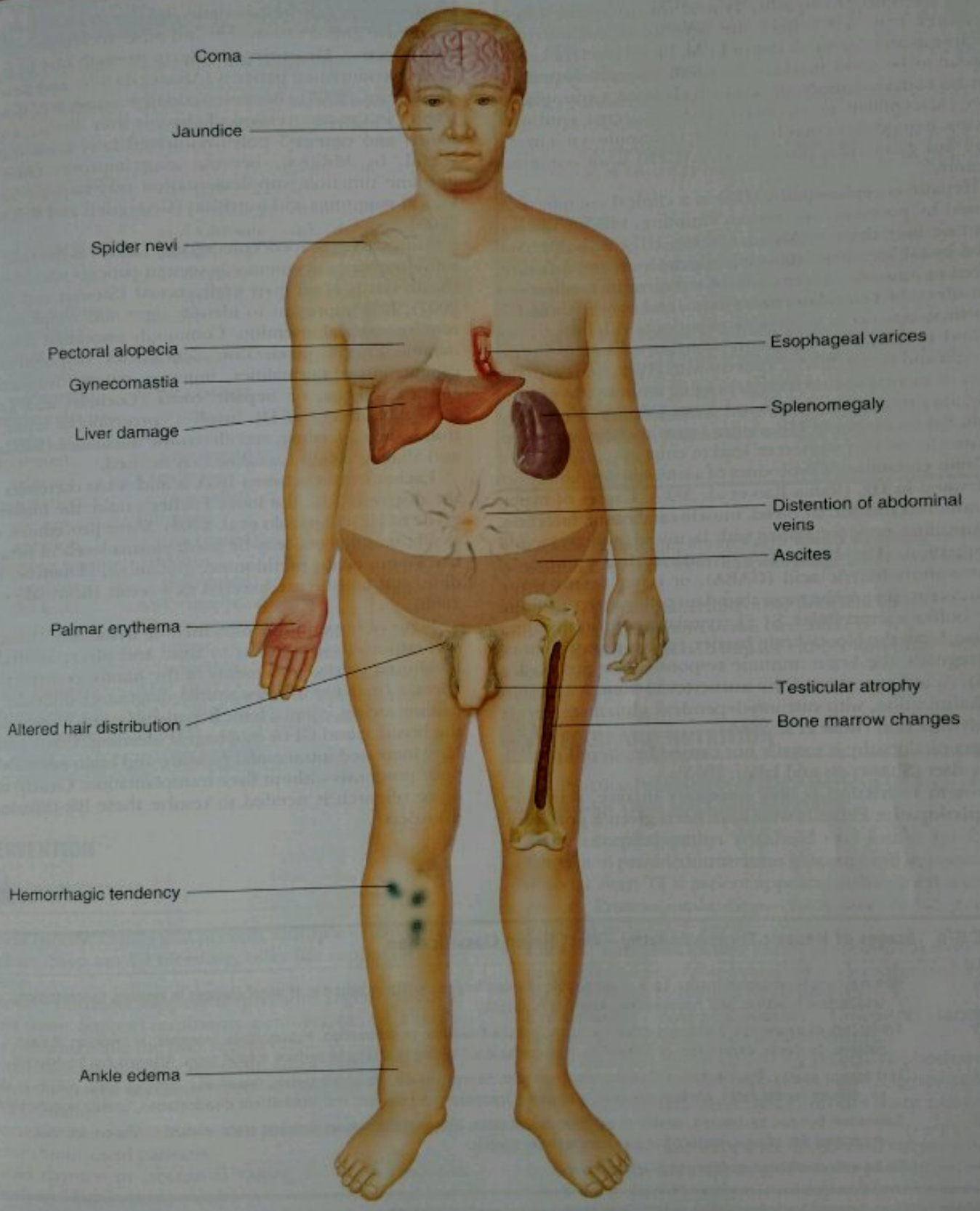
HEPATIC FAILURE, ENCEPHALOPATHY, AND COMA

NUTRITIONAL ACUITY RANKING: LEVEL 3–4



Asset provided by Anatomical Chart Co.

DEFINITIONS AND BACKGROUND

Hepatic failure is common in critical illnesses. Acetaminophen overdose is the leading cause of the acute form. Hallmarks include coagulopathy, usually an INR of 1.5 or more, and encephalopathy. Typical nutrition assessment measures may not reflect the severity of malnutrition because ascites can mask loss of LBM. Blood levels of lactate appear to be good markers for predicting which patients can be managed medically and which need a transplantation (MacQuillan et al, 2005). If hepatorenal syndrome occurs, hemodialysis may be needed; creatinine is not useful here but glomerular filtration rate (GFR) is an important measure.

