

Nutrition in Cirrhosis

Luis S. Marsano, MD, FACP, FAASLD, AGAF, FASGE
Professor of Medicine
Jewish Hospital Distinguished Chair in Hepatology
Medical Director of Liver Transplant Program
Division of Gastroenterology, Hepatology and Nutrition
University of Louisville and Louisville VAMC
2019

Protein-Calorie Malnutrition (PCM) in Cirrhosis

- Protein-calorie malnutrition (PCM) is extremely common in cirrhosis (20% in compensated, 50% in decompensated), it is potentially reversible, and negatively affects outcomes.
 - Females lose more frequently fat tissue;
 - Males lose more muscle tissue.
- There is not complete agreement in how to define PCM in cirrhosis, but different parameters have been used
 - anthropometrics, skinfold thickness (triceps-biceps-subscapular-suprailiac), mid-arm muscle circumference (< 23 cm) , hand grip dynamometry, indirect calorimetry, immune response, subjective global assessment, etc.

Protein-Calorie Malnutrition (PCM) in Cirrhosis

- PCM worsens with disease progression.
 - By “body composition analysis” is:
 - Child-A 34%,
 - Child-B 69%,
 - Child-C 94%
- Many complications of liver disease, like infections, encephalopathy and ascites, are worsen by negative nitrogen balance.
- Muscular mass is important in removing circulating ammonia.
- Sarcopenia in cirrhosis is more prevalent in males (63%) than in females (28%).

Protein-Calorie Malnutrition in Cirrhosis

- Clinical phenotypes of Malnutrition:
 - sarcopenia,
 - adipopenia,
 - proportional sarcopenia + adipopenia (hepatic cachexia),
 - “sarcopenic obesity” (with normal or high visceral and subcutaneous fat), specially in NASH,
 - micronutrient deficiencies.

Protein-Calorie Malnutrition in Cirrhosis

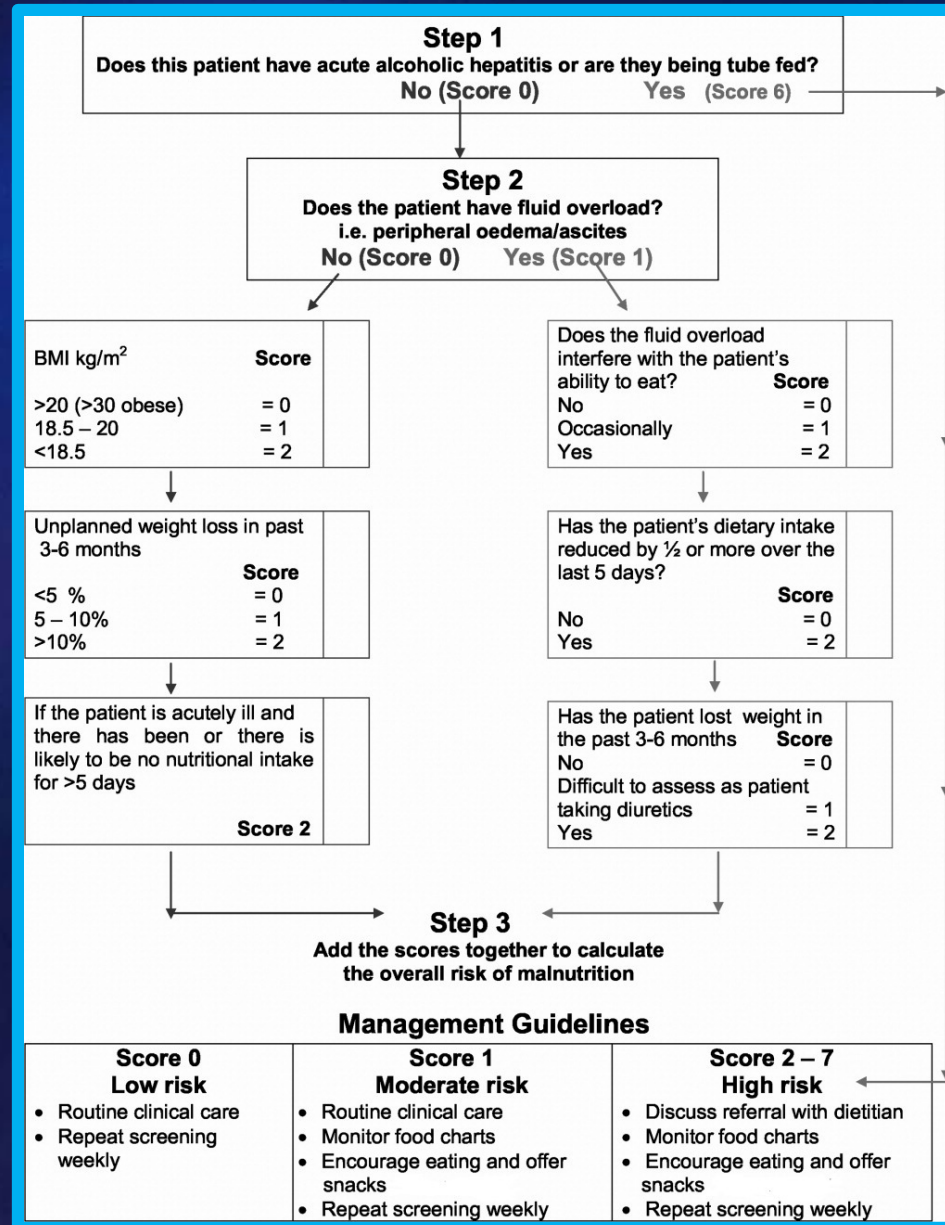
- The most clinically useful parameters to assess PCM and Sarcopenia are:
 - Hand grip dynamometry (< 30 kg) in males,
 - Subjective global assessment in both males and females (underestimates malnutrition),
 - Royal Free Hospital – Global Assessment (BMI + MAMC + dietary intake history) in males (Hepatology 2006;44:823-835)
 - Core Muscular mass by CT Scan or MRI
- Hand grip dynamometry
 - predicts development of major complications of cirrhosis in males with well compensated cirrhosis (but not in women), and
 - is associated with “health-related quality of life” (Nutrition 2005;21:113-117 and Eur J Gastroenterol Hepatol 2011;23:982-989)
- Degree of “core muscular mass” sarcopenia
 - is associated with waiting-list and post-transplant mortality.

Nutrition Screening Tools

- BMI: if $< 18.5 \text{ kg/m}^2$ in cirrhotic, most patient will have sarcopenia
- Child Pugh C: sarcopenia almost universal
- Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT):
 - Components: alcoholic hepatitis, tube feed need, fluid overload (edema, ascites), weight loss, BMI, Acute illness, ability to eat, dietary intake, likely length of NPO.
 - Correlates with clinical deterioration, Child-Pugh Score, MELD, and clinical complications (ascites, HE, HRS)
 - Improvement of RFH-NPT correlates with improved survival

Royal Free Hospital Nutritional Prioritizing Tool

Hepatology. 2013 Jul;58(1):325-36



Detailed Nutritional Assessment

● Sarcopenia:

● CT Scan at L3 level:

- Area of psoas + para spinal + abdominal wall muscles (cm^2) normalized to height gives “skeletal muscle index” (cm^2/m^2)
- Cut off: males = $50 \text{ cm}^2/\text{m}^2$; female = $39 \text{ cm}^2/\text{m}^2$
- Lower predictive value in females
- Sarcopenia increases liver transplant mortality (hazard ratio 1.84)

● Anthropometry:

- Mid Arm Muscle Circumference (MAMC) = Mid Arm Circumference - Triceps skin fold $\times 0.314$;
- Correlates well with sarcopenia by CT;
- Is an independent predictor of liver transplant mortality

● Liver Frailty Index:

- Correlates with liver transplant mortality

Detailed Nutritional Assessment

- Global Assessment tools:

- Subjective Global Assessment (SGA):
 - Underestimates prevalence of muscle loss
 - Fair to good inter-observer reproducibility
- Royal Free Hospital-global assessment (RFH-GA)
 - Reproducible, predicts survival, predicts posttransplant complications.

