Nutrition in Cirrhosis

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2015

Protein-Calorie Malnutrition (PCM) in Cirrhosis

- Protein-calorie malnutrition (PCM) is extremely common in cirrhosis, it is potentially reversible, and negatively affects outcomes.
- 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.
- 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 encephalopathy and ascites, are worsen by negative nitrogen balance.
- Muscular mass is important in removing circulating ammonia.
- Prevalence of PCM in cirrhosis varies from 6 to 99% depending on which parameters are used and in how severe is the liver disease (degree of decompensation).
- Sarcopenia in cirrhosis is more prevalent in males (63%) than in females (28%).

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

Protein-Calorie Malnutrition in Cirrhosis

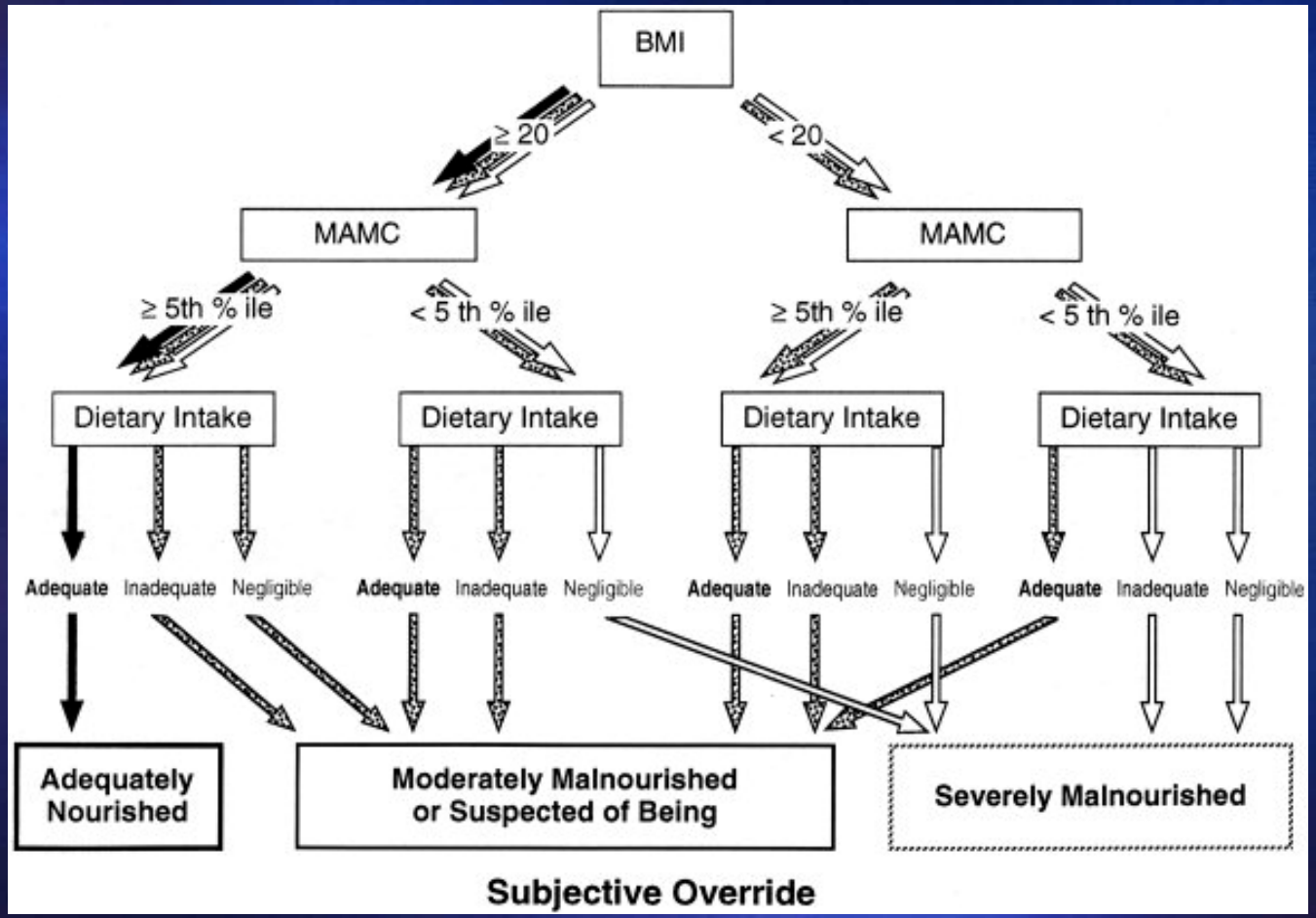
- The most clinically useful parameters to asses PCM and Sarcopenia are:
  - Hand grip dynamometry (< 30 kg) in males,
  - Subjective global assessment in both males and females (underestimates malnutrition),
  - Royal Free Hospital – Global Assessment (BMI + MAMC + dietary intake history) in males (Hepatology 2006;44:823-835)
- 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 Hepatol2011;23:982-989)
- Degree of "core muscular mass" sarcopenia, measured by CT Scan or MRI, is associated with waiting-list and post-transplant mortality.

