, and Italy have shown that the practice of protein restriction is still widespread[11,50,51] and this needs to be urgently addressed.

The number of patients with cirrhosis who are overweight or obese has increased in recent years.[22,52] Considerable difficulties arise in managing these patients because they may be malnourished, despite the increase in their overall body weight and size. There is no information on energy or protein requirements in this patient population, and no caveats are provided in the ESPEN guidelines[8]; thus, generic recommendations should be applied.[8] However, it is clearly difficult to ensure the required intakes of energy and protein in these patients while also attempting to optimize body weigh, because overrestriction of daily energy intake will result in endogenous breakdown of muscle regardless of the protein intake.

Weight loss should be encouraged in patients with well-compensated cirrhosis who are overweight or obese and is best achieved by gentle, carefully monitored, and proportionate reductions in both total energy and protein intakes (Table 5), together with an increase in physical activity. In patients with decompensated cirrhosis, attempts to reduce body weight should be very carefully monitored; it is best effected by reducing the carbohydrate and fat content of the diet while maintaining a high protein intake, which may need to exceed those recommended if, when the patient is losing weight, there is evidence of further protein depletion (Table 5). This is achievable because dietary protein retention remains efficient with daily intake of up to 2 g/kg without precipitating or exacerbating HE.[53]

Thus, as a general rule, patients with cirrhosis, even those with HE, should be provided with high-energy, high-protein diets.[7,8,43,47] However, it is important to realize that these recommendations, which are based on the ESPEN guidelines,[8] are for the maintenance of nutritional status; requirement may increase during stressful situations and when repletion or weight gain is desired. Two additional issues that should also be taken into account when managing these patients are the pattern of dietary intake and the source of dietary nitrogen.

Pattern of Dietary Intake. Timing of caloric ingestion is important in effecting changes in substrate utilization and hence avoiding undue utilization of gluconeogenesis to maintain splanchnic glucose output. This is particularly important in patients with HE because utilization of amino acids for glucose production depletes tissue protein stores and produces ammonia.[48] Patients should avoid fasting for longer than 3-6 hours during the daytime and so should be encouraged to take small, frequent meals evenly distributed throughout the day. In addition, a recent systematic review[54] has shown that, in patients with cirrhosis, a late-evening snack (1) reverses the aberrant substrate utilization pattern, (2) has a more efficacious effect on substrate utilization and nitrogen retention than daytime calorie supplementation alone, (3) may improve HRQoL and survival, and (4) may reduce the frequency and severity of HE.

The optimal caloric content and formulation for the late-evening snack cannot be determined on the basis of the published data. However, evidence suggests that it should contain at least 50 g of complex carbohydrate.[54] Compliance may be a problem,[10] but patients should nevertheless be encouraged to modulate their eating patterns along these lines.

Dietary Nitrogen Sources. The type of protein ingested may be important because patients with cirrhosis show variations in their tolerance to dietary protein, depending on its source. Thus, early, mainly uncontrolled, studies showed that dairy protein is better tolerated than protein from mixed sources and that vegetable protein is better tolerated than meat protein.[55-57] Vegetable protein diets contain significantly more dietary fiber than isonitrogenous meat protein diets; fiber has prebiotic properties that result in decreased transit time, reduced intraluminal pH, and increased fecal ammonia excretion.[58-61] Ingestion of vegetable fiber may also result in beneficial alterations in the microbiota.[62] In addition, vegetable protein is poor in the sulphated amino acids, methionine and cysteine, which are the precursors of mercaptans and indole/oxindole compounds, which, in turn, have been implicated in the genesis of HE.[63] Conversely, they are high in ornithine and arginine, which may facilitate ammonia disposal through the urea cycle.[64]

Although there is a good theoretical basis for the use of vegetable protein diets in patients with cirrhosis and HE, the results of the clinical studies undertaken to date are less convincing.[65] However, despite the limitations in the clinical evidence, the panel agreed that patients with recurrent or persistent HE should take a diet richer in vegetable and dairy protein than meat and fish protein. However, the tolerability or palatability of diets rich in vegetable protein vary considerably, depending on the dietary fiber content of the staple diet. In general, patients should be encouraged to take as high a percentage of vegetable protein as they can, and provided that they are not also salt restricted, which makes the diet unpalatable, daily

intakes of 30-40 g of vegetable protein can usually be achieved. Vegetable protein diets are also beneficial in those overweight patients with cirrhosis who are attempting to lose weight.