- Reported Dietary Intake:

- Looks at intake of food, fluids and supplements, number of meals, timing of meals, calories, quality and quantity of protein.
- Looks at barriers to intake: nausea, vomiting, food aversions, taste, low Na intake, early satiety, diarrhea, constipation, etc.
- Uses 3-day food diary or 3 x 24-hour food diary.

Subjective Global Assessment Form

Subjective Global Assessment Guidance For Body Composition

MEDICAL HISTORY

Patient name: _____ Date: ____/____/____

NUTRIENT INTAKE

- ☐ No change; adequate
- Inadequate; duration of inadequate intake _____
☐ Suboptimal solid diet ☐ Full fluids or only oral nutrition supplements ☐ Minimal intake, clear fluids or starvation
- Nutrient intake in past 2 weeks*
☐ Adequate _____ ☐ Improved but not adequate _____ ☐ No improvement or inadequate _____

WEIGHT

Usual weight: _____ Current weight: _____

- Non fluid weight change past 6 months
☐ <5% loss or weight stability ☐ 5-10% loss without stabilization or increase ☐ >10% loss and ongoing
 If above not known, has there been a subjective loss of weight during the past six months?
☐ None or mild ☐ Moderate ☐ Severe
- Weight change past 2 weeks* Amount (if known) _____
☐ Increased ☐ No change ☐ Decreased

SYMPTOMS (Experiencing symptoms affecting oral intake)

- Pain on eating ☐ Anorexia ☐ Vomiting ☐ Nausea ☐ Dysphagia ☐ Diarrhea
- Oral problems ☐ Feels full quickly ☐ Constipation
- None ☐ Intermittent/mild/low ☐ Constant/severe/multiple
- Symptoms in the past 2 weeks*
☐ Resolution of symptoms ☐ Improving ☐ No change or worsened

FUNCTIONAL CAPACITY (Fatigue and progressive loss of function)

- No dysfunction
- Reduced capacity; duration of change _____
☐ Difficulty with ambulation/home activities ☐ Bed/chair ridden
- Functional Capacity in the past 2 weeks*
☐ Improved ☐ No change ☐ Decreased

METABOLIC REQUIREMENT

High metabolic requirement ☐ No ☐ Yes

PHYSICAL EXAMINATION

- Loss of body fat ☐ No ☐ Mild/Moderate ☐ Severe
- Loss of muscle mass ☐ No ☐ Mild/Moderate ☐ Severe
- Presence of edema/ascites ☐ No ☐ Mild/Moderate ☐ Severe

SGA RATING

- ☐ A Well-nourished Normal ☐ B Mild/moderately malnourished Some progressive nutritional loss ☐ C Severely malnourished Evidence of wasting and progressive symptoms

CONTRIBUTING FACTOR

- ☐ CACHEXIA - (fat and muscle wasting due to disease and inflammation) ☐ SARCOPENIA - (reduced muscle mass and strength)

SUBCUTANEOUS FAT

Physical examination	Normal	Mild/Moderate	Severe
Under the eyes	Slightly bulging area	Somewhat hollow look, slightly dark circles	Hollowed look, depression, dark circles
Triceps	Large space between fingers	Some depth to fat tissue, but not ample, loose fitting skin	Very little space between fingers, or fingers touch
Ribs, lower back, sides of trunk	Chest is full; ribs do not show. Slight to no protrusion of the iliac crest	Ribs obvious, but indentations are not marked. Iliac Crest somewhat prominent	Indentation between ribs very obvious. Iliac crest very prominent

MUSCLE WASTING

Physical examination	Normal	Mild/Moderate	Severe
Temple	Well defined muscle	Slight depression	Hollowing, depression
Clavicle	Not visible in males; may be visible but not prominent in females	Some protrusion; may not be all the way along	Protruding/prominent bone
Shoulder	Roundness	No square look; acromion process may protrude slightly	Square look; bones prominent
Scapula/ribs	Bones not prominent; no significant depressions	Mild depressions or bone may show slightly; not all areas	Bones prominent; significant depressions
Quadriceps	Well defined	Depression/atrophy medially	Prominent knee, severe depression medially
Interosseous muscle between thumb and forefinger (back of hand)**	Muscle protrudes; could be fat in females	Slightly depressed	Flat or depressed area

FLUID RETENTION

Physical examination	Normal	Mild/Moderate	Severe
Edema	None	Pitting edema of extremities / pitting to knees, possible sacral edema if bedridden	Pitting beyond knees, sacral edema if bedridden, may also have generalized edema
Ascites	Absent	Present (may only be present on imaging)	

A - Well-nourished no decrease in food/nutrient intake; < 5% weight loss; no/minimal symptoms affecting food intake; no deficit in function; no deficit in fat or muscle mass **OR** an individual with criteria for SGA B or C but with recent adequate food intake; non-fluid weight gain; significant recent improvement in symptoms allowing adequate oral intake; significant recent improvement in function; and chronic deficit in fat and muscle mass but with recent clinical improvement in function.

B - Mild/moderately malnourished definite decrease in food/nutrient intake; 5% - 10% weight loss without stabilization or gain; mild/some symptoms affecting food intake; moderate functional deficit or recent deterioration; mild/moderate loss of fat and/or muscle mass **OR** an individual meeting criteria for SGA C but with improvement (but not adequate) of oral intake, recent stabilization of weight, decrease in symptoms affecting oral intake, and stabilization of functional status.

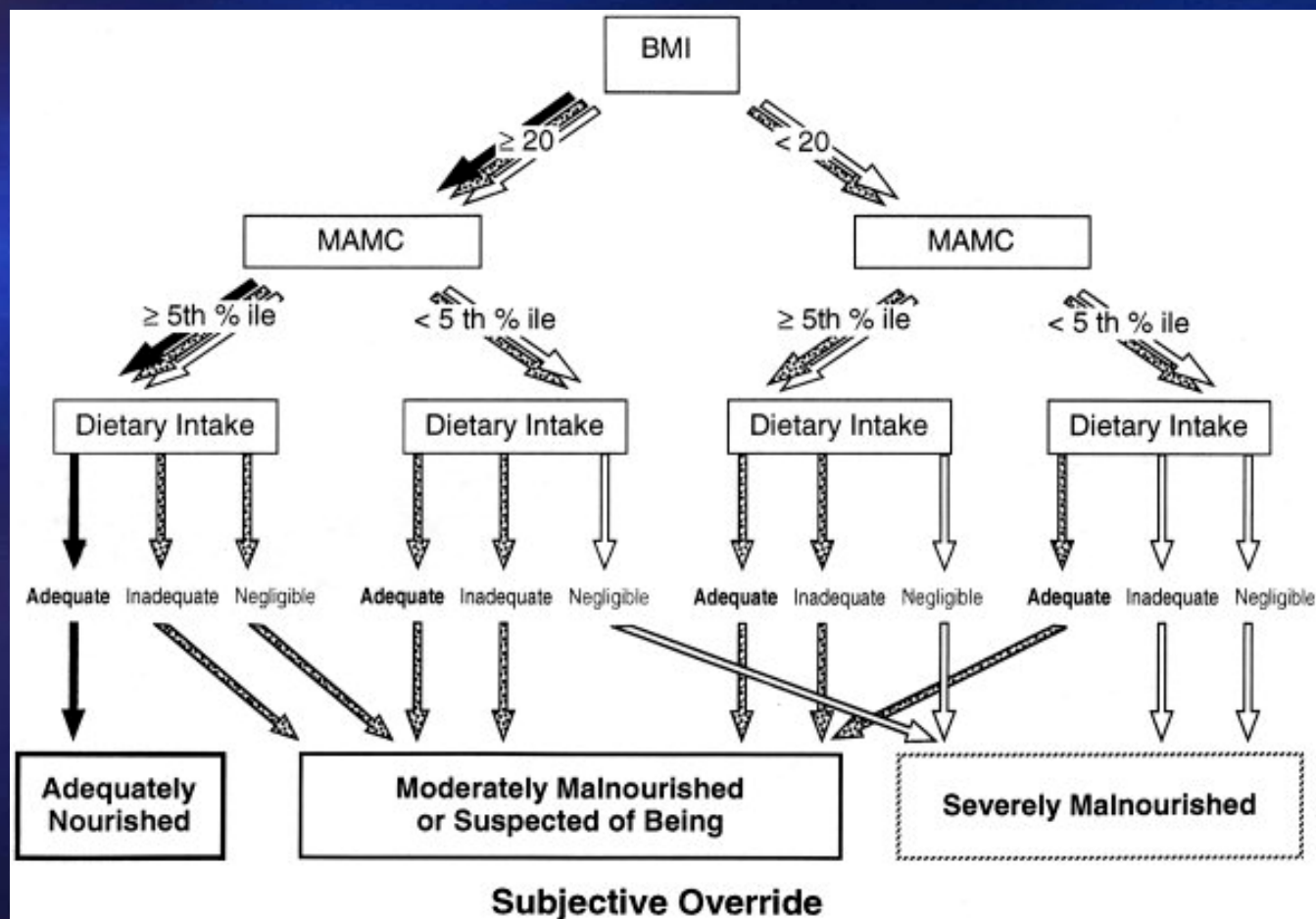
C - Severely malnourished severe deficit in food/nutrient intake; > 10% weight loss which is ongoing; significant symptoms affecting food/nutrient intake; severe functional deficit **OR** recent significant deterioration obvious signs of fat and/or muscle loss.