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.

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



Hepatology
Volume 44, Issue 4, pages 823-835, 27 SEP 2006 DOI: 10.1002/hep.21358
http://onlinelibrary.wiley.com/doi/10.1002/hep.21358/full#fig1

Mechanism of PCM

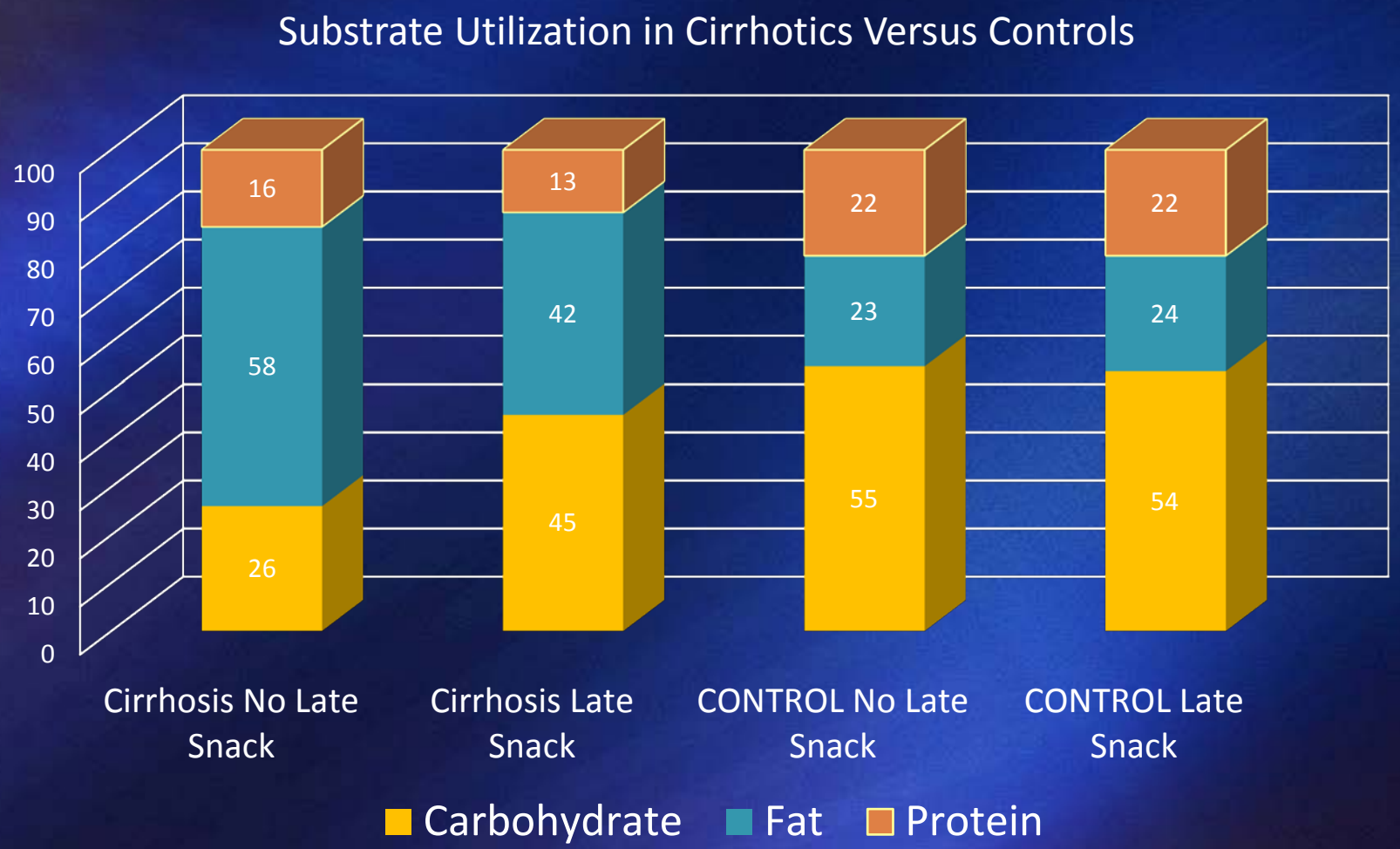
- Skeletal mass depends on muscular protein synthesis, protein destruction and in “satellite cell” proliferation.
  - Satellite cells are myogenically committed stem cells that are needed for maintenance and growth of muscle.
- Muscular growth need muscular protein synthesis + satellite cell proliferation (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.
- 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.

