Preventive Approaches in Chronic Liver Diseases Part III: Decompensated Liver Cirrhosis

by Mohammad R. Taheri, Thomas R. Riley III

Medical complications are frequent in patients with decompensated liver cirrhosis (LC). This article addresses preventive measures in the setting of decompensated LC. A 2 gram sodium and 1–1.5 grams of protein per kilogram of body weight per day diet is recommended. The use of prophylactic antibiotic in spontaneous bacterial peritonitis (SBP) is considered only in selected cases, and never exceeding six months. A maximum dose of furosemide 40 mg/day and spironolactone up to 300 mg/day is recommended to prevent hepato-renal syndrome. Patients presenting with severe acute alcoholic hepatitis should be considered for Pentoxifylline. Cirrhotics presenting with SBP should be treated with antibiotics and albumin infusion, reducing the chances of HRS development. Magnesium supplementation (for prevention of muscle cramps), end of life discussion (if no candidate for liver transplantation), urea containing moisturizers (preventing lower extremities cellulitis) and intermittent histamine H1 blockers (for sleep disturbances) as needed should be considered in these patients.

INTRODUCTION

Liver cirrhosis (LC) is a relatively frequent cause of death in the United States accounting for more than 27,000 deaths per year as of 2002 (1). Medical complications are frequent in patients with LC and more so when the liver disease becomes decompensated (2). LC is considered decompensated when patients develop at least one complication of the disease (hepatic encephalopathy, gastrointestinal bleeding due to portal hypertension, ascites, coagulopathies, hepatocellular carcinoma or severe infections). Compensated LC becomes decompensated at a rate of about 5%–10% yearly (3). The major causes of death in patient with decompensated liver disease without liver transplantation are liver failure, hepatocellular carcinoma (HCC), variceal bleeding, infections and renal failure (3).

Liver transplantation is a rapidly growing field. There have been more than 81,000 liver transplants in United States alone through the end of 2006 (4). The average one- and three-year survival in the U.S. is about 85.7% and 77.7% respectively (5). Liver transplantation remains the only prospect for long-term survival in patients with decompensated cirrhosis (6,7).

Our main objective in this article is to provide evidence-based strategies to prevent complications of decompensated LC and provide the primary caregiver with strategies to detect and avoid possible complications for patients before liver transplantation. This manuscript is the last part of three articles dealing with preventive measure for liver disease by primary care-

(continued on page 35)
DIETARY RESTRICTIONS

Patients with LC are considered a big challenge from a nutritional standpoint. Not only do those with LC have a problem with salt retention (which leads to edema) but also are severely malnourished. Malnourished patients with cirrhosis have a higher rate of complications and an overall increased mortality rate compared to well-nourished cirrhotics (8). In several studies it has been shown that patients with poor nutritional status before transplantation have increased complications and higher mortality rates postoperatively (9,10). Malnutrition develops in these patients independent of the cause of the cirrhosis and the degree of malnutrition is directly correlated to the progression of the disease (11).

The primary cause of malnutrition in these patients is poor oral intake. This is multifactorial. Garrett-Laster, et al showed that cirrhotic patients have an altered sense of taste and smell due to deficiencies of vitamin A and/or zinc (12). The dietary restrictions that are commonly recommended to these patients can also be discouraging for adequate oral intake. Malabsorption is another key factor in the development of malnutrition in these patients (13). Several other causes for this malnutrition has been suggested including hypermetabolism status and altered pattern of fuel consumption (14).

To assess the nutritional status of cirrhotic patients is not an easy task. This should be evaluated by nutritionist that identify those at risk of developing these complications and provide therapy that reduce overall mortality rate (15). A balanced diet containing 1–1.5 grams of protein per kilogram of body weight daily is recommended in patients with compensated liver cirrhosis. However, patients with advanced cirrhosis can develop encephalopathy if they consistently consume large portions of protein at one time. These patients should eat small but more frequent servings to maintain a diet of 1 gm of protein per kg per day (2). When less than 50% of a meal is consumed a dietary supplement should be given. This is critical in order to maintain the nutritional requirements in these patients to avoid protein excess at any one meal.