Cachexia - If there is an underlying predisposing disorder (e.g. malignancy) and there is evidence of reduced muscle and fat and no or limited improvement with optimal nutrient intake, this is consistent with cachexia.

Sarcopenia - If there is an underlying disorder (e.g. aging) and there is evidence of reduced muscle and strength and no or limited improvement with optimal nutrient intake.

Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis

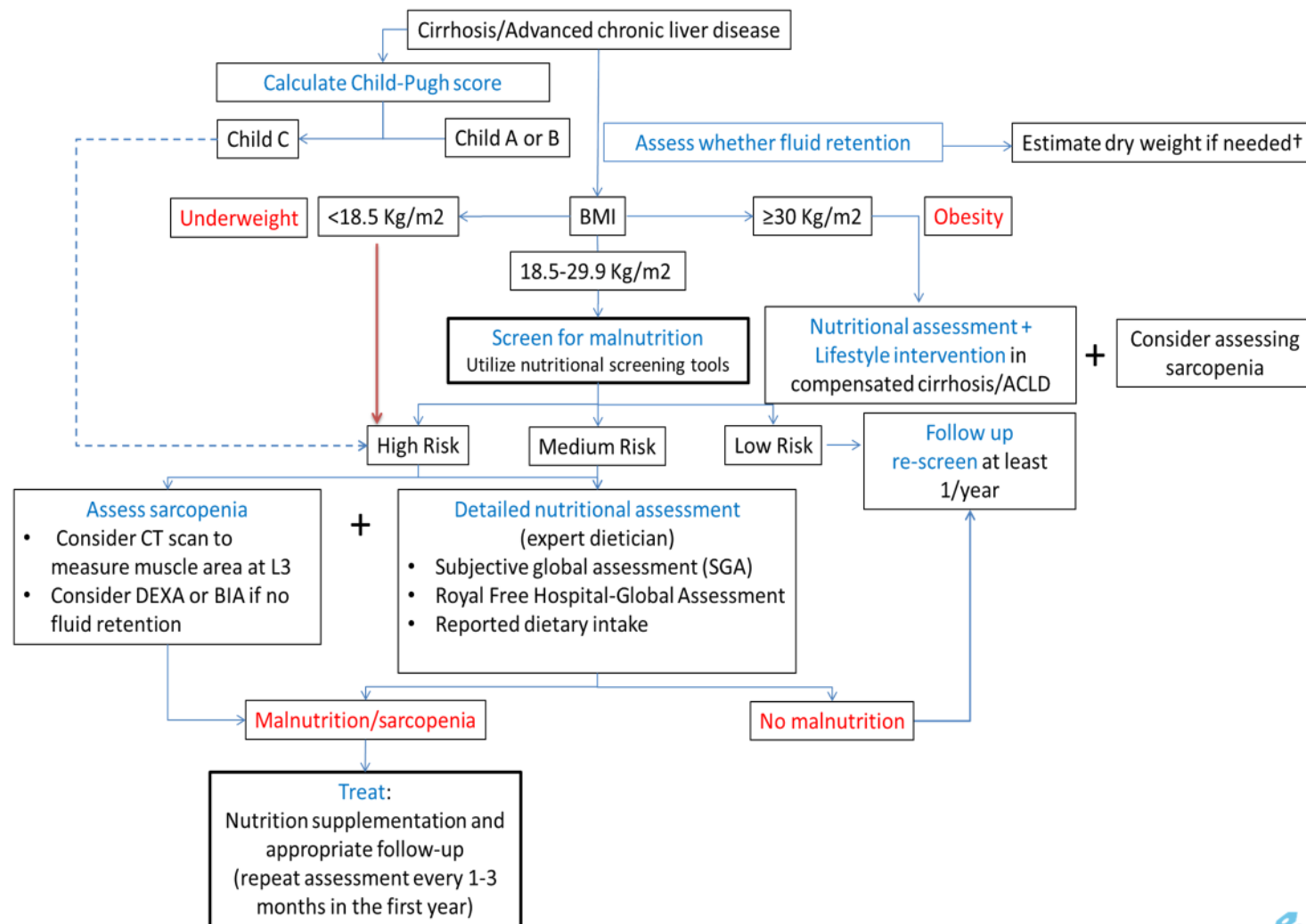
Royal Free Hospital – Global Assessment of Nutrition in Cirrhosis



Assessment & Interpretation of Obesity in Cirrhosis

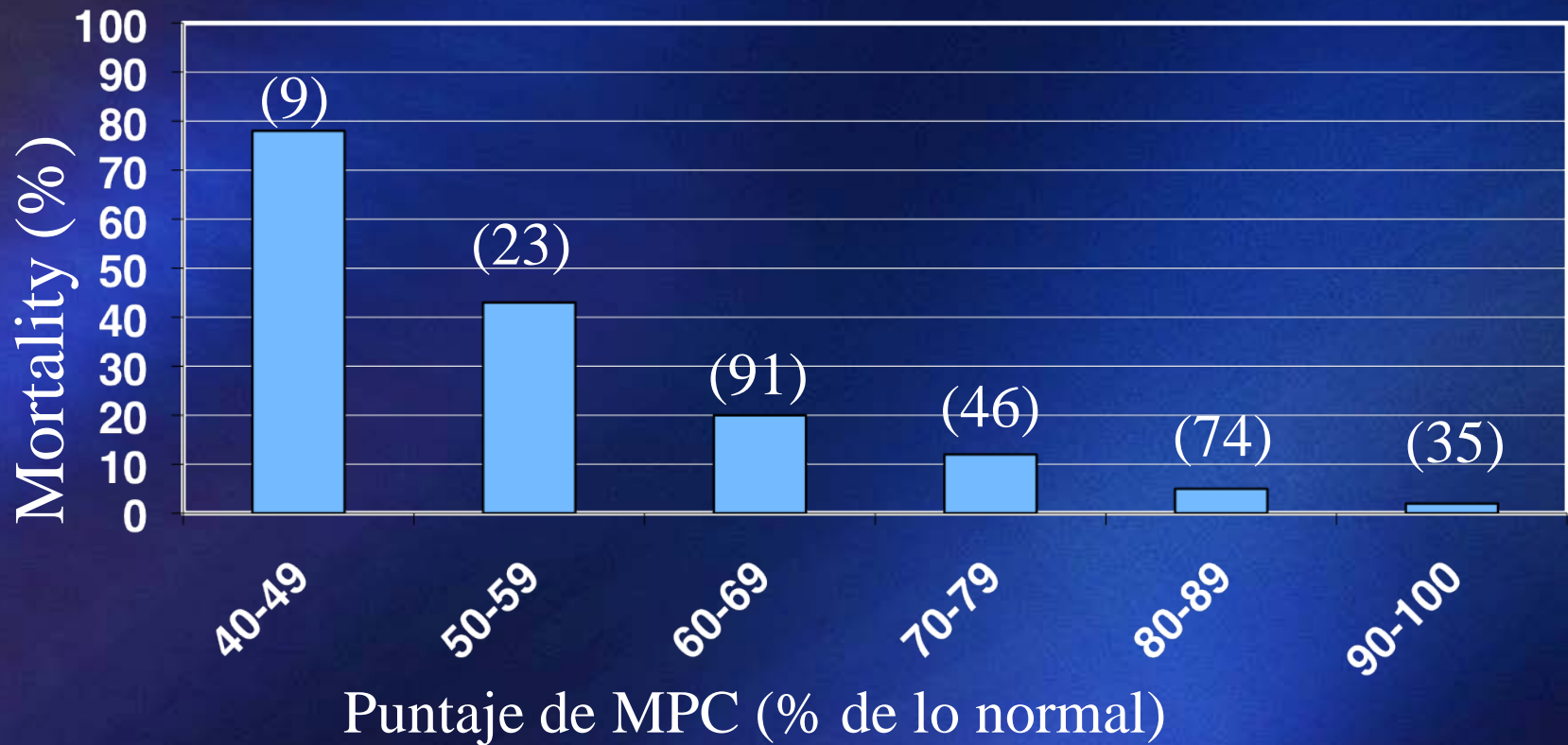
- Sarcopenic obesity is common in cirrhosis.
- BMI > 30 is consistent with obesity in the absence of fluid retention
- In fluid retention, BMI should be calculated base on dry-weight divided by the square of the patient's height.
- Dry Weight Calculation:
 - Weight before fluid retention, or
 - Weight after total paracentesis if without edema, or
 - Weight corrected by subtracting:
 - 5% for mild ascites,
 - 10% for moderate ascites,
 - 15% for severe ascites,
 - plus 5% for bilateral pedal edema)