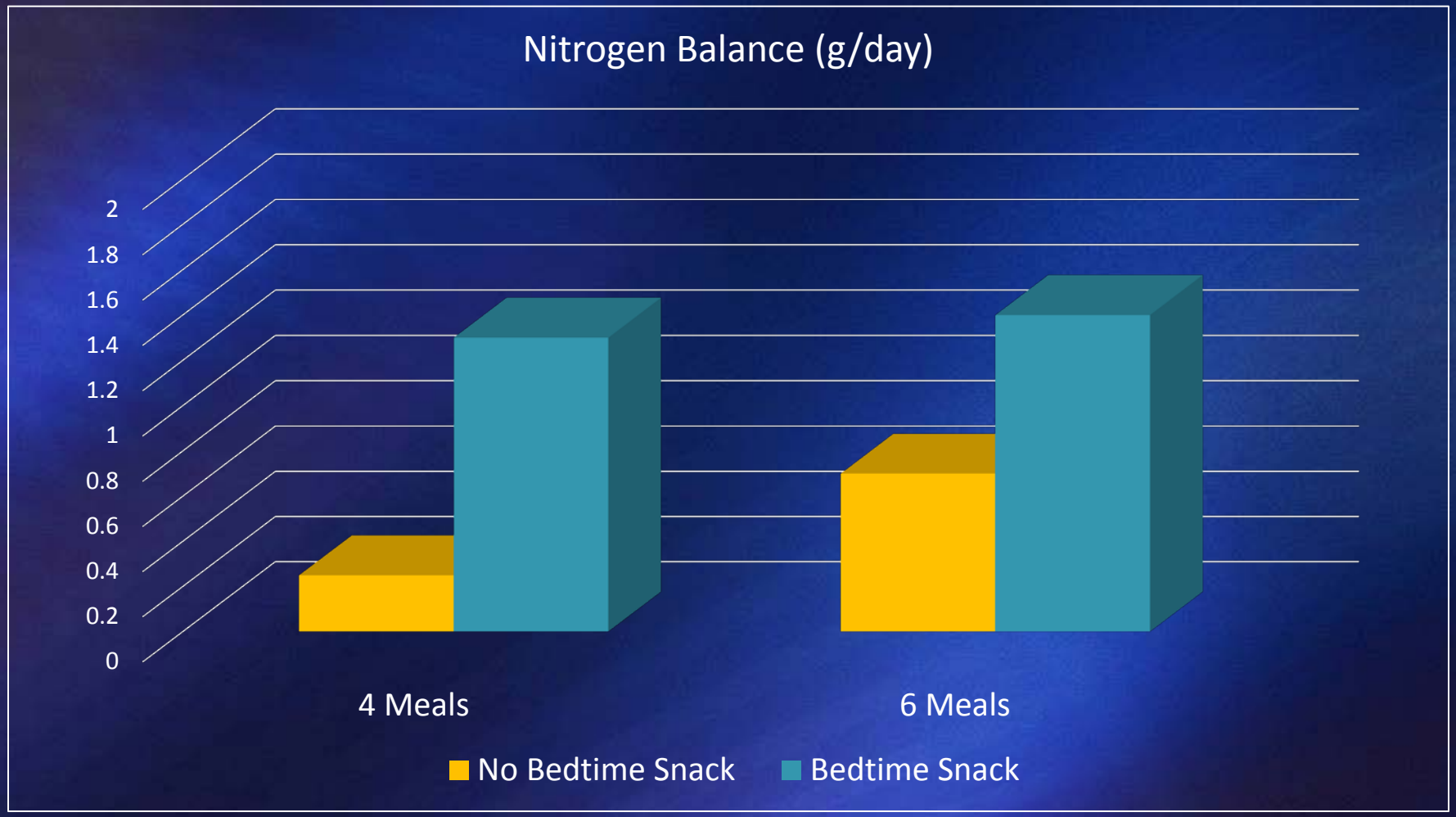
Effect of Late Snack in Substrate Utilization

