

INTEGRATED HEALTHCARE PRACTITIONERS

Integrated Healthcare Practitioners' Dietary and Nutritional Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 1.0 CREDIT NUTRITIONAL MEDICINE AND BY THE CNPBC; ONE CE HOUR.

Liver Cirrhosis — Naturopathic strategies

Abstract

Liver injury exists on a continuum from transiently elevated liver enzymes, to fatty deposits for example in non-alcoholic steatohepatitis (NASH), to liver fibrosis, which is the beginning of liver cirrhosis. Once the process has begun, liver cirrhosis can progress asymptotically for years until the point where a critical threshold is reached, and remaining hepatocytes can no longer compensate for lost function – decompensated liver disease. This article reviews staging of liver cirrhosis, and focuses on naturopathic treatment strategies that can maximize liver function in cases of moderate to advanced cirrhosis as well as hepatic encephalopathy (HE). These strategies include adequate dietary intake of calories and protein, and restriction of sodium. Nutritional supplementation strategies include branched chain amino acids, probiotics, acetyl-L-carnitine, zinc, silymarin, LOLA (L-ornithine, L-aspartate), and phosphatidylcholine. This paper reviews the evidence supporting these interventions as well as dosing recommendations based on the literature.

Introduction

Cirrhosis is the 12th leading cause of death in the United States, accounting for almost 30 thousand deaths per year (Starr 2011). The leading causes of cirrhosis include chronic alcohol abuse and viral hepatitis; however cirrhosis is the common end pathway of several types of liver injury, including non-alcoholic fatty liver disease (NAFLD), autoimmune hepatic or biliary disease, and obstructive tumors of the liver or biliary ducts (Starr 2011). Liver cirrhosis or “scarring” leads to gradual loss of liver function and the eventual emergence of decompensated liver disease, including hepatic encephalopathy and ascites. This paper will discuss naturopathic strategies that can assist in the management of cirrhosis, particularly decompensated cirrhosis. Intervention with a selection of natural agents offers the potential for delaying and/or alleviating some of the symptoms associated with this condition, for which conventional treatments remain limited.

Pathophysiology

Cirrhosis is “a late stage of hepatic fibrosis that has resulted in widespread distortion of normal hepatic architecture... characterized by regenerative nodules surrounded by dense fibrotic tissue” (Merck 2011). The replacement of functional hepatocytes with non-functioning fibrous tissue results in progressive loss of liver function. Table 1 describes the sequelae of advanced cirrhosis. According to Wolf, these arise from three common underlying malfunctions: “decreased hepatic synthetic function

(eg, coagulopathy), decreased detoxification capabilities of the liver (eg, hepatic encephalopathy), [and] portal hypertension (eg, variceal bleeding)” (2011).

Conventional treatment

Cirrhosis is non-reversible, and current treatments are supportive in nature (Merck 2011). These include lactulose to promote bowel elimination of ammonia; neomycin or rifaximin, antibiotics that decreased ammonia producing bacteria in the gut; and salt restriction, diuretics, and paracentesis (peritoneal “tap” procedure with fluid removal) if necessary for ascites (Foster 2010, Starr 2011). The last resort for liver failure is an organ transplant (Merck 2011).

Cirrhosis is staged using the Child-Turcotte-Pugh Scoring System (See Table 2). Severity is scored as (Merck 2011):

- Child Class A=5-6 points (1y survival 100%);
- Child Class B=7-9 points (1y survival 80%);
- Child Class C=10-15 points (1y survival 45%)

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Hepatic encephalopathy (HE) ranges from minimal encephalopathy (grade 1-2) to coma (grade 4) in end stage liver disease (ESLD). Minimal encephalopathy is present in 30-84% of patients with cirrhosis (Chadalavada 2010); patients may have an apparently normal mental status, with abnormalities detected only with psychometric testing, but may have intermittent episodes of worsened encephalopathy that may be triggered by infection, diuretic therapy, hypovolemia, renal failure, GI bleeding, infection, and constipation (Chadalavada 2010, Wolf 2011). Certain psychoactive medications may also worsen HE (Wolf 2011). HE is graded symptomatically (Merck 2011):

- Grade 1) Sleep disturbance; impaired concentration; depression, anxiety, or irritability
- Grade 2) Drowsiness, disorientation, poor short-term memory; uninhibited behaviour
- Grade 3) Somnolence, confusion, amnesia, anger, paranoia, bizarre behaviour
- Grade 4) Coma

Dietary Guidelines

The goals of dietary treatment for cirrhosis are three-fold:

1) Maintain adequate caloric intake (30-35 kcal/kg dry weight = 1800 kcal/ 60kg person) (Bemeur 2010). Patients with cirrhosis are often undernourished due to anorexia and poor

nutrient absorption. Recommendations for dietary composition are 50-60% of calories as carbohydrate; 20-30% as protein; and 10-20% as fat (Chadalavada 2010).