Nutritional screening and assessment in patients with cirrhosis



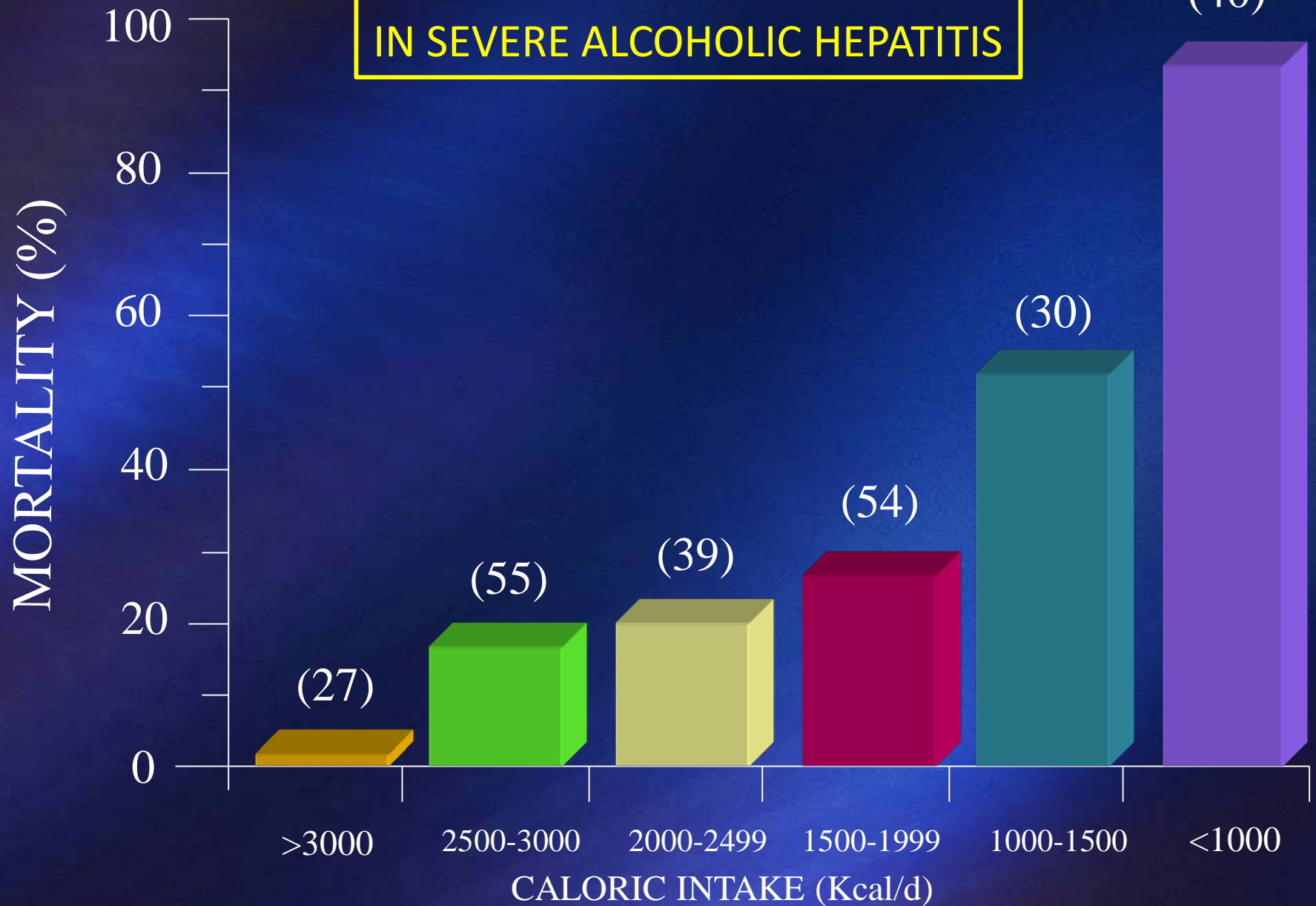
[†]In a case of fluid retention, body weight should be corrected by evaluating the patient's dry weight by post-paracentesis body weight or weight recorded before fluid retention if available, or by subtracting a percentage of weight based upon severity of ascites (mild, 5%; moderate, 10%; severe, 15%), with an additional 5% subtracted if bilateral pedal oedema is present

One-month Mortality in Severe Alcoholic Hepatitis Relation with degree of Protein-Calorie Malnutrition (PCM)



Patients with Lower Nutritional Score (%) have Higher Mortality

CALORIE INTAKE vs MORTALITY
IN SEVERE ALCOHOLIC HEPATITIS



Mendenhall, et al. Alc Clin Exp Res 19:635, 1995.

Causes of Malnutrition in Advanced Cirrhosis

Nutr Clin Pract 2013;28:15-29

● INADEQUATE NUTRIENT INTAKE

- Anorexia
- Nausea and/or vomiting
- Bloating/ abdominal distention
- Abdominal discomfort
- Ascites
- Encephalopathy
- Delayed gastric emptying
- Restrictive diet (Na, Protein, ...)
- Dysgeusia (Zn deficiency)
- Alcohol intake
- Socioeconomic barriers

● METABOLIC DISTURBANCES

- Altered glucose, lipid and protein metabolism
- Altered pattern of energy consumption
- Insulin resistance

● MALABSORPTION

- Cholestasis (bile acid deficiency)
- Small bowel bacterial overgrowth

● DECREASED LIVER STORAGE CAPACITY

Mechanism of PCM

- Skeletal mass depends on muscular protein synthesis, protein destruction and in “satellite cell” proliferation.
 - Satellite cells are myogenically committed stem cells that are needed for maintenance and growth of muscle.
- Muscular growth need muscular protein synthesis + satellite cell proliferation (2-4% of muscle mass).
- The most important factor causing sarcopenia is decreased protein synthesis.
 - Increased protein destruction adds to the problem worsening muscle loss.
- There are 3 factor affecting muscle synthesis and regeneration:
 - IGF (insulin-like growth factor): stimulates protein synthesis and satellite cell proliferation. **Decreased in cirrhosis.**
 - Myostatin: inhibits protein synthesis and satellite cell proliferation: **Increased in cirrhosis.**
 - Ammonia: increases myostatin. **Elevated in cirrhosis.**

Mechanism of PCM

- Resting Energy Expenditure (corrected by lean body mass) is increased in cirrhosis.
- Measured energy expenditure is higher than predicted energy expenditure in 30% of patients with cirrhosis patients.
- Cirrhotic patients have decreased glycogen synthesis and glycogen storage.
- Cirrhotic patients have “accelerated starvation” with excessive production of energy from fat, and with excessive gluconeogenesis from aminoacids after an overnight fast.