Hepatic encephalopathy (HE) is a clinical complication caused by portosystemic venous shunting, with or without intrinsic liver disease (Munoz, 2008). HE can be precipitated by GI bleeding, abnormal electrolytes, renal failure, infection, diuretic therapy, use of sedatives or medications that affect the central nervous system, and constipation. HE is estimated to occur in 30–45% of patients with liver cirrhosis and in 10–50% of patients with portosystemic shunts (Eroglu and Byrne, 2009). Patients with HE present with the onset of mental status changes ranging from subtle psychologic abnormalities to profound coma (Munoz, 2008). See Table 8-6 for stages of HE. Acute forms may be reversible; chronic forms may worsen or lead to coma.

Brain glutamine, a byproduct of ammonia detoxification, is elevated in HE (Rama Rao et al, 2005). Causes of hyperammonemia include GI bleed, muscle catabolism, infection, dehydration, noncompliance with lactulose/neomycin, and constipation. The basis of neurotoxicity from ammonia, gamma-aminobutyric acid (GABA), or other agents is not clear. Astrocytes are the most abundant cell type in the brain; they buffer extracellular K(+), regulate neurotransmitter release, form the blood–brain barrier, release growth factors, and regulate the brain immune response (Gee and Keller, 2005). Acute exposure of the astrocytes to ammonia results in alkalinization, with calcium-dependent glutamate release and dysfunction (Rose et al, 2005).

Encephalopathy is usually not caused by altered protein in the diet (Shawcross and Jalan, 2005).

Protein restriction is only necessary in rare, refractory encephalopathy. Patients who have been given a portacaval shunt (TIPS) may benefit from mild protein restriction; nutritional status improves after the shunt.

Decreased dopamine and BCAAs occur in HE; increased AAAs and serotonin also occur. Nevertheless, the use of BCAA solutions is not fully supported by the literature.

Measuring nutritional status in HE can be a challenge. Subjective global assessment and other techniques are not very effective. Measuring handgrip strength may be useful in undernourished patients (Alvares da Silva and Reverbel da Silveira, 2005). Because oxidative stress is a possible trigger in the progression of chronic liver disease, antioxidants and omega-3 polyunsaturated fatty acids may be useful. In addition, because zinc improves taste and immune function, supplementation may improve neurological symptoms and nutrition (Grungrieff and Reinhold, 2005).

Minimal hepatic encephalopathy (MHE) is the mild cognitive impairment commonly seen in patients who have cirrhosis, but it often goes undiagnosed (Stewart and Smith, 2007). It is important to identify signs and symptoms that require medical attention. Commonly associated disorders include energy production deficiencies (hypoglycemia), coagulation abnormalities, immune system dysfunctions, cerebral edema, or **hepatic coma** (Cochran and Losek, 2009). Treatment of HE involves correction of sepsis, gastrointestinal bleeding, and electrolyte imbalance (Sundaram and Shaikh, 2009). Lactulose may be used.

Fischer's ratio between BCAAs and AAAs correlates with the degree of HE; the lower Fischer's ratio, the higher the grade of HE (Koivusalo et al, 2008). Some procedures, such as albumin dialysis, may be used; plasma levels of neuroactive amino acids, methionine, glutamine, glutamate, histidine, and taurine are lowered as a result (Koivusalo et al., 2008).

Signs of impending coma include irritability, change in mentation; disorientation to time and place; asterixis or involuntary jerky movements of the hands; constructional apraxia (inability to draw simple diagrams;) difficulty with writing; ascites, edema; fetor hepaticus (sweet, musty odor of the breath); and GI or esophageal bleeding. Coma patients have increased intracranial pressure and brain edema with a poor prognosis without liver transplantation. Clearly, much more research is needed to resolve these life-threatening disorders.