The branched-chain amino acids (BCAAs), valine, leucine, and isoleucine, are essential amino acids, which, unlike others, are not metabolized by the liver, but by skeletal muscle. Plasma BCAA concentrations are reduced in patients with cirrhosis, whereas concentrations of one or both of the aromatic amino acids, phenylalanine and tyrosine, are increased, together with methionine.[66] These changes result from a combination of impaired hepatic function, portal-systemic shunting, hyperinsulinemia, hyperglucagonemia, and hyperammonemia. It was originally postulated that BCAA supplements would benefit patients with HE because they would (1) facilitate ammonia detoxification by supporting glutamine synthesis in skeletal muscle and in the brain and (2) decrease brain influx of excess aromatic amino acids, which compete with BCAAs for passage across the blood-brain barrier.[67] However, there is little convincing evidence, at present, that these original assumptions were correct or that BCAA supplementation has a significant beneficial effect on HE.[68,69] However, use of oral BCAA supplements, in daily divided doses, may facilitate the provision of an adequate nitrogen intake in the occasional patient who is truly protein intolerant.[70]

There is accumulating evidence that long-term oral BCAA supplementation may, however, confer nutritional benefit, and improve event-free survival, in patients with cirrhosis.[71-73] These favorable effects are most likely attributable to leucine alone, which (1) stimulates the secretion of hepatocyte growth factor by hepatic stellate cells, thereby stimulating hepatic regeneration,[74] (2) stimulates muscle protein synthesis through altered patterns of translation of specific messenger RNAs,[75] and (3) increases insulin secretion,[76] which may be a useful therapeutic approach for improving glucose utilization as well as reducing muscle catabolism. However, there are no long-term nutritional intervention studies in patients with cirrhosis to confirm the proposed benefits of leucine *per se* as a pharmaconutrient.

Thus, some adjustments relating to timing of feeding and sources of dietary nitrogen may be beneficial in patients with cirrhosis and HE and are therefore recommended (Tables 3 and 5).

Prebiotics and Probiotics

Prebiotics, probiotics, and synbiotics are functional food components that modulate gut microflora to benefit host well-being and health. Prebiotics are selectively fermented ingredients that allow specific changes in both the composition and/or activity of the GI microflora. Probiotics are live microorganisms that, when administered in adequate amounts, alter gut flora; they are available in fermented dairy products and fortified foods, but tablets, capsules, powders, and sachets of freeze-dried bacteria are also available. Synbiotics are supplements that combine prebiotics and probiotics.

The gut microbiota plays an important role in the generation of ammonia; thus, its modulation using prebiotics, probiotics, and synbiotics has been evaluated as a therapeutic option in patients with HE in several small studies. No information is available currently on the effects of these agents on nutritional status.

Lactulose is classified, by some, as a prebiotic and its efficacy as a treatment for HE is proven.[77] Soluble fiber (e.g., gum from pulses and pectin from fruit) is generally fermentable and, as such, has prebiotic properties. Some information is available, from a small number of studies, on the effect of fiber on neuropsychiatric status in patients with cirrhosis.[59,78-80] However, studies differ in both the type and amount of fiber provided, making it extremely difficult to assess the fiber-specific effects within the experimental paradigms. Nevertheless, based on these studies, it would appear that fermentable or prebiotic fiber may have a beneficial effect on neuropsychiatric performance in this patient population.[81,82] Thus, fiber itself or fiber-enriched diets, which would include diets made up of predominantly vegetable protein (*vide supra*), may benefit patients with cirrhosis and HE. However, care must be taken not to induce diarrhea, particularly in patients who are already taking lactulose.