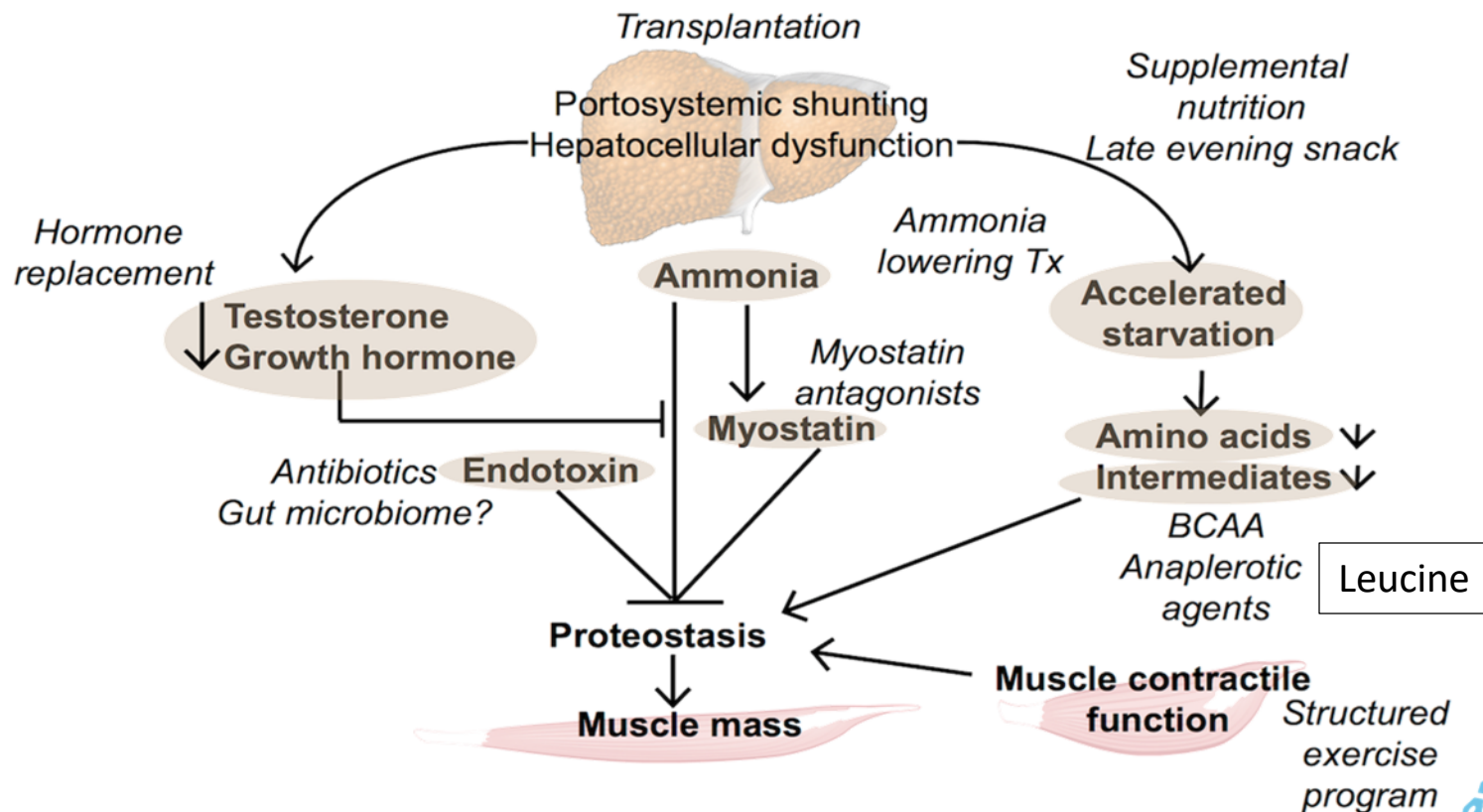
Mechanism of PCM

- When gluconeogenesis is utilized to cover glucose needs, this causes loss of aminoacids, increases ammonia production, and increases protein needs.
- A late evening snack reverses this starvation mode and improves nitrogen balance.
 - The snack should have at least 50 g of complex carbohydrates;
 - The addition of 26-30 g of protein will be ideal.
- Frequent meals (Vaisman N; Am J Clin Nutr 2010;92:137–140) and improved nutrition are useful in controlling hepatic encephalopathy.

Mechanisms resulting in sarcopenia and failure to respond to standard supplementation



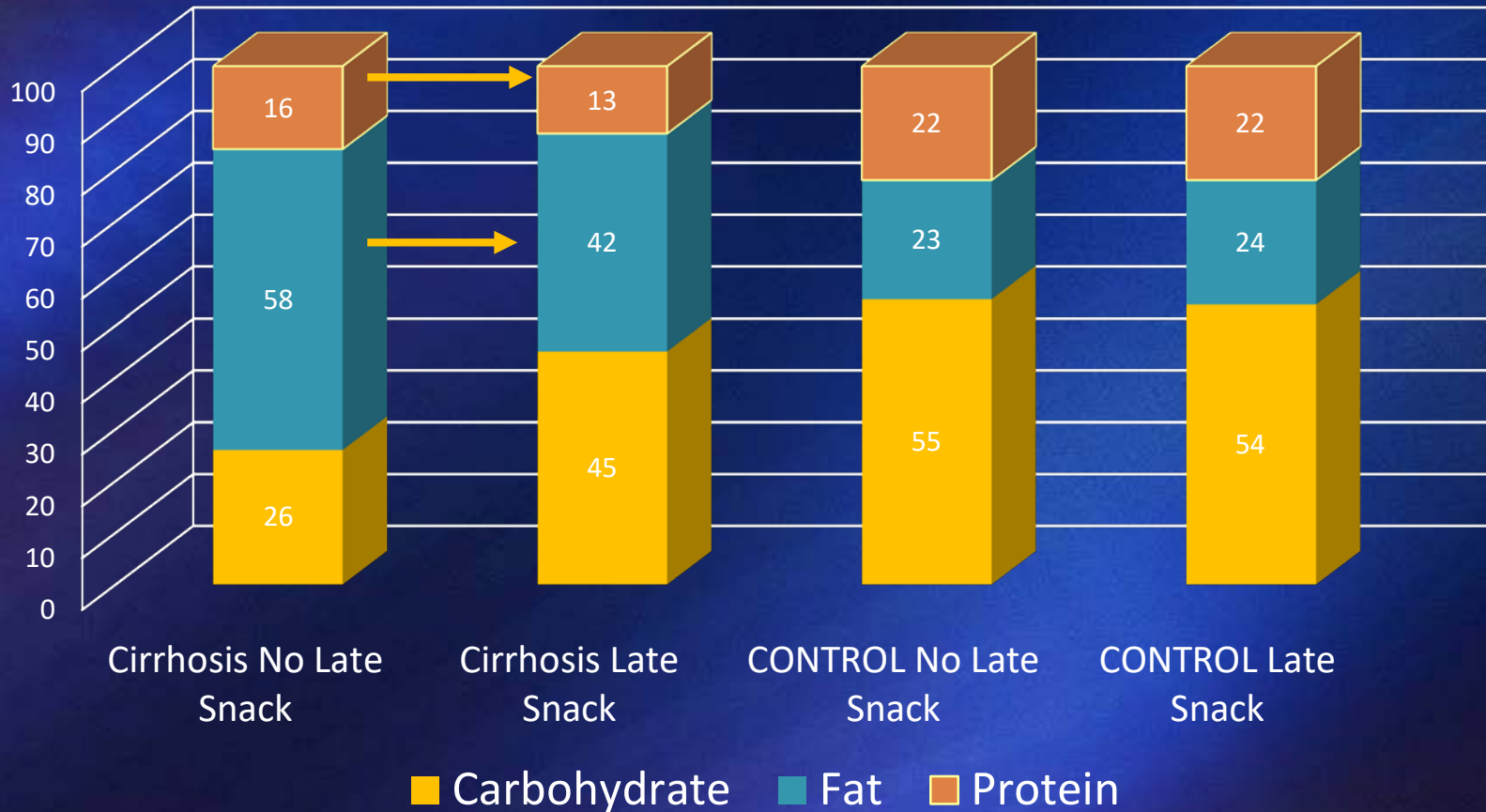
- Anabolic resistance and dysregulated proteostasis result in failure to respond to standard supplementation
- These mechanisms represent potential therapeutic targets