TABLE 8-6 Stages of Hepatic Encephalopathy—West Haven Classification

Grade 0	Minimal hepatic encephalopathy. Lack of detectable changes in personality or behavior. Minimal changes in memory, concentration, intellectual function, and coordination. Asterixis is absent.
Grade 1	Trivial lack of awareness. Shortened attention span. Impaired addition or subtraction. Hypersomnia, insomnia, or inversion of sleep pattern. Euphoria, depression, or irritability. Mild confusion. Slowing of ability to perform mental tasks. Asterixis can be detected.
Grade 2	Lethargy or apathy. Disorientation. Inappropriate behavior. Slurred speech. Obvious asterixis. Drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time.
Grade 3	Somnolent but can be aroused, unable to perform mental tasks, disorientation about time and place, marked confusion, amnesia, occasional fits of rage, present but incomprehensible speech.
Grade 4	Coma with or without response to painful stimuli.

Adapted from: Emedicine. Accessed September 5, 2009, at http://www.emedicine.com/med/topic3185.htm.

ASSESSMENT, MONITORING, AND EVALUATION

CLINICAL INDICATORS

Genetic Markers: HE is generally acquired.

Clinical/History

- Height
- Weight
- Euvolemic (dry) weight
- BMI
- Diet history
- I & O
- BP
- Muscle stiffness or rigidity
- Changes in mentation or personality
- Daytime sleepiness
- Decreased self-care
- Dysfunctional movements, agitation
- Flapping tremor (positive Babinski reflex)
- Jaundice
- Ascites
- Early satiety?
- Musty odor of breath and urine
- Electroencephalogram (EEG)
- Handgrip strength
- Acute Physiology and Chronic Health Evaluation (APACHE II) score

Lab Work

- Serum lactate levels
- BUN (decreased)
- Creatinine (not valid?)
- Bilirubin (increased)
- Alk phos (increased)
- AST (increased)
- Tumor necrosis factor (elevated)
- ALT, GGT
- Ca^{++}, Mg^{++}
- H & H (decreased)
- Serum iron, ferritin
- Na^{+}, K^{+}
- Chol, Trig
- UA
- Ammonia
- Alb (decreased)
- Transthyretin
- Nitrogen (N) balance
- CRP
- PT or INR
- Transferrin
- Gluc (decreased)
- Actin-free Gc globulin (Af-Gc)
- Plasma isoleucine, leucine, valine
- Plasma tryptophan, phenylalanine, tyrosine
- Fischer's ratio
- Serum insulin, epinephrine
- Thyroxine

SAMPLE NUTRITION CARE PROCESS STEPS

Underweight and Altered Nutritional Lab Values

Assessment Data: Dietary intake records; temporal wasting; low weight and BMI of 17; loss of LBM in arms and legs; ascites; confusion and signs of impending coma. Altered LFTs and albumin 2.1 g/dL.

Nutrition Diagnoses (PES):

NC 3.1 Underweight related to decreased appetite prior to admission as evidenced by 90% DBW, BMI 17.

NC 2.2 Altered nutrition related lab value related to liver dysfunction as evidenced by elevated ALT, ALP, AST, NH3, albumin 2.7 g/dL.

Interventions:

Food and Nutrient Delivery: ND 1.2 Modify, distribution type or amount of food and nutrients within meals or specified time (recommend diet change to 2 g sodium, 60 g protein, and six small meals per day; focus on lower animal proteins)

Education: E 1.1 Purpose of nutrition education

Counseling: C 2.2 Goal setting(improve lab values with change)

Coordination of Care: RC 1.1 Team meeting

Monitoring and Evaluation: Track food intake (food diary or history); improvement in albumin or other lab values. Improvement in weight and BMI.

INTERVENTION

OBJECTIVES

- Treat specific causes and prevent multiple organ system failure. Stop any GI bleeding; offer life support if comatose.
- Provide nutrition support to promote regeneration of liver tissue. Support respiratory, neurological, GI, circulatory systems while the liver regenerates.
- Avoid skeletal muscle catabolism from inadequate oral intake, severely restricted diets or nothing by mouth (NPO) status.
- Decrease ammonia and toxin production. Normalize serum amino acid patterns.
- Avoid daytime or nocturnal fasting by using frequent meals and late evening snacks.
- Prevent hypokalemia, sepsis, starvation, and acute crises.
- Reduce circulating amines and lessen shunting of blood around the liver. Control hemorrhage and blood loss into the gut.
- Correct anemia, zinc, and other deficiencies such as magnesium, thiamin, and folate (see Table 8-7).
- Prevent progression to hepatic cancer and improve quality of life.