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



Effect of Bedtime Snack and Meal Frequency in Nitrogen Balance

McCullough AJ AASLD Postgraduate Course 2013; 142-150



Energy Requirements

- Formulas to calculate Energy Requirements (Benedict-Harris) are specially poor in cirrhosis (ascites, edema, high resting energy expenditure, hyperdynamic state, …)
- Insulin Resistance is universal in cirrhosis, independent of the cause of liver injury.
- 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.
- Best is to measure Resting Energy Expenditure by Indirect Calorimetry, otherwise
- RECOMMENDATION: Give 35-40 kcal/kg of Ideal Body Weight

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 (pre-biotic 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.

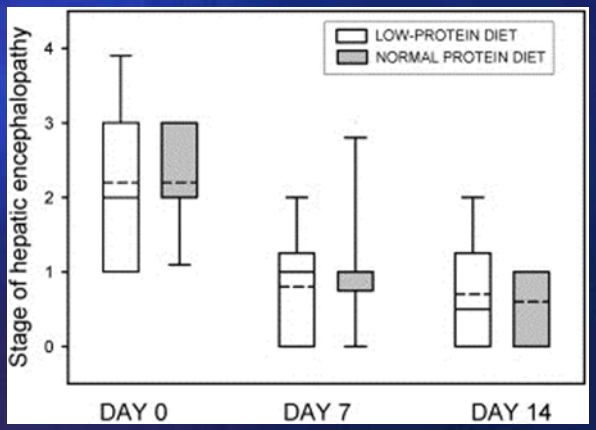
Recommended Intake in Cirrhosis
(With or without Hepatic Encephalopathy)

	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 IBW)	35-40	25-35*	20-25*	35-40	25-35*	20-25*	35-40	25-35*	20-25*
Daily Protein (g/kg IBW)	1.2-1.5	1-1.5	1-1.5	1.2-1.5	1.2-1.5	1.2-1.5	1.2-1.5	1.2-1.5	1.2-1.5

* Reducing Carbohydrates and Fat

Nutrition in Hepatic Encephalopathy

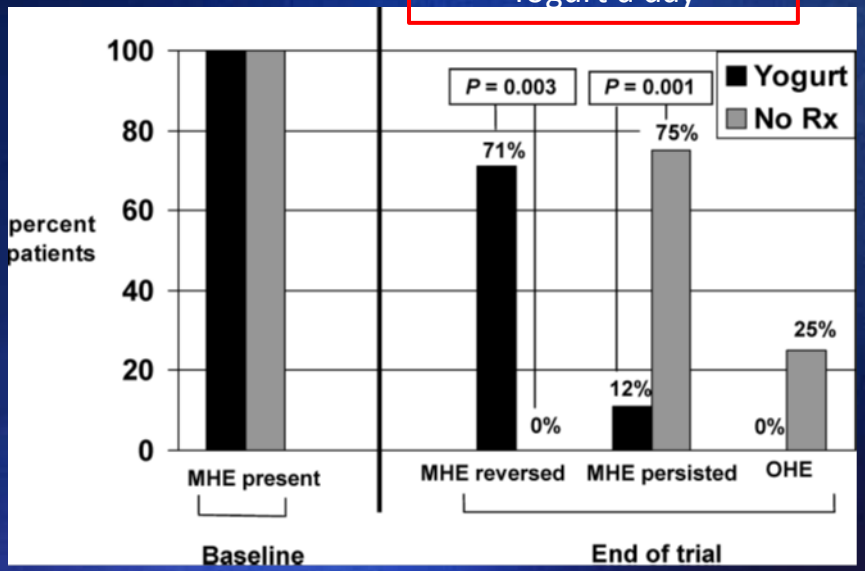
Low- vs Normal-Protein Diet in HE
Cordoba J; J Hepatol 2004;41:38–43