Effect of Late Snack in Substrate Utilization

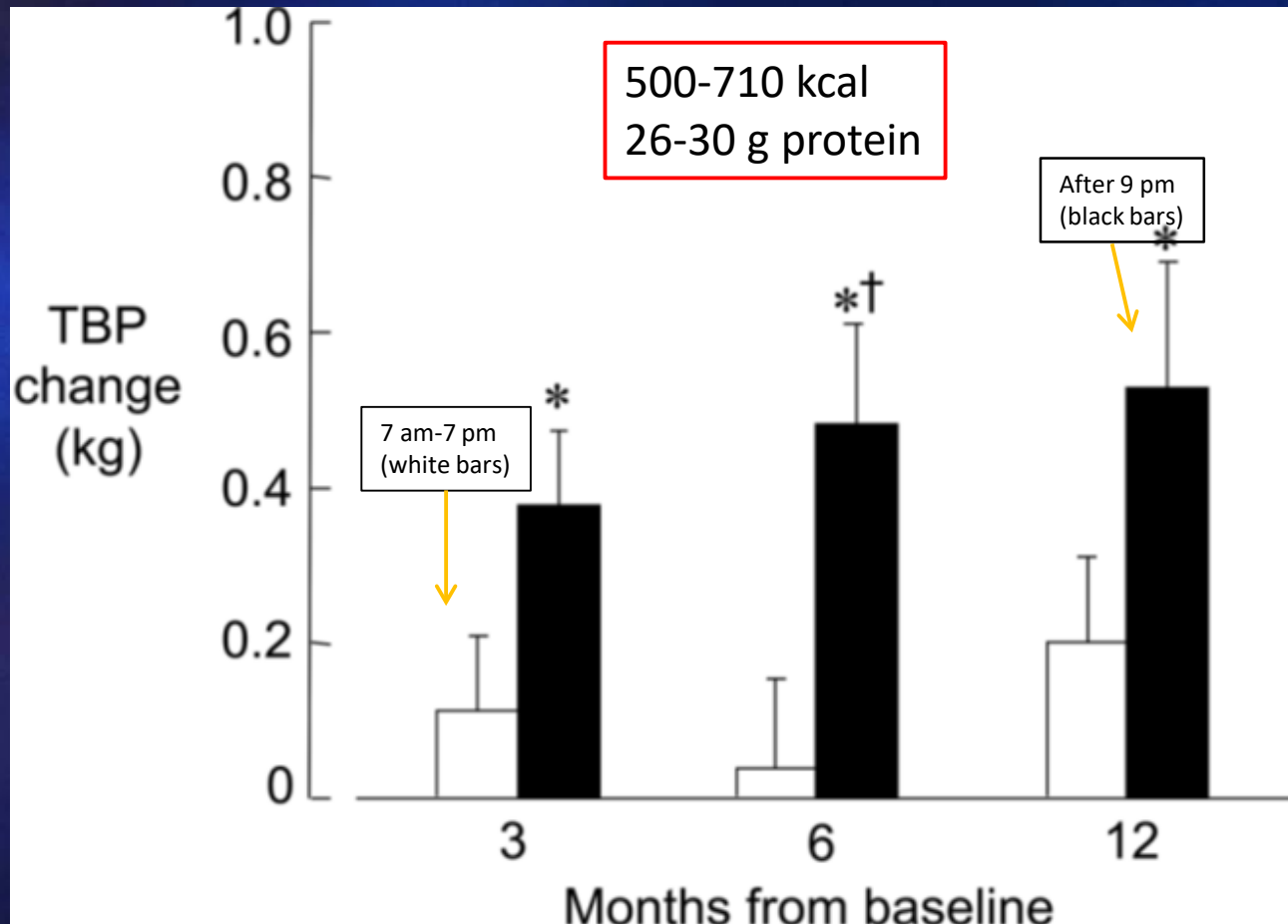
Chang WK et al. J Parent Enter Nutr 1997;21:96-97

Substrate Utilization in Cirrhotics Versus Controls



Day-time vs Night-time Nutrition Supplementation

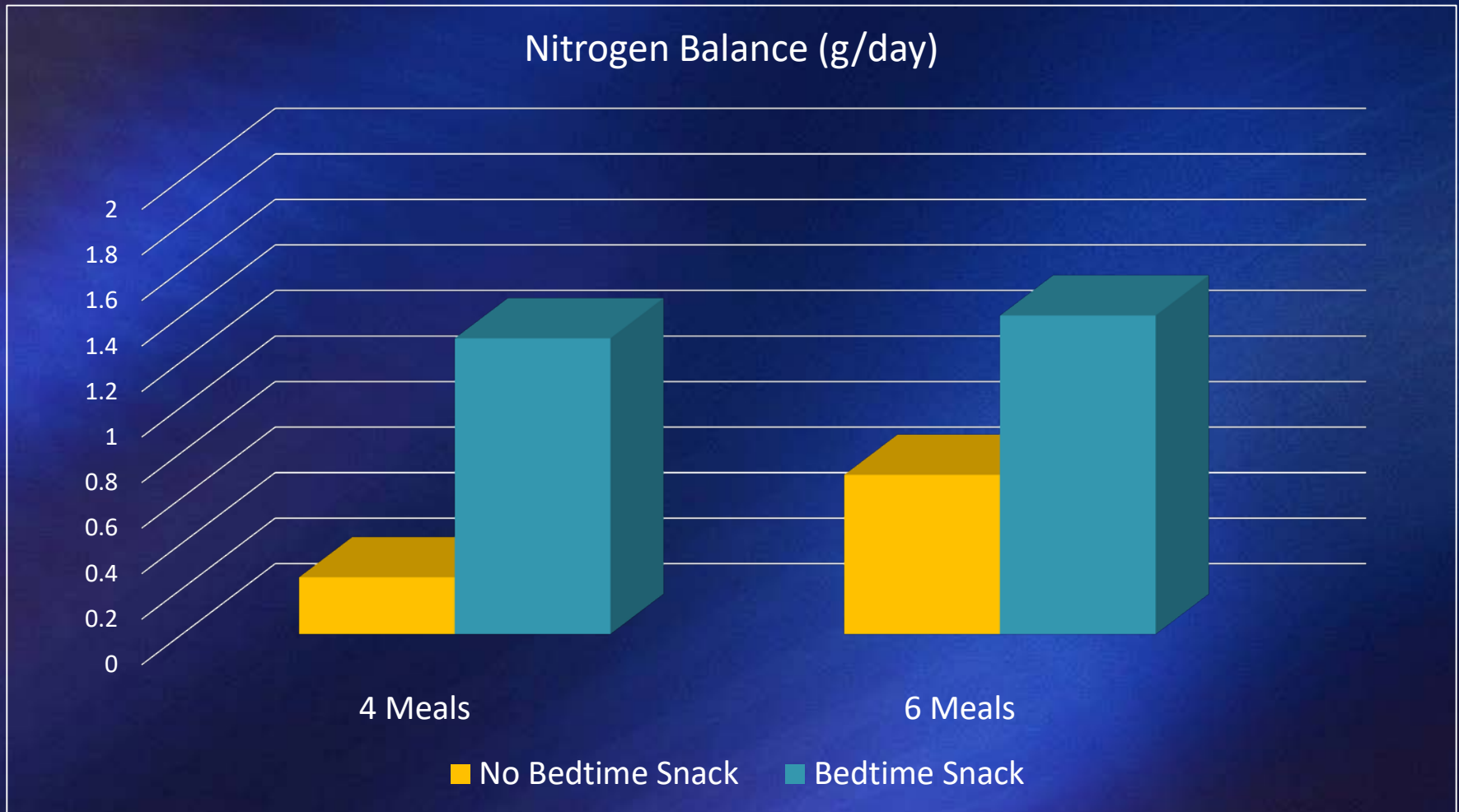
Plank LD; Hepatology 2008;48(2):557-66



**Bed-time Nutrition Increases
Nitrogen Retention & Muscular Mass**
(equivalent to 2 kg of muscle, after 12 months)

Effect of Bedtime Snack and Meal Frequency in Nitrogen Balance

McCullough AJ AASLD Postgraduate Course 2013; 142-150



Bedtime Supplement is more important than Frequent meals

Energy Requirements

- Formulas to calculate Energy Requirements (Benedict-Harris) are specially poor in cirrhosis (ascites, edema, high resting energy expenditure, hyperdynamic state, ...)
 - Best is to measure Resting Energy Expenditure by Indirect Calorimetry, otherwise
- Insulin Resistance is universal in cirrhosis, independent of the cause of liver injury;
 - use complex carbohydrates.
- Hypoglycemia is common in cirrhosis with sepsis.
- Lipid formulations can give many calories in low volume and do not add free-water, that can worsen hyponatremia.
- Lipids do not precipitate hepatic encephalopathy;
 - 25-30% of calories should come from fat.
- **RECOMMENDATION: Give 35-40 kcal/kg of Actual Body Weight, corrected for Ascites, in non-obese individuals.**