Agrawal et al.[83] have recently shown that lactulose and probiotics are equally effective for secondary prophylaxis in patients with a history of HE, compared to no treatment, and that both are well tolerated. However, recent systematic reviews of the use of probiotics to treat HE have not been as encouraging.[84,85] Holte et al.,[84] for example, assessed the efficacy of probiotics and synbiotics in the treatment of predominantly minimal HE and concluded that "probiotics may be an effective treatment for HE, though rigorous evaluation in standardized, RCTs [randomized, controlled trials] with clinically relevant outcomes is still needed." McGee et al.[85] undertook a much more detailed review of the use of probiotics in the treatment of HE, covering a much wider range of outcomes. Nevertheless, they

"did not find convincing evidence that probiotics had a significant beneficial or harmful effect on patients with HE" and commented that "the methodological quality of trials to date are far from optimal." They concluded that "probiotics cannot be recommended based on the findings of this review."

Thus, the benefits and harms of probiotics are still uncertain and many fundamental questions concerning their use remain. Further research is clearly needed (Table 4).

Micronutrients

Vitamins. Deficiencies of the water-soluble vitamins, particularly thiamine, are associated with a wide range of neuropsychiatric symptoms.[86] Patients with both alcohol-related and non-alcohol-related cirrhosis may be vitamin deficient[87,88] and may, at autopsy, show evidence of Wernicke's encephalopathy (WE) or cerebellar degeneration not apparent clinically during life.[89,90]

Ataxia, confusion, and memory loss are features of both HE and WE; however, the latter may be distinguished by the additional presence of nystagmus, ptosis, and paralysis of lateral conjugate gaze.

Vitamin status is not easily assessed; multivitamin supplementation is cheap and generally free of side effects. Thus, use of oral vitamin supplements could be justified in patients admitted with decompensated cirrhosis. Vigorous parenteral thiamine supplementation is mandatory whenever WE is suspected.

Minerals. Changes in circulating levels of calcium, magnesium, and iron, though not directly implicated in the pathophysiology of HE, can produce changes in mental function, ranging from confusion to coma or secondary dementia,[91] which may confound its diagnosis. Hypercalcemia and hypomagnesemia should be excluded or corrected in confused or comotose patients with cirrhosis; plasma magnesium levels should be carefully monitored in patients post-LT because both cyclosporine and tacrolimus can induce hypomagnesemia.[92] Iron deficiency should be excluded or corrected in patients with persistent, otherwise unexplained, mild cognitive dysfunction.[93]

Low circulating levels of sodium can alter brain function both directly and by interacting with the mechanisms causing HE; hyponatremia is thus a recognized risk factor for the development of HE.[94,95] Dietary sodium intake is usually reduced in patients with ascites, although the evidence for the long-term utility of this manoeuver is poor and debated.[96] However, intakes should not be reduced below 60 mmol/day because otherwise the diet becomes unpalatable, resulting in reductions in total energy and protein intakes.[97] Hyponatremia is more likely to occur when the intake of sodium is low, while the intake of water is maintained or increased.[98] Thus, careful monitoring of sodium and water balance is required. Hyponatremia should be corrected slowly, especially in patients with HE, because the risk of developing central pontine myelinolysis is high, especially in relation to LT.[99]

Zinc deficiency has been implicated in the development of HE because ornithine transcarbamylase, which is involved in ammonia detoxification via urea production, and glutamine synthetase, which plays a role in ammonia detoxification in muscle and liver, are zinc-dependent enzymes. Tissue zinc concentrations are reduced in patients with cirrhosis,[100] but the effects of zinc supplementation on cognitive function in patients with HE have been conflicting,[101,102] although the largest double-blind clinical trial undertaken to date showed no significant benefit of zinc supplementation on neuropsychometric performance.[103]

Manganese is an important component of a number of cerebral enzymes, in particular, glutamine synthetase. Accumulation in the brain after occupational manganese exposure can lead to development of a parkinsonism in otherwise healthy people.[104] Patients with cirrhosis have elevated total body manganese levels, most likely reflecting the combined effects of hepatocellular failure, impaired biliary excretion, and the presence of portal-systemic shunting of blood.[105] This may lead to selective manganese accumulation in the globus pallidus, caudate nucleus, and putamen, and the adjacent areas of the basal ganglia manifest as hyperintensity of these brain areas on T1-MRI.[105,106] However, there is no clear relationship between the presence, extent, and time course of manganese accumulation and development of HE.[106-108] Nevertheless, it would seem sensible to avoid the use of nutritional supplements containing manganese in this patient group.