FOOD AND NUTRITION

Follow Practice Parameters of the American College of Gastroenterology (Blei and Cordoba, 2009):

- **Acute encephalopathy:** Withhold oral intake for 24–48 hours, and provide intravenous glucose until improvement is noted. Start TF if patient appears unable to eat after this period. Protein intake begins at a dose of 0.5 g/kg/d; progress to 1–1.5 g/kg/d.
- **Chronic encephalopathy:** Focus protein intake on dairy products and vegetable-based diets. Consider oral BCAAs for individuals intolerant of all protein.
- **Problematic encephalopathy:** Consider lactulose, neomycin, oral zinc, and surgical shunts.
- With coma, use TF with 0.5–0.6 g protein/kg body weight; advance to 1–1.5 g/kg euvolemic weight. Higher intake of BCAAs and glutamine-enriched products are not usually beneficial.
- Glucose is needed to reduce likelihood or presence of hypoglycemia. Start feeding slowly to prevent refeeding syndrome; then to progress to desired level of intake in the malnourished patient. It is prudent to start with

TABLE 8-7 Nutrient Relationships in Hepatic Failure and Hepatic Encephalopathy

Increased sodium and fluid	Edema; fluid retention
Decreased protein	Swollen belly (ascites) from decreased albumin production
Decreased protein and fat with malabsorption	Somnolence, euphoria, asterixis, coma
Decreased vitamin A	Increased respiratory infections
Decreased vitamins C and K	Hemorrhage; scurvy
Decreased magnesium, niacin, thiamin	Hallucinations, delirium, bei-beri, pellagra
Decreased B-complex vitamins, iron, and protein	Glossitis, anemias
Decreased thiamin	Amnesia, confabulation, Korsakoff's psychosis
Decreased niacin	Memory loss
Decreased folacin	Degeneration of spinal cord
Decreased vitamin K	Muscle weakness
Decreased magnesium	Marked anxiety, hyperirritability, confusion, seizures, tremor
Decreased zinc	Poor taste acuity, impaired wound healing

15–20 kcal/kg and progress as tolerated over several days.

- For the patient who is not comatose, diet should provide moderate-to-high levels of protein (Shawcross and Jalan, 2005). Protein restriction has been discontinued in most cases.
- Use enteral nutrition to correct protein–energy malnutrition. A calorie-dense product is desirable. A nasogastric tube placement may be better tolerated when there is ascites.
- To minimize muscle catabolism, diet should provide extra energy from carbohydrates and fats. Use 30 kcal/kg to maintain and 35 kcal/kg body weight to replete tissue; calculate needs using indirect calorimetry whenever possible. Fats should be 30–35% of kilocalories, using MCT if needed.
- When necessary, administer PN with 50% of energy as nonprotein kilocalories. Because PN does not use the gut, where bacteria may otherwise produce ammonia, parenteral protein is well tolerated and may be given as 1.0–1.5 g/kg. Parenteral solutions have risks of infection and metabolic complications.
- Ensure adequate intake of fluids and electrolytes as monitoring determines. Often, sodium is limited to aid diuresis. Restrict fluid only with dilutional hyponatremia (usually 1000–1500 mL).
- Vitamin–mineral supplements may be needed for niacin, thiamin, folate, phosphate, zinc, calcium, and magnesium.
- Monitor fat-soluble vitamin intake (vitamins A, D, E, and K) carefully and avoid excesses. Avoid copper and manganese at this time, and do not give iron supplements randomly.
- If oral diet is tolerated, use a bedtime snack to avoid hypoglycemia. Small meals and snacks throughout the day may increase intake; oral liquid supplements can be made readily available. Avoid severe restrictions of protein, sodium, fluid, fiber. Liquids are often better tolerated than bulky meals.

Common Drugs Used and Potential Side Effects

- Drug-induced ALF accounts for approximately 20% of ALF in children and a higher percentage of ALF in adults; the most common cause of drug-induced ALF in children is acetaminophen (Murray et al, 2008). N-acetylcysteine is effective in ALF caused by acetaminophen overdose, with better results related to how soon it is given (Khashab et al, 2007).
- For other treatments of HE, see Table 8-8.

Herbs, Botanicals, and Supplements

- Healthy enterocytes can degrade peptides and amino acids and use ammonia via glutamate, glutamine, citrulline, and urea synthesis (Bergen and Wu, 2009). Probiotic, CO_2-producing lactobacilli are useful for enhancing gut microbial metabolism in HE (Bergen and Wu, 2009; Bongaerts et al, 2005). Other treatments using prebiotics and probiotics are under study; see Table 8-9.
- Avoid high doses of vitamins A and D, which may be toxic to the diseased liver.
- Herbs and botanical supplements should not be used without discussing with physician. For example, chaparral use can lead to liver failure. Kava kava and many other products should also be avoided in this population. *Silybum marianum* (milk thistle) is not proven to have a therapeutic role in liver failure.