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

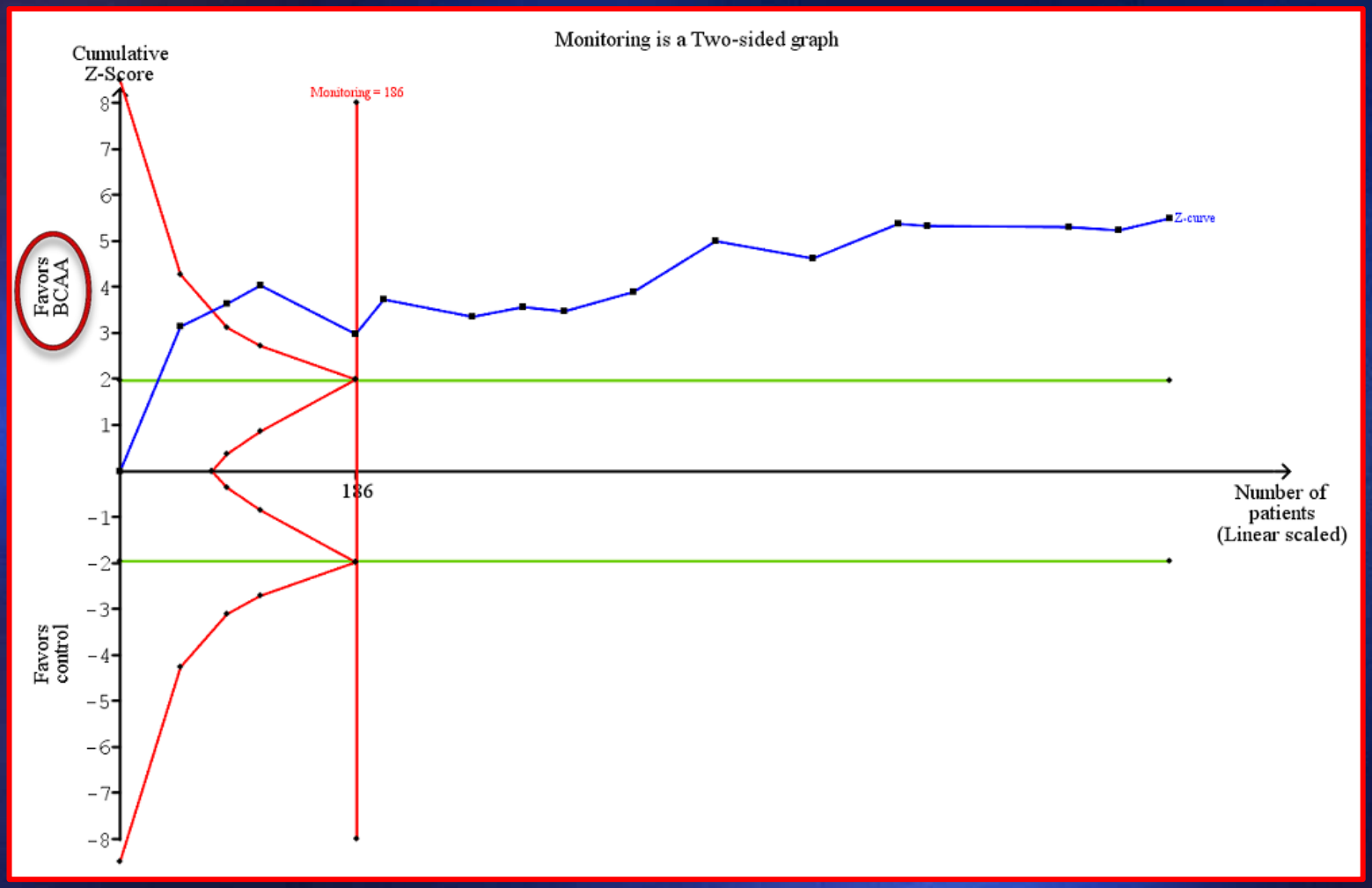
12 ounces of Probiotic Yogurt a day



Probiotic Yogurt Improves Covert HE & Protects against Overt HE