Summary statements and recommendations regarding micronutrient provision are included in Tables 4 and 5.

The Way Forward

It is clear from this review of the nutritional issues in patients with cirrhosis and HE that the area has not received the research input it needs, particularly given the importance and interdependence of malnutrition and HE in determining outcome in this patient population. Current technology does not allow for the accurate assessment of body composition and hence for a more precise description of the specific components

that constitute malnutrition in a given individual. In consequence, management cannot be specifically directed, although some guidance can be provided based on current knowledge (Table 5). Where gaps in the knowledge and evidence base exist, recommendations for further research are included, but efforts must also be made to ensure that the exciting advances in the field of nutriceuticals and the novel strategies to reverse cachexia being used in other chronic diseases and in aging are also translated into the field of hepatology.[109]

References

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-231.
2. Stewart CA, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. Liver Transpl 2007;13:1366-1371.
3. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis. Nutrition 2001;17:445-450.
4. McCullough AJ. Malnutrition in liver disease. Liver Transpl 2000;(4 Suppl 1):S85-S96.
5. Olde Damink SW, Jalan R, Redhead DN, Hayes PC, Deutz NE, Soeters PB. Interorgan ammonia and amino acid metabolism in metabolically stable patients with cirrhosis and a TIPSS. Hepatology 2002;36:1163-1171.
6. Merli M, Giusto M, Lucidi C, Giannelli V, Pentassuglio I, Di Gregorio V, et al. Muscle depletion increases the risk of overt and minimal hepatic encephalopathy: results of a prospective study. Metab Brain Dis 2012 Dec 7. doi: 10.1007/s11011-012-9365-z.
7. Plauth M, Merli M, Kondrup J, Weimann A, Ferenci P, Müller MJ. ESPEN guidelines for nutrition in liver disease and transplantation. Clin Nutr 1997;16:43-55.
8. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr 2006;25:285-294.
9. Plauth M, Cabre E, Campillo B, Kondrup J, Marchesini G, Schutz T, et al. ESPEN Guidelines on Parenteral Nutrition: Hepatology. Clin Nutr 2009;28:436-444.
10. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology 2008;48:557-566.
11. Merli M, Riggio O. Dietary and nutritional indications in hepatic encephalopathy. Metab Brain Dis 2009;24:211-221.
12. Kachaamy T, Bajaj JS. Diet and cognition in chronic liver disease. Curr Opin Gastroenterol 2011;27:174-179.
13. Chadalavada R, Sappati Biyyani RS, Maxwell J, Mullen K. Nutrition in hepatic encephalopathy. Nutr Clin Pract 2010;25:257-264.
14. Shekelle PG, Ortiz E, Rhodes S, Morton SC, Eccles MP, Grimshaw JM, et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? JAMA 2001;286:1461-1467.
15. McCullough AJ, Mullen KD, Kalhan SC. Measurements of total body and extracellular water in cirrhotic patients with and without ascites. Hepatology 1991;14:1102-1111.
16. Tessari P. Protein metabolism in liver cirrhosis: from albumin to muscle myofibrils. Curr Opin Clin Nutr Metab Care 2003;6:79-85.