Protein Requirements

- There is great range in protein requirements in cirrhosis when compared with controls.
- Compensated cirrhotics should receive at least 1 g/kg IBW of protein to cover nitrogen needs.
 - Nitrogen retention can be improved up to 1.8-2 g/kg IBW.
- Patients with Hepatic Encephalopathy tolerate and benefit from normal protein diets.
 - Protein restriction should be avoided.
- Dairy protein is better tolerated than protein from mix-sources.
- Vegetable protein is better tolerated than animal protein (prebiotic effect of fiber?).
 - When possible give 30-40 g of vegetable protein/day.
- BCAAs can be used in patients “protein intolerant”; the high leucine stimulates “hepatocyte growth factor” secretion by stellate cells, muscle protein synthesis and insulin secretion.
- **RECOMMENDATION: Most cirrhotics should receive 1.2-1.5/kg IBW.**

Recommended Intake in Cirrhosis

(With or without Hepatic Encephalopathy)

	Adequately Nourished			Moderately Malnourished			Severely Malnourished		
Body Weight	Normal-Overweight	Obese	Obese III	Low-Overweight	Obese	Obese III	Low-Overweight	Obese	Obese III
BMI (dry weight)	20-30	30-40	> 40	18-30	30-40	> 40	18-30	30-40	> 40
Daily Energy (kcal/kg BW)	35-40	25-35*	20-25*	35-40	25-35*	20-25*	35-40	25-35*	20-25*
Daily Protein (g/kg BW)	1.2-1.5	> 1.5 (of IBW)	> 1.5 (of IBW)	1.2-1.5	> 1.5 (of IBW)	> 1.5 (of IBW)	1.2-1.5	> 1.5 (of IBW)	> 1.5 (of IBW)

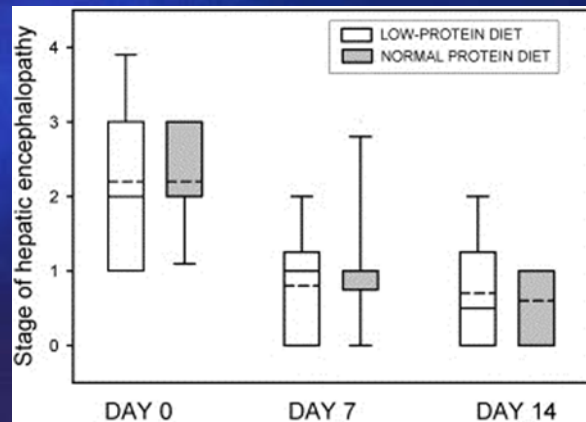
In Non-Obese use Actual Body weight, corrected by ascites/edema
In Obese use Ideal Body Weight