Branched-chain amino acids for people with hepatic encephalopathy

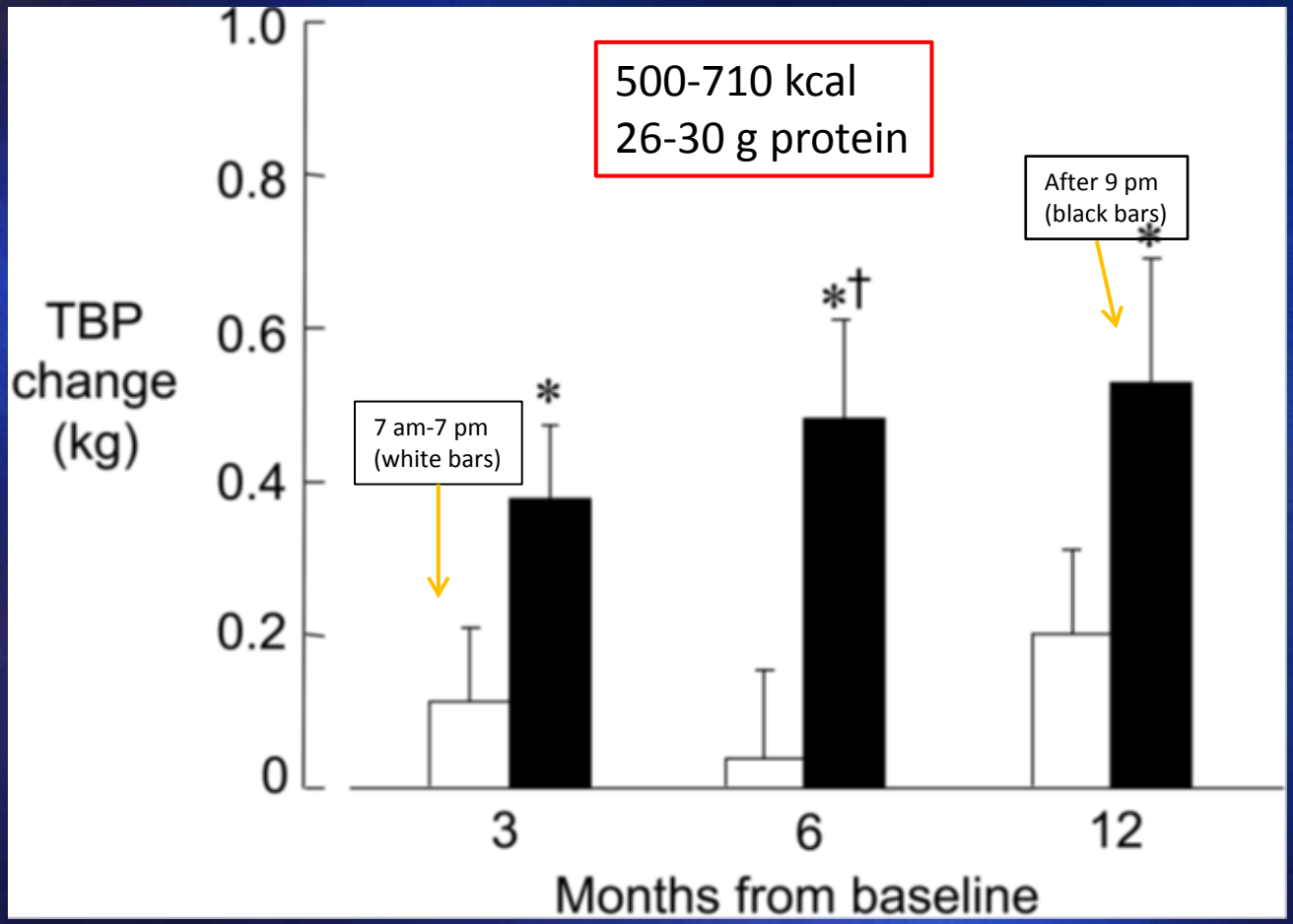
Cochrane Database Syst Rev. 2015 Feb 25;2



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.