NUTRITION EDUCATION, COUNSELING, CARE MANAGEMENT

- Hospitalization is usually required; discuss symptoms that require immediate medical attention.
- Dietary intake must be adjusted according to the changing status of the patient. Large meals increase portal pressure; use smaller meals more frequently.
- Milk and eggs tend to produce less ammonia than meats or poultry.
- Discuss the importance of refraining from use of alcoholic beverages.
- A better appetite at certain meals may be common. Identify if breakfast or another meal is best tolerated. Some patients sleep late and have a sleep reversal pattern.
- Discuss proper menu planning. Avoid skipping meals.

Patient Education—Foodborne Illness

- If home TF is needed, teach appropriate sanitation and food-handling procedures.

TABLE 8-8 Medications Used for Hepatic Encephalopathy

Medication	Description
Antibiotics: Neomycin	Orally administered antibiotics kill some of the bacteria present within the intestines that produce the dangerous toxins. Be careful not to miss doses. Adverse side effects are common.
Rifaximin	Rifaximin is a nonabsorbed antibiotic with a broad spectrum of activity against aerobic and anaerobic Gram-positive and Gram-negative organisms. It has a better safety and tolerability profile than that of lactulose and possibly neomycin.
Cholestyramine or ursodeoxycholic acid	For itching.
Dietary supplements	Vitamin D and calcium may be needed if osteopenia occurs. Fat-soluble excesses should be avoided since the liver is damaged.
Laxatives: Lactulose (Chronulac, Duphalac, Cholac Syrup, Constulose)	Lactulose is a synthetic sugar used to treat constipation. It is broken down in the colon into products that pull water out from the body and into the colon to soften stools. It also removes ammonia. One or two bowel movements a day are needed. Take lactulose with juice. It may cause abdominal bloating or gas. Be careful not to miss doses, but avoid excesses which can cause diarrhea.
Zinc sulfate or acetate	RNA oxidation and an increase of free intracellular zinc is a consequence of astrocyte swelling and ROS/RNOS production. RNA oxidation may impair postsynaptic protein synthesis, which is critically involved in learning and memory consolidation. Zinc supplementation is recommended.
Medications to avoid	Certain medications can increase the brain's sensitivity to ammonia and other toxins and should not be taken: sedative drugs (Valium, Ativan, Xanax), pain medications (Darvocet, codeine, Vicodin, Percocet, Demerol), antinausea agents (Phenergan, Compazine), antihistamines (Benadryl)

TABLE 8-9 Prebiotics, Probiotics, and Healthy Foods Shopping List[a]

Grains	Beans and Peas (canned/dried)	Oils
Whole grain breads[b] (rye,[c] barley,[c] wheat,[c] oat,[b] buckwheat[b])	Beans:[b] black, pinto, garbanzo, kidney lima, soy, small red, small white, cannellini, Black eyed peas, exotics	Olive
Pasta,[b] whole grain[b]	Lentils:[b] black, red, brown, French	Canola or vegetable
Bulgur,[b] wheat berries[c]	Split peas (yellow, green)	Peanut
Polenta, cornmeal	Edamame (soy beans)	Sesame
Tortillas		Walnut
Flours,[b] whole grain (pastry)[b]		Exotic
Rice, brown		
Oats		
Wild rice		
Exotic grains (spelt, quinoa)		
Cereals, prepared whole grain		
Barley,[b] pearled[c]		

Baking	Nuts and Seeds	Dairy and Cold Case
Flour, whole grain	Almonds[b]	Pesto
Jam or jelly	Cashews	Salsa
Syrup	Coconuts, fresh	Yogurt[d]
Honey	Flaxseed[b]	Yogurt smoothies[d]
Sugar	Hazelnuts	Kefir[d]
Baking soda/powder	Macadamias	Cottage cheese[b] (check for live cultures or[d] prebiotic inulin)[b]
Tapioca	Peanuts	Skim Milk
Vanilla	Pecans	Acidophilus milk[d]
Yeast	Pine nuts	Cheese
Chocolate	Pistachios	Eggs
Corn Starch	Poppy seeds	Dips
Baking mixes	Pumpkin seeds	Spreads
Carob	Sesame seeds	Tofu[e]
	Sunflower seeds	Miso (soy paste)[e]
	Walnuts	
	Tahini (ground sesame seeds)	
	Nut butters from the above	