2) Adequate protein intake (1.2 – 1.5 g/kg protein daily) (Bemeur 2010). Traditionally, a low-protein diet (0-40g/d) has been advocated, since ammonia is derived from protein. Recently there is a growing consensus that this strategy is counterproductive. Inducing a state of protein and/ or calorie malnutrition results in catabolism of muscle protein, and has the double effect of increasing ammonia and causing malnutrition & loss of muscle mass; and patients with cirrhosis have increased protein requirements (Cabral 2011). Instead protein restriction should be limited to a small number of protein-intolerant patients in grade 3-4 HE, if there is a lack of response to other therapies, and only for short periods of time (Bemeur 2010). Wolf says, “the vast majority of patients can tolerate a protein-rich diet (>1.2 g/kg/d) including well-cooked chicken, fish, vegetable protein, and, if needed, protein supplements” (2011).

Recent studies have shown that protein intake is safe and has little impact on HE (Cordoba 2004), and a trial by Gheorghie found that a casein-vegetable-based, high-protein high-calorie (HPHC) diet decreased serum ammonia levels and resulted in improved mental status in patients with overt HE (2005).

Table 1. Sequelae of Cirrhosis (Merck 2011, Wolf 2011)

Symptom	Definition	Cause
Portal hypertension	Increased blood pressure within the portal vein; causes esophageal, rectal, or gastric varices that may bleed	Due to growth of new, low-volume, high-pressure microvasculature within fibrotic tissue
Fat malabsorption	Malabsorption of dietary fat and fat soluble vitamins	Insufficient production of bile
Ascites	Accumulation of excessive intraperitoneal fluid; risk of spontaneous bacterial peritonitis	Low plasma osmolar pressure due to insufficient albumin production
Coagulopathy	Increased bleeding time	Insufficient production of clotting factors or low platelets
Hepatic encephalopathy (HE)	Syndrome of personality changes, intellectual impairment, and a depressed level of consciousness	Accumulation of ammonia and other toxic byproducts in the brain
Hepatorenal syndrome/ renal failure	Renal failure defined as: creatinine clearance <40 mL/min or serum creatinine >1.5 mg/dL; urine volume <500 mL/d; and urine sodium <10 mEq/L present	Imbalance of vaso-constrictive and -dilating factors, causing constriction of the renal arteries and poor renal perfusion

Table 2. Child-Turcotte-Pugh Scoring System for Cirrhosis (adapted from Wolf 2011).

Clinical variable	1 point	2 points	3 points
Encephalopathy	None	Grade 1-2	Grade 3-4
Ascites	Absent	Slight	Moderate or large
Bilirubin (mg/dL)	< 2	2-3	> 3
Bilirubin in PBC or PSC (mg/dL)	< 4	4-10	10
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (seconds prolonged or INR)	< 4 s or INR < 1.7	4-6 s or INR 1.7-2.3	> 6 s or INR > 2.3

3) Salt restriction. To minimize sodium/ water retention and ascites, an initial limit of <2000mg sodium/d is utilized; if this is ineffective, a limit of <500mg/d is used.

Dietary changes (eg. fibre intake) to ensure regular elimination through the gut should also be implemented.

Supplemental Interventions

Select nutritional supplements have been shown to improve liver function and decrease ammonia levels, resulting in clinical improvements in patients with HE.

Branched chain amino acids (leucine, isoleucine, valine) are probably the best- studied supplemental intervention for HE. Although their use has been debated, the discussion seems to have settled in favour of BCAAs (Cabral 2011). The European Society for Parenteral and Enteral Nutrition (ESPEN) has strengthened its recommendation for BCAAs in decompensated liver cirrhosis to grade B (Plauth 2006). BCAAs promote protein synthesis and decrease blood ammonia levels (Cabral 2011); compete with aromatic amino acids (phenylalanine, tyrosine, tryptophan) for uptake into the CNS, where these are thought to contribute to HE (Cabral 2011, Iwasa 2003); stimulate human growth factor (HGF), which promotes hepatic regeneration; and there is some indication that they might lower risk of hepatocellular carcinoma (Kobayashi 2008). Clinical trials have shown that BCAA administration improves neurophysiological function and psychometric testing in HE (Egberts 1986, Higuchi 1994, Plauth 1993). In a randomized double blind trial, Marchesini found that BCAA supplemented at 0.24 g/kg (approx. 14g for a 60kg person) for three months rapidly improved neuropsychological function, and resulted in mild improvement in nutritional parameters and liver function tests (1990).