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)

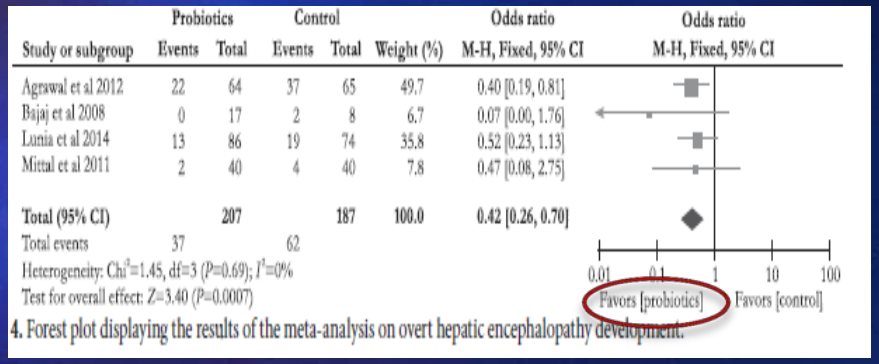
Prebiotics and Probiotics as Nutrition Therapy

- 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 Over 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



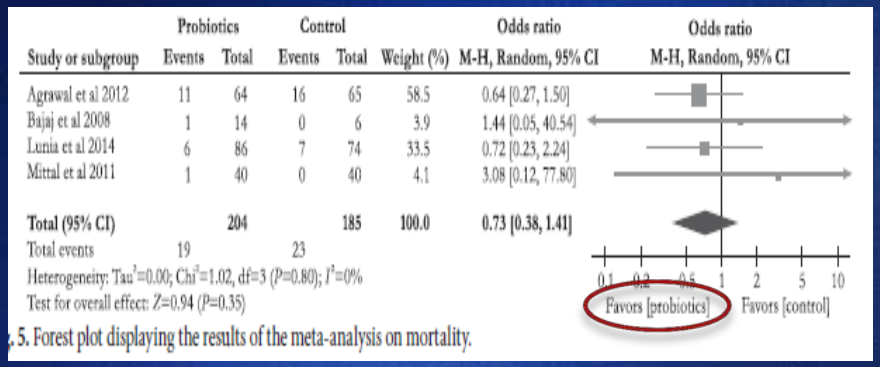
Study or subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
Agrawal et al 2012	22	64	37	65	49.7	0.40 [0.19, 0.81]
Bajaj et al 2008	0	17	2	8	6.7	0.07 [0.00, 1.76]
Lunia et al 2014	13	86	19	74	35.8	0.52 [0.23, 1.13]
Mittal et al 2011	2	40	4	40	7.8	0.47 [0.08, 2.75]
Total (95% CI)		**207**		**187**	**100.0**	**0.42 [0.26, 0.70]**
Total events	37		62			

Heterogeneity: Chi^2=1.45, df=3 (P=0.69); I^2=0%

Test for overall effect: Z=3.40 (P=0.0007)

4. Forest plot displaying the results of the meta-analysis on overt hepatic encephalopathy development.

Probiotics did not affect mortality



Study or subgroup	Probiotics Events	Probiotics Total	Control Events	Control Total	Weight (%)	Odds ratio M-H, Random, 95% CI
Agrawal et al 2012	11	64	16	65	58.5	0.64 [0.27, 1.50]
Bajaj et al 2008	1	14	0	6	3.9	1.44 [0.05, 40.54]
Lunia et al 2014	6	86	7	74	33.5	0.72 [0.23, 2.24]
Mittal et al 2011	1	40	0	40	4.1	3.08 [0.12, 77.80]
Total (95% CI)		**204**		**185**	**100.0**	**0.73 [0.38, 1.41]**
Total events	19		23			

Heterogeneity: Tau^2=0.00; Chi^2=1.02, df=3 (P=0.80); I^2=0%

Test for overall effect: Z=0.94 (P=0.35)

5. Forest plot displaying the results of the meta-analysis on mortality.

Micronutrients

- Thiamine deficiency is common, specially in the alcoholic, and may be subclinical.
- Other vitamin deficiencies (A, D, E, K, Folate, B_6, B_{12}, 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 Ledinghen 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