(continued)

TABLE 8-9 Prebiotics, Probiotics, and Healthy Foods Shopping List[a] *(continued)*

Beverages	Condiments	Meat, Poultry, Fish, Other
Coffee	Vinegar (apple cider, balsamic, red wine, malt)[e]	Chicken
Tea	Horseradish	Turkey
Chocolate or cocoa	Mustard	Beef
Beer[e]	Mayonnaise	Pork
Wine[e]	Catsup	Lamb
Soymilk	Worcestershire[e]	Fish
Nut milk	Soy sauce/Tamari[e]	Exotics: bison, ostrich, etc.
Rice milk	Chutney	Tofu[e]
Kombucha (tea/live cultures)[e]	Salsa	Tempeh (soy beans)[e]
	Chile oil or sauce	Seitan (wheat gluten)
	Wasabi	Natto (fermented beans)[e]
		Soy turkey, soy lunchmeat, etc.

Fermented/Pickled[e]	Snacks	Freezer Items	Deli
Pickled cucumbers	Popcorn	Vegetables	Bean salads
Olives	Dips made from beans, vegetables	Fruits	Grain salads
Pickled beets	Crackers with whole grain	Waffles	Vegetable salads
Kimchi (fermented cabbage)	Chips, whole grain		
Sauerkraut	Snack bars[b] (check ingredients for whole grains,[b] inulin,[b] probiotics[d])		

Vegetables		Fruits		Herbs and Spices
Artichokes[c]	Ginger root	Apples	Yacon[c]	Allspice
Asparagus[c]	Greens (spinach[c], chard, leafy greens etc.)	Apricots	Figs	Anise
Avocados	Horseradish	Asian pears	Gooseberries	Basil
Bamboo shoots	Jerusalem artichoke[c]	Bananas[c]	Grapefruit	Black Pepper
Beans, green or waxed	Jicama[c]	Berries (raspberry, blackberry, strawberry, gooseberry, elderberry, red currants, exotics)	Grapes	Caraway
Beans, lima (unshelled)	Kale		Guava	Chili
Beets	Kohlrabi		Jujubee	Cilantro
Bok choy	Leeks[c]		Kiwi	Cinnamon
Broccoli	Lettuce, iceberg		Kumquat	Clove
Broccoli rabe	Lettuce, leaf		Lemon	Coriander
Brussel sprouts	Lettuce (dandelion greens[c], endive, watercress)		Lime	Cumin
Burdock[c]	Mushrooms	Cactus pears	Mango	Dill
Cabbage (red, green, Chinese)	Okra	Cherries	Melon, musk	Fennel
Cauliflower	Onions[c]	Coconut, fresh	Nectarines	Ginger
Carrots	Onions, dry[c]	Cranberries	Oranges	Mace
Celery	Onions, green[c]	Currants	Papaya	Marjoram
Celery root	Palm hearts	Dates	Passion fruit	Mint
Chestnuts	Parsnips	**Vegetables (continued)**	Peaches	Nutmeg
Chicory[c]	Peas (unshelled)	Rutabagas	Pears	Oregano
Corn (in husks)	Peppers, chili	Salsify[c]	Persimmon	Parsley
Cucumbers	Peppers, bell	Seaweed, edible	Pineapple	Rosemary
Daikon radish	Potatoes	Shallots[c]	Plantain	Sage
Dandelion greens[c]	Potatoes, sweet, yams	Snow peas	Plums, pluot, plumcot	Savory
Eggplant	Pumpkin	Sprouts, bean, alfalfa, etc	Pomegranate	Tarragon
Endive	Radishes	Squash, summer varieties	Pommelo	Thyme
Fennel	Rhubarb	Squash, winter varieties	Raisins	Turmeric
Fiddleheads		Taro	Star fruit	Vanilla
Garlic[c]		Tomatillo	Quince	
		Tomatoes	Watermelon	
		Turnips		
		Watercress		

NOTE—read labels: Strain. What probiotic is inside? *Lactobacillus casei Shirota, Lactobacillus acidophilus, Bifidobacteriumlactis, Saccharomyces cereviase boullardii*. CFU (Colony Forming Units). How many live microorganisms are in each serving? When does it expire? Packaging should ensure an effective level of live bacteria through the "best by" or expiration date. Suggested serving size. How much do I take? Health benefits. What can this product do for me? Proper storage conditions. Where do I keep it to ensure maximum survival of the probiotic? Corporate contact information. Who makes this product? Where to do I go for more information?