17. Monegal A, Navasa M, Guanabens N, Peris P, Pons F, Martinez de Osaba MJ, et al. Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. Calcif Tissue Int 1997;60:148-154.
18. Morgan MY, Madden AM. The assessment of body composition in patients with cirrhosis. Eur J Nucl Med 1996;23:213-225.
19. Morgan MY, Madden AM, Jennings G, Elia M, Fuller NJ. Two-component models are of limited value for the assessment of body composition in patients with cirrhosis. Am J Clin Nutr 2006;84:1151-1162.
20. Alvares-da-Silva MR, Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. Nutrition 2005;21:113-117.
21. Figueiredo FA, Dickson ER, Pasha TM, Porayko MK, Therneau TM, Malinchoc M, et al. Utility of standard nutritional parameters in detecting body cell mass depletion in patients with end-stage liver disease. Liver Transpl 2000;6:575-581.
22. Huisman EJ, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. Eur J Gastroenterol Hepatol 2011;23:982-989.
23. Fernandes SA, Bassani L, Nunes FF, Aydos ME, Alves AV, Marroni CA. Nutritional assessment in patients with cirrhosis. Arq Gastroenterol 2012;49:19-27.
24. Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. Am J Clin Nutr 2007;85:1257-1266.
25. Madden AM, Morgan MY. Hand-grip strength in cirrhosis—its relationship to nutritional status and severity of liver disease. Hepatology 1998;28(suppl):1788.
26. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver Transpl 2012;18:1209-1216.
27. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg 2010;211:271-278.
28. Englesbe MJ, Lee JS, He K, Fan L, Schaubel DE, Sheetz KH, et al. Analytic morphomics, core muscle size, and surgical outcomes. Ann Surg 2012;256:255-261.
29. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2012;10:166-173.
30. Hornby ST, Nunes QM, Hillman TE, Stanga Z, Neal KR, Rowlands BJ, et al. Relationships between structural and functional measures of nutritional status in a normally nourished population. Clin Nutr 2005;24:421-426.
31. Figueiredo FA, De Mello Perez R, Kondo M. Effect of liver cirrhosis on body composition: evidence of significant depletion even in mild disease. J Gastroenterol Hepatol 2005;20:209-216.
32. Figueiredo FA, Perez RM, Freitas MM, Kondo M. Comparison of three methods of nutritional assessment in liver cirrhosis: subjective global assessment, traditional nutritional parameters, and body composition analysis. J Gastroenterol 2006;41:476-482.
33. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr 1987;11:8-13.
34. Hasse J, Strong S, Gorman MA, Liepa G. Subjective global assessment: alternative nutrition-assessment technique for liver-transplant candidates. Nutrition 1993;9:339-343.
35. Naveau S, Belda E, Borotto E, Genuist F, Chaput JC. Comparison of clinical judgment and anthropometric parameters for evaluating nutritional status in patients with alcoholic liver disease. J Hepatol 1995;23:234-235.
36. Morgan MY, Madden AM, Soulsby CT, Morris RW. Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. Hepatology 2006;44:823-835.
37. Arora S, Mattina C, McAnenny C, O'Sullivan N, McGeeney L, Calder N, et al. The development and validation of a nutritional prioritising