Kawamura found that in patients with early cirrhosis (Child class A), administration of 12.45g/d BCAAs for 3.2y resulted in significantly slower changes in markers of progression (2009). In addition, BCAAs lowered the incidence of overall major cirrhotic complications to 14.8% (4 of 27 patients) compared to 30.4% (7 of 23 patients) in the control group at 3 years ($P = 0.043$); potentially prolonging the waiting period until liver organ transplantation is necessary (Kawamura 2009). Similar findings have been corroborated in other studies, where 12g/d BCAAs for 2y reduced risk of the following complications by 33% (HR 0.67, 95% CI 0.49-0.93): death by any cause, development of liver cancer, rupture of esophageal varices, or progress of hepatic failure (Muto 2005).

Conversely, Les et al found that administration of 30g BCAAs daily for approximately one year to 116 patients resulted in improvements in symptoms of minimal HE, but did not reduce rates of recurrence for having an episode of acute HE (2011). This may be in part due to the multifactorial nature of the influences

on acute HE (see above sections). BCAAs as part of a more comprehensive nutritional and lifestyle approach might be of benefit in this respect.

Probiotics. Administration of probiotic bacteria has been shown to reduce ammonia levels by competing with urease- producing species such as *Klebsiella* and *Proteus* species (Pereg 2011). Malaguarnera found that compared to lactulose treated patients, those treated with *Bifidobacterium* had significantly improved mental functioning and lower ammonia levels (2010, 2007). Liu found that probiotics plus fiber lowered ammonia levels and improved Child-Turcotte-Pugh functional class in nearly 50% of cases with minimal HE (2004).

Acetyl L carnitine In advanced HE, use of intravenous acetyl L carnitine (ALC) in addition to BCAA has been shown to benefit neurological status (Glasgow coma scale); EEG parameters; serum ammonia; and improve HE grade from 4 to 3 in some patients (54% in one study) compared to BCAA alone (Malaguarnera 2006, 2009).

In earlier stages, oral ALC has shown benefit on neurophysiological function tests, prothrombin time ($P < 0.001$), bilirubin serum levels ($P < 0.01$), AST ($P < 0.001$), fasting serum ammonia levels ($P < 0.001$), and a significant increase in albumin serum levels ($P < 0.005$) (Malaguarnera 2008). Although the mechanism by which ALC exerts its effects in HE is unclear, carnitine is known to participate in ketone body production, facilitate mitochondrial function through transfer of acetylCoA, and aid production of acetylcholine (Shores 2008).

Zinc supplementation (225mg zinc acetate) for six months significantly decreased HE grade and blood ammonia levels ($P = 0.03$ and $P = 0.01$), and improved Child-Pugh score and neuropsychological tests compared with standard therapy ($P = 0.04$ and $P = 0.02$) in patients with grade 1 or 2 recurrent episodic HE unresponsive to standard therapies (lactulose and a protein-restricted diet) (Takuma 2010). A smaller cross-over trial of 15 patients found lack of effect from 600mg zinc sulfate (Riggio 1991), while an earlier randomized double-blind trial of 22 HE patients did find benefit (Reding 1984). Authors postulated that zinc “probably improved hepatic encephalopathy by correcting the zinc deficiency that compromises conversion of ammonia to urea” (Reding 1984). Although these studies utilize very high dosages, it is possible that more modest dosages (~30mg) may also be of benefit.

Silymarin has not been studied specifically for HE, however it has been studied extensively as a hepatoprotective for liver cirrhosis. A randomized double blind placebo controlled trial of silymarin 140mg three times daily in patients with alcoholic liver cirrhosis found that silymarin significantly prolonged survival: 4-year survival rate 58% in silymarin-treated patients and 39% in the placebo group ($P = 0.036$) (Ferenci 1989). A more recent meta

analysis by Saller including 19 trials found a lack of evidence of silymarin on progression of viral hepatitis, but a reduction in AST ($p = 0.01$) in alcoholic liver disease in silymarin-treated patients compared with placebo (2008). In liver cirrhosis, total mortality was 16.1% with silymarin and 20.5% with placebo (non-significant), and liver-related mortality was 10.0% with silymarin vs. 17.3% with placebo ($p = 0.01$) (Saller 2008).

LOLA (L-ornithine, L-aspartate) is another intervention that has been demonstrated to lower ammonia and improve neurological function (Poo 2006). LOLA stimulates the urea cycle and glutamine synthesis which promote ammonia detoxification (Rees 2000).

Phosphatidylcholine Although better studied for NAFLD, a single study reports benefits with use of 2.0g daily of an intravenous formula of “essential phospholipids” including phosphatidylcholine (PC) in patients with stage 3-4 HE (Bruha 2000). Ammonia reductions of ~50% were reported in the treatment group but none in the control group, and survival time was longer in the treatment group: 50.3 versus 34.7 days. A second study reports improvements in liver function (AST, bilirubin) with 1.5g polyenylphosphatidylcholine in subgroups of patients out of a cohort of veterans with chronic alcohol abuse; the groups that benefited most were those with hepatitis C and heavy drinkers (Lieber 2003). It is possible that oral PC may also be of benefit in earlier stages of HE/ cirrhosis.