* Reducing Carbohydrates and Fat

Nutrition in Hepatic Encephalopathy

Low- vs Normal-Protein Diet in HE

Cordoba J; J Hepatol 2004;41:38–43

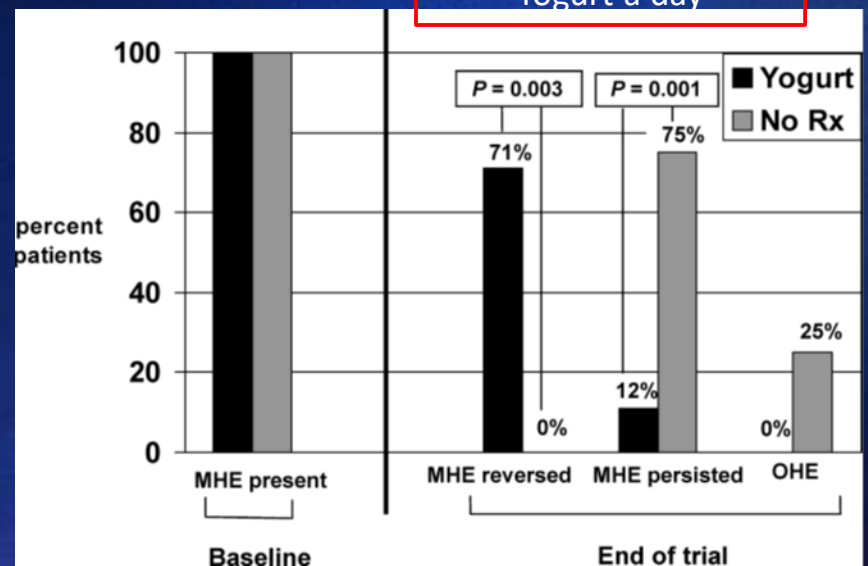


Diet with “normal protein intake” improves HE equally as “low protein” diet

Probiotic Yogurt in Covert Hepatic Encephalopathy

Bajaj JS; Am J Gastroenterol 2008;103:1707-1715

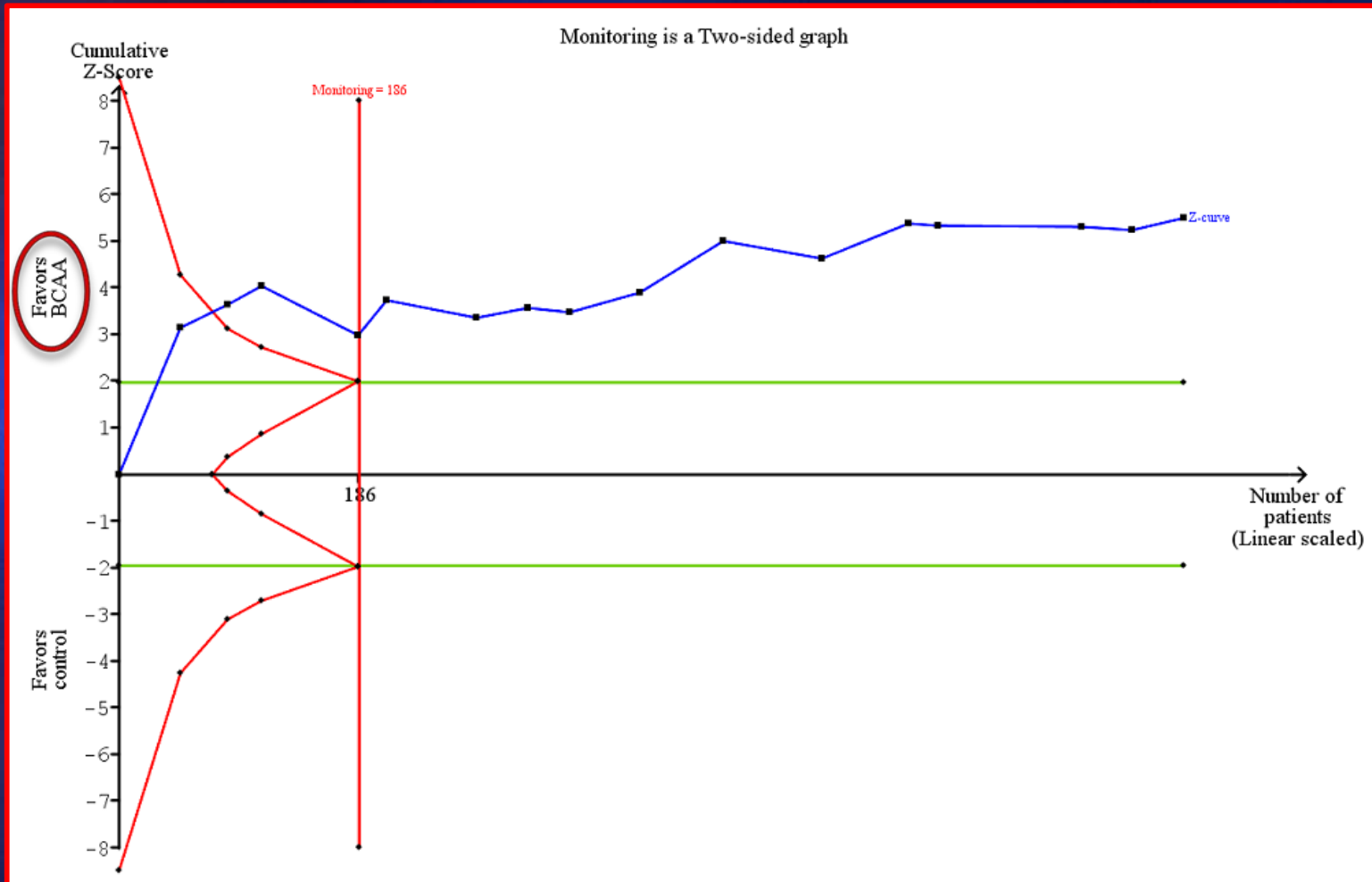
12 ounces of Probiotic Yogurt a day



Probiotic Yogurt Improves Covert HE & Protects against Overt HE

Branched-chain amino acids for people with hepatic encephalopathy

Cochrane Database Syst Rev. 2015 Feb 25;2



Trial sequential analysis of branched-chain amino acids (BCAA) versus control interventions (placebo, no intervention, neomycin, or lactulose) for hepatic encephalopathy: Beneficial for HE but NOT for mortality.

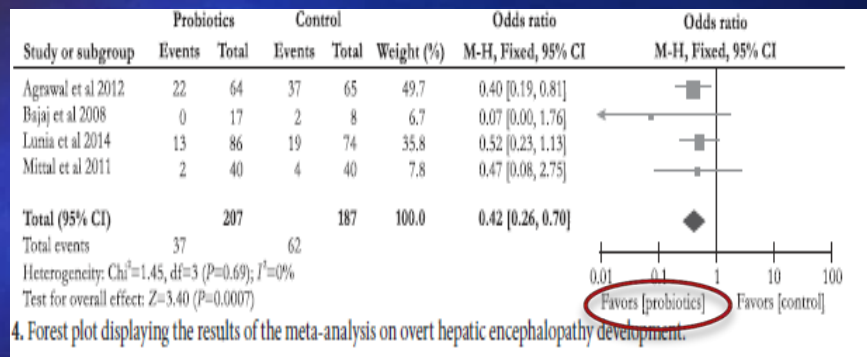
Prebiotics and Probiotics as Nutrition Therapy

- Prebiotics are selectively fermented ingredients that modify the activity and/or composition of the GI flora. Lactulose and soluble fiber are Prebiotics that improve HE.
- Probiotics are live microorganisms that can alter intestinal flora when given in adequate quantity.
- Symbiotics are the combination of Pre- and Pro-biotics.
- Meta-analysis of the high quality studies of the effect of Probiotics in HE show beneficial effect in decreasing risk of Overt HE without increasing adverse events.
- Live-culture Yogurt (a symbiotic) has shown to improve Minimal or Covert HE and to protect against Overt HE.
- Fiber intake of 25-45 g a day increases fullness and helps in weight control; also works as a prebiotic.

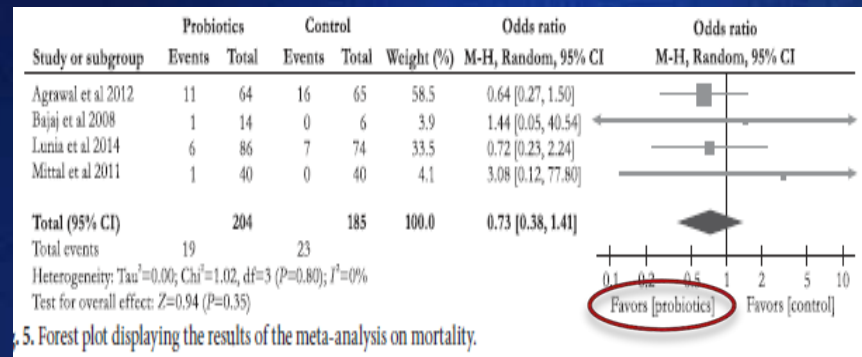
Meta-Analysis of the Effects of ProBiotics in Hepatic Encephalopathy

Xu J et al. Hepatobiliary Pancreat Dis Int. 2014 Aug;13(4):354-60

Probiotics decrease the risk of Overt HE



Probiotics did not affect mortality



In Patients with Cirrhosis, Probiotics decrease the Risk of Overt Hepatic Encephalopathy but Do Not Affect Mortality

Micronutrients

- Thiamine deficiency is common, specially in the alcoholic, and may be subclinical.
- Other vitamin deficiencies (A, D, E, K, Folate, B₆, B₁₂, C niacin) may be present and difficult to identify.
 - Daily multivitamins will correct deficiencies.
- Sodium restriction is needed when ascites or edema are present; usually the diet will be restricted to 88 mMol (2 g) of Na a day.
 - To make a liter of ascites are needed 3 g of Na.
- Hyponatremia, either dilutional or due to excessive diuretic use is common.
 - Is important to avoid intravascular contraction.
 - In case of dilutional hyponatremia, total fluid intake will have to be restricted.
- Zinc deficiency may worsen HE because ornithine transcarbamylase and glutamine synthetase are Zn dependent enzymes, and both help in ammonia detoxification.
- Fe deficiency is common. Se may also be deficient. Leg cramps often improve with supplementation of Ca, Mg and Zn.

Additional Nutritional Management Recommendations in Cirrhosis

Amodio et al. Hepatology 2013;58:325-336

	RECOMMENDATION
Meal Pattern	Small frequent (≥ 6) meals a day while awake
Late-Evening Snack	At least 50 g complex carbohydrates (+ optional 26-30 g protein) nightly
Nitrogen Source	Per patient preference; encourage dairy + vegetable protein as tolerated
Fiber	25-45 g per day, especially if overweight
Micronutrients	Daily Multivitamin with minerals (avoid copper and manganese in cholestasis)
Poorly controlled HE	Consider Probiotics and/or BCAA supplements (at bedtime)

Nutrition Route

- Oral diet intake +/- oral supplements is always preferred.
- If patient cannot cover nutrition needs orally, then naso-enteric tube (with aspiration precautions) is indicated even when varices are present (De Ledington V; Dig Dis Sci 1997;42:536–541). Avoid PEG (Loser C; Z Gastroenterol 1996;34:404–8)(Baltz JG; Gastrointestinal Endoscopy 2010;72:1072-75). Use standard formula.
- In use of intestine is not possible, use parenteral nutrition.
 - Glucose should not exceed 5-6 g/kg/d
 - Monitor for hyperglycemia
 - In hyperglycemia, limit glucose to 2-3 g/kg/d
 - Lipids should not exceed 1 g/kg/d
 - Limit Na (60-88 mMol/d) and monitor electrolytes
 - Use cyclic regimen (decreases liver enzymes elevation)
 - Limit copper and manganese in cholestasis

CONCLUSIONS

- The patient with cirrhosis has higher than usual energy requirements (35-40 kcal/kg IBW).
- In patients with Cirrhosis, frequent meals (6) plus a bedtime nutritional supplement increases their muscular mass and decreases their risk of Hepatic Encephalopathy.
- Protein Requirements in cirrhosis are the same than in a healthy adult (1.2-1.5 g/kg IBW); Protein intake should not be restricted.
- Dairy and Vegetable protein are better tolerated.
- Judicious sodium restriction helps in controlling ascites and edema.
- Oral Nutrition is preferred.
- Probiotics and Prebiotics (including fiber) are beneficial.
- Multivitamins and Mineral can be helpful.
- To prevent potentially lethal infections, all animal products should be cooked or pasteurized; fruits and vegetables should be washed carefully.