tool for use in patients with chronic liver disease. J Hepatol 2012;56(Suppl 2):S241.
38. Müller MJ, Böttcher J, Selberg O, Weselmann S, Böker KH, von zur Mühlen A, et al. Hypermetabolism in clinically stable patients with liver cirrhosis. Am J Clin Nutr 1999;69:1194-1201.
39. McCullough AJ, Raguso C. Effect of cirrhosis on energy expenditure. Am J Clin Nutr 1999;69:1066-1068.
40. Petrides AS, Groop LC, Riely CA, DeFronzo RA. Effect of physiologic hyperinsulinemia on glucose and lipid metabolism in cirrhosis. J Clin Invest 1991;88:561-570.
41. Krahenbuhl L, Lang C, Ludes S, Seiler C, Schafer M, Zimmermann A, et al. Reduced hepatic glycogen stores in patients with liver cirrhosis. Liver Int 2003;23:101-109.
42. Owen OE, Reichle FA, Mozzoli MA, Kreulen T, Patel MS, Elfenbein IB, et al. Hepatic, gut, and renal substrate flux rates in patients with hepatic cirrhosis. J Clin Invest 1981;68:240-252.
43. Owen OE, Trapp VE, Reichard GA, Jr., Mozzoli MA, Moctezuma J, Paul P, et al. Nature and quantity of fuels consumed in patients with alcoholic cirrhosis. J Clin Invest 1983;72:1821-1832.
44. Madden AM, Morgan MY. Patterns of energy intake in patients with cirrhosis and healthy volunteers. Br J Nutr 1999; 82:41-48.
45. Madden AM, Morgan MY. Resting energy expenditure should be measured in patients with cirrhosis, not predicted. HEPATOLOGY 1999;30:655-664.
46. McCullough AJ, Tavill AS. Disordered energy and protein metabolism in liver disease. Semin Liver Dis 1991;11:265-277.
47. Swart GR, van den Berg JW, Wattimena JL, Rietveld T, van Vuure JK, Frenkel M. Elevated protein requirements in cirrhosis of the liver investigated by whole body protein turnover studies. Clin Sci 1988;75:101-107.
48. Kabadi UM. The association of hepatic glycogen depletion with hyperammonemia in cirrhosis. HEPATOLOGY 1987;7:821-824.
49. Cordoba J, Lopez-Hellin J, Planas M, Sabin P, Sanpedro F, Castro F, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41:38-43.
50. Soulsby CT, Morgan MY. Dietary management of hepatic encephalopathy in cirrhotic patients: survey of current practice in United Kingdom. BMJ 1999;318:1391.
51. Heyman JK, Whitfield CJ, Brock KE, McCaughan GW, Donaghy AJ. Dietary protein intakes in patients with hepatic encephalopathy and cirrhosis: current practice in NSW and ACT. Med J Aust 2006;185:542-543.
52. Marchesini G, Moscatiello S, Di DS, Forlani G. Obesity-associated liver disease. J Clin Endocrinol Metab 2008;93(11 Suppl 1):S74-S80.
53. Nielsen K, Kondrup J, Martinsen L, Døssing H, Larsson B, Stilling B, et al. Long-term oral refeeding of patients with cirrhosis of the liver. Br J Nutr 1995;74:557-567.
54. Tsien CD, Arthur J McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. J Gastroenterol Hepatol 2012;27:430-441.
55. Bessman AN, Mirick GS. Blood ammonia levels following the ingestion of casein and whole blood. J Clin Invest 1958;37:990-998.
56. Fenton JCB, Knight EJ, Humpherson PL. Milk-and-cheese diet in portal-systemic encephalopathy. Lancet 1966;1:164-166.
57. Greenberger NJ, Carley J, Schenker S, Bettinger I, Stamnes C, Beyer P. Effect of vegetable and animal protein diets in chronic hepatic encephalopathy. Am J Dig Dis 1977;22:845-855.
58. Weber FL, Jr., Minco D, Fresard KM, Banwell JG. Effects of vegetable diets on nitrogen metabolism in cirrhotic subjects. Gastroenterology 1985;89:538-544.
59. Uribe M, Dibildox M, Malpica S, Guillermo E, Villallobos A, Nieto L, et al. Beneficial effect of vegetable protein diet supplemented with psyllium plantago in patients with hepatic encephalopathy and diabetes mellitus. Gastroenterology 1985;88:901-907.