From: International Scientific Association for Probiotics and Prebiotics, http://www.ISAPP.net.

Adapted from: Gut Insight © 2009 Gut Insight: probiotics and prebiotics for digestive health and well-being by Jo Ann Tatum Hattner, MPH, RD, with Susan Anderes, MLIS. San Francisco: Hattner Nutrition, 2009. Used with permission.

Other resources: U.S. Probiotics, http://www.usprobiotics.org/.

[a]Seventy percent of the body's immunity is in the gut. There are 300–1000 species of bacteria, 100 trillion in the gut (about 3 lb). Alcohol, smoking, stress, poor bowel hygiene, aging, intestinal infections, antibiotics, and a poor diet can affect intestinal microbiota. The normal levels of lactobacilli, bifidobacteria, and other "good bacteria" may be decreased. Imbalanced flora may lead to abnormal GI function, such as constipation, diarrhea, flares of inflammatory bowel disease or irritable bowel syndrome, other pancreatic or abdominal inflammations, allergic responses, and an impaired immune system. Choosing foods wisely can improve gut health.

[b]Prebiotic potentials.

[c]Prebiotic stars.*

[d]Probiotics.

[e]Fermented foods.

For More Information

- Hepatic Encephalopathy
  http://www.nlm.nih.gov/medlineplus/ency/article/000302.htm
- Medline
  http://www.nlm.nih.gov/medlineplus/ency/article/000302.htm

HEPATIC FAILURE, ENCEPHALOPATHY, AND COMA—CITED REFERENCES

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.* 21:113, 2005.

Bergen WG, Wu G. Intestinal nitrogen recycling and utilization in health and disease. *J Nutr.* 139:821, 2009.

Blei AT, Cordoba J. Practice Guidelines: Hepatic Encephalopathy. Accessed October 9, 2009, at http://www.nature.com/ajg/journal/v96/n7/abs/ajg2001494a.html.

Bongaerts G, et al. Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy. *Med Hypotheses.* 64:64, 2005.

Cochran JB, Losek JD. Acute liver failure in children. *Pediatr Emerg Care.* 23:129, 2009.

Eroglu Y, Byrne WJ. Hepatic encephalopathy. *Emerg Med.* 27:401, 2009.

Gee JR, Keller JN. Astrocytes: regulation of brain homeostasis via apolipoprotein E. *Int J Biochem Cell Biol.* 37:1145, 2005.

Grungrieff K, Reinhold D. Liver cirrhosis and "liver" diabetes mellitus are linked by zinc deficiency. *Med Hypotheses.* 64:316, 2005.

Khashab M, et al. Epidemiology of acute liver failure. *Curr Gastroenterol Rep.* 9:66, 2007.

Koivusalo AM, et al. Albumin dialysis has a favorable effect on amino acid profile in hepatic encephalopathy. *Metab Brain Dis.* 23:387, 2008.

Macquillan GC, et al. Blood lactate but not serum phosphate levels can predict patient outcome in fulminant hepatic failure. *Liver Transpl.* 11:1073, 2005.

Munoz SJ. Hepatic encephalopathy. *Med Clin Am.* 92:795, 2008.

Murray KF, et al. Drug-related hepatotoxicity and acute liver failure. *J Pediatr Gastrointest Nutr.* 48:395, 2008.

Rama Rao KV, et al. Differential response of glutamine in cultured neurons and astrocytes. *J Neurosci Res.* 79:193, 2005.

Rose C, et al. Acute insult of ammonia leads to calcium-dependent glutamate release from cultured astrocytes: an effect of pH. *J Biol Chem.* 280:20937, 2005.

Shawcross D, Jalan R. Dispelling myths in the treatment of hepatic encephalopathy. *Lancet.* 365:431, 2005.

Stewart CA, Smith GE. Minimal hepatic encephalopathy. *Nat Clin Pract Gastroenterol Hepatol.* 4:677, 2007.

Sundaram V, Shaikh OS. Hepatic encephalopathy: pathophysiology and emerging therapies. *Med Clin N Am.* 93:819, 2009.