Other agents for which evidence specific to cirrhosis/ HE is lacking at present, but which may be of benefit based on their mechanism of action include alpha lipoic acid, N-acetyl-cysteine, eicosapentanoic acid, and betaine.

Conclusion

Liver cirrhosis severity ranges from having little or no symptoms (compensated disease), to having minimal-to-severe HE, ascites, and other complications as the pathology progresses. Conventional treatment for cirrhosis and HE remain limited. A selection of natural interventions has shown promise in ameliorating symptoms associated with HE when present, and potentially delaying the onset and progression of HE and cirrhosis, respectively in earlier stages. In addition to specific dietary guidelines, these agents include BCAAs, probiotics, acetyl L carnitine, silymarin, zinc, LOLA, and phosphatidylcholine. •

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Table 3. Natural Interventions for Liver Cirrhosis

Intervention	Daily dose	Rationale	References
Branched chain amino acids	25+g in divided doses	Prevent muscle catabolism & consequent ↑ ammonia; improve LV function	Plauth 2006; Les 2011; Kawamura 2009; Marchesini 1990; Muto 2005
Probiotic	100 bCFU 2x/d	↓ ammonia production in gut; ↓ risk of C.diff if given antibiotic	Malaguarnera 2010, 2007; Liu 2004
Acetyl L carnitine	2000mg 1-2x/d	Improves brain metabolic function; ↓ ammonia	Malaguarnera 2003, 2005, 2006, 2008, 2009
Silymarin	240-480mg (up to 600mg)	Hepatoprotective, improves survival	Ferenci 1989; Saller 2008; Tamayo 2007
LOLA	6g 3x/d	↑ ammonia detoxification by upregulating urea cycle	Poo 2006; Stauch 1998
Zinc	225mg polaprezinc; 600mg zinc acetate	↑ ammonia detoxification by upregulating urea cycle	Takuma 2010; Reding 1984
Phosphatidylcholine	1-2g (2 tbsp)	Improves liver function & ↓ ammonia	Bruha 2000; Lieber 2003

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Questions

1. Which of the following is true about liver cirrhosis?
 - a) It is caused by various types of injuries that lead to deposition of fibrous "scar" tissue
 - b) It is the 12th leading cause of death in the US
 - c) It usually progresses gradually from compensated to decompensated liver disease
 - d) all of the above

2. Portal hypertension is caused by
 - a) accumulation of ammonia and other metabolic byproducts within the liver
 - b) low plasma osmolar pressure
 - c) growth of new low-volume, high-pressure vasculature within the fibrotic tissue
 - d) overweight/ obesity

3. Cirrhosis is staged using the Child-Turcotte-Pugh Scoring System. Child Class A predicts a one-year survival rate of 100%.
 - a) true
 - b) false

4. Among patients with cirrhosis, protein restriction should be limited to a small number of patients with grade 3-4 HE who may be protein-intolerant, if there is a poor response to other therapies.
 - a) true
 - b) false

5. Recommended protein intake for most patients with liver cirrhosis is:
 - a) 0.9- 1.0 g/kg protein daily
 - b) 1.2 – 1.5 g/kg protein daily
 - c) under 0.40 g/kg protein daily
 - d) none of the above

6. Branched chain amino acids (BCAA) have been shown to:
 - a) improve neurophysiological function and performance on psychometric tests
 - b) lower risk of major complications of cirrhosis
 - c) slow progression of cirrhosis
 - d) all of the above

7. Probiotics are thought to reduce ammonia levels and benefit hepatic encephalopathy by out-competing urease- producing strains of bacteria in the gut.
 - a) true
 - b) false

8. Silymarin is well studied for its hepatoprotective effects. A meta-analysis examining its use in patients with liver cirrhosis found:
 - a) significant reduction of total mortality: 16.1% with silymarin and 20.5% with placebo
 - b) significant reduction of liver-related mortality: 10.0% with silymarin vs. 17.3% with placebo.
 - c) reduced progression of hepatitis B
 - d) significant reduction of serum bilirubin

9. Oral and intravenous acetyl-L-carnitine has been shown to improve neurological function and ammonia levels in patients with hepatic encephalopathy.
 - a) true
 - b) false

10. One of the way that zinc is hypothesized to benefit hepatic encephalopathy is by catalyzing the conversion of ammonia to urea.
 - a) true
 - b) false

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Address: _____ **City:** _____

Province: _____ **Postal Code:** _____ **Phone:** _____

Email: _____ **Fax:** _____

Practice Registration #: _____ **Area of Clinical Focus:** _____

Size of Practice (# of Doctors): 0-5 5-10 10 & up **Years of Practice:** 0-5 5-10 10 & up