60. Vester Boler BM, Rossoni Serao MC, Bauer LL, Staeger MA, Boileau TW, Swanson KS, et al. Digestive physiological outcomes related to polydextrose and soluble maize fibre consumption by healthy adult men. Br J Nutr 2011;31:1-8.
61. Bosscher D, Breynaert A, Pieters L, Hermans N. Food-based strategies to modulate the composition of the intestinal microbiota and their associated health effects. J Physiol Pharmacol 2009;60(Suppl 6):5-11.
62. MacFarlane GT, MacFarlane S. Fermentation in the human large intestine: its physiologic consequences and the potential contribution of prebiotics. J Clin Gastroenterol 2011;45(Suppl):S120-S127.
63. Zieve L, Doizaki WM, Zieve J. Synergism between mercaptans and ammonia or fatty acids in the production of coma: a possible role for mercaptans in the pathogenesis of hepatic coma. J Lab Clin Med 1974;83:16-28.
64. de Bruijn KM, Blendis LM, Zilm DH, Carlen PL, Anderson GH. Effect of dietary protein manipulations in subclinical portal-systemic encephalopathy. Gut 1983;24:53-60.
65. Amodio P, Caregaro L, Patteno E, Marcon M, Del PF, Gatta A. Vegetarian diets in hepatic encephalopathy: facts or fantasies? Dig Liver Dis 2001;33:492-500.
66. Morgan MY, Milsom JP, Sherlock S. Plasma ratio of valine, leucine and isoleucine to phenylalanine and tyrosine in liver disease. Gut 1978;19:1068-1073.
67. Fischer JE, Baldessarini RJ. False neurotransmitters and hepatic failure. Lancet 1971;2:75-80.
68. Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy. Cochrane Database Syst Rev 2003;(2):CD001939.
69. Les I, Doval E, García-Martínez R, Planas M, Cárdenas G, Gómez P, et al. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. Am J Gastroenterol 2011;106:1081-1088.
70. Dam G, Ott P, Aagaard NK, Vilstrup H. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. Metab Brain Dis 2013 Jan 15. doi: 10.1007/s11011-013-9377-3.
71. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology 2003;124:1792-1801.
72. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol 2005;3:705-713.
73. Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition 2007;23:113-120.
74. Holecek M. Three targets of branched-chain amino acid supplementation in the treatment of liver disease. Nutrition 2010;26:482-490.
75. Kimball SR, Jefferson LS. Regulation of global and specific mRNA translation by oral administration of branched-chain amino acids. Biochem Biophys Res Commun 2004;313:423-427.
76. Leenders M, Van Loon LJ. Leucine as a pharmaconutrient to prevent and treat sarcopenia and type 2 diabetes. Nutr Rev 2011;69:675-689.
77. Shukla S, Shukla A, Mehboob S, Guha S. Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy. Aliment Pharmacol Ther 2011;33:662-671.
78. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. HEPATOLOGY 2004;39:1441-1449.
79. Malaguarnera M, Greco F, Barone G, Gargante MP, Malaguarnera M, Toscano MA. Bifidobacterium longum with fructo-oligosaccharide (FOS) treatment in minimal hepatic encephalopathy: a randomized, double-blind, placebo-controlled study. Dig Dis Sci 2007;52:3259-3265.
80. Malaguarnera M, Gargante MP, Malaguarnera G, Salmeri M, Mastrojeni S, Rampello L, et al. Bifidobacterium combined with fructo-oligosaccharide versus lactulose in the treatment of patients with hepatic encephalopathy. Eur J Gastroenterol Hepatol 2010;22:199-206.
81. Huchzermeyer H, Schumann C. Lactulose—a multifaceted substance. Z Gastroenterol 1997;35:945-955.

82. Sitkin S. Minimal hepatic encephalopathy: possibilities of dietary fibres treatment. J Hepatol 2012;56:S67.
83. Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. Am J Gastroenterol 2012;107:1043-1050.
84. Holte K, Krag A, Gluud LL. Systematic review and meta-analysis of randomized trials on probiotics for hepatic encephalopathy. Hepatol Res 2012;42:1008-1015.
85. McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. Cochrane Database Syst Rev 2011;11:CD008716.
86. Wexberg E. Diseases of the nervous system caused by nutritional deficiency. Southern Med J 1937;30:334-341.
87. Morgan AG, Kelleher J, Walker BE, Losowsky MS. Nutrition in cryptogenic cirrhosis and chronic aggressive hepatitis. Gut 1976;17:113-118.
88. Majumdar SK, Shaw GK, O'Gorman P, Aps EJ, Offerman EL, Thomson AD. Blood vitamin status (B1, B2, B6, folic acid and B12) in patients with alcoholic liver disease. Int J Vitam Nutr Res 1982;52:266-271.
89. Victor M, Adams RD, Collins GH. The Wernike-Korsakoff Syndrome and Related Neurologic Disorders Due to Alcoholism and Malnutrition, 2nd ed. Philadelphia, PA: PA Davis; 1989.
90. Kril JJ, Butterworth RF. Diencephalic and cerebellar pathology in alcoholic and nonalcoholic patients with end-stage liver disease. HEPATOLOGY 1997;26:837-841.
91. Huskisson E, Maggini S, Ruf M. The influence of micronutrients on cognitive function and performance. J Int Med Res 2007;35:1-19.
92. McDiarmid SV, Colonna JO 2nd, Shaked A, Ament ME, Busuttil RW. A comparison of renal function in cyclosporine and FK-506-treated patients after primary orthotopic liver transplantation. Transplantation 1993;56:847-853.
93. Yavuz BB, Cankurtaran M, Haznedaroglu IC, Halil M, Ulger Z, Altun B, et al. Iron deficiency can cause cognitive impairment in geriatric patients. J Nutr Health Aging 2012;16:220-224.
94. Guevara M, Baccaro ME, Torre A, Gomez-Anson B, Rios J, Torres F, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol 2009;104:1382-1389.
95. Cordoba J, Garcia-Martinez R, Simon-Talero M. Hyponatremic and hepatic encephalopathies: similarities, differences and coexistence. Metab Brain Dis 2010;25:73-80.
96. Gu XB, Yang XJ, Zhu HY, Xu BY. Effect of a diet with unrestricted sodium on ascites in patients with hepatic cirrhosis. Gut Liver 2012;6:355-361.
97. Soulsby CT, Madden AM, Morgan MY. The effect of dietary sodium restriction on energy and protein intake in patients with cirrhosis. HEPATOLOGY 1997;26(suppl 382A):S113.
98. Cosgray RE, Hanna V, Davidhizar RE, Smith J. The water-intoxicated patient. Arch Psychiatr Nurs 1990;4:308-312.
99. Lee EM, Kang JK, Yun SC, Kim KH, Kim SJ, Hwang KS, et al. Risk factors for central pontine and extrapontine myelinolysis following orthotopic liver transplantation. Eur Neurol 2009;62:362-368.
100. Bode JC, Hanisch P, Henning H, Koenig W, Richter FW, Bode C. Hepatic zinc content in patients with various stages of alcoholic liver disease and in patients with chronic active and chronic persistent hepatitis. HEPATOLOGY 1988;8:1605-1609.
101. Morgan MY, Blei A, Grungreiff K, Jalan R, Kircheis G, Marchesini G, et al. The treatment of hepatic encephalopathy. Metab Brain Dis 2007;22:389-405.
102. Takuma Y, Nouso K, Makino Y, Hayashi M, Takahashi H. Clinical trial: oral zinc in hepatic encephalopathy. Aliment Pharmacol Ther 2010;32:1080-1090.
103. Bresci G, Parisi G, Banti S. Management of hepatic encephalopathy with oral zinc supplementation: a long-term treatment. Eur J Med 1993;2:414-416.
104. Olanow CW. Manganese-induced parkinsonism and Parkinson's disease. Ann N Y Acad Sci 2004;1012:209-223.
105. Inoue E, Hori S, Narumi Y, Fujita M, Kuriyama K, Kadota T, et al. Portal-systemic encephalopathy: presence of basal ganglia lesions with high signal intensity on MR images. Radiology 1991;179:551-555.
106. Layrargues GP, Shapcott D, Spahr L, Butterworth RF. Accumulation of manganese and copper in pallidum of cirrhotic patients: role in the pathogenesis of hepatic encephalopathy? Metab Brain Dis 1995;10:353-356.
107. Morgan MY. Cerebral magnetic resonance imaging in patients with chronic liver disease. Metab Brain Dis 1998;13:273-290.
108. Naegele T, Grodd W, Viebahn R, Seeger U, Klose U, Seitz D, et al. MR imaging and (1) H spectroscopy of brain metabolites in hepatic encephalopathy: time-course of renormalization after liver transplantation. Radiology 2000;216:683-691.
109. Dasarathy S. Consilience in sarcopenia of cirrhosis. J Cachexia Sarcopenia Muscle 2012;3:225-237.