A fibrotic liver provides an increased resistance to portal system inflow causing sinusoidal portal hypertension. This is associated with a state of systemic vasodilation which leads to redistribution of the circulating blood volume to the dilated vasculature and reduced renal perfusion. Due to this and also systemic baroreceptors and volume receptors mediated reflexes, sodium retentive mechanisms are triggered in the kidneys. These mechanisms include the renin-angiotensin-aldosterone system and sympathetic nervous system activity. To avoid these complications in patients with cirrhosis, a negative salt balance is required which can be achieved with a diet of less than 2 grams of sodium daily. This has been shown to be effective in these patients (16,17).

Although sodium restriction is recommended universally, tight restriction might lead on to noncompliance by patients. Patients should be aware that the restriction to two grams of sodium intake does not mean only cooking salt. Food groups that are to be avoided include most canned foods, commercial tomato juices, prepared bottled sauces, prepared sandwich spreads, pickles, olives, snack foods, crackers, processed meats, convenience foods, fast food, and soups (18). A case study done by Riley, in 2000, showed two cases of refractory ascites in cirrhotic patients related to dill pickle ingestion after proper training on 2 grams sodium diet; therefore, a periodic careful review of the diet is necessary in these patients (18). Once ascites develops in these patients, they should continue on a low salt diet and start diuretic and aldosterone antagonist medications.

SPONTANEOUS BACTERIAL PERITONITIS PREVENTION

One of the most common clinical complications of LC is the development of ascites. Once ascites develops, LC is considered decompensated and carries a poor prognosis (2). Further complications like renal failure or development of spontaneous bacterial peritonitis (SBP) worsen the prognosis. At this point, the patient should be evaluated for possible liver transplantation.

When a patient develops ascites, paracentesis should be performed in order to diagnose the etiology of the ascites. The diagnosis should be done by measuring the SAAG (serum to ascites albumin gradient). If this gradient is less than 1.1 mg/dL, etiologies other than portal hypertension should be considered (19). SBP is diagnosed when the neutrophil count in ascitic
fluid is greater than 250 cells per mm³ or cultures of ascitic fluid are positive (6).

The bacteria frequently infecting the ascitic fluid are the normal intestinal flora with *Escherichia Coli* being the most frequent pathogen. Patients with cirrhosis developing SBP have a significant in-hospital mortality rate of up to 40% (20). The risk of developing SBP in patients with ascites is directly related to prior episodes of SBP, variceal hemorrhage and low protein levels in ascitic fluid (less than 1.0 grams/deciliter) (21,22). This raises an important question regarding the usage of antibiotic prophylaxis in patients with ascites for prevention of SBP.

Several studies have been done to evaluate the benefits of antibiotic prophylaxis for SBP. Soriano, et al (1991) did a prospective randomized study in 63 patients regarding usage of a prophylactic quinolone in patients with low protein ascites. They showed a reduction of SBP from 22.5% (in non-treated patients) to 0% (in treated patients) (p < 0.05); however, they did not show a decrease in mortality in the treated population (23). Bernard, et al did a meta-analysis of five trials regarding usage of prophylactic antibiotics in cirrhosis with gastrointestinal hemorrhage. They concluded that there is a reduction of infection of about 32% (p < 0.001) with short-term antibiotic prophylaxis and an increase on short-term survival of about 9% in treated patients (24).

The American Association for the Study of Liver Diseases (AASLD) practice guidelines recommends short-term (seven days) treatment with IV antibiotics for patients in hospital with cirrhosis and gastrointestinal bleeding to prevent bacterial infection while the patient is bleeding. Also, they recommend long-term antibiotic usage after an episode of SBP and if the patient has low ascitic fluid protein levels (less than 1 g/dL) or high serum bilirubin (greater than 2.5 mg/dL (25).

On the other hand, not all studies done regarding this issue are positive. Some studies have shown that patients treated with long-term prophylaxis develop highly resistant organisms and this could have a severe effect on pre- and post-transplant management.

The study done by Novella, et al showed the benefit of continuous long-term selective intestinal decontamination with norfloxacin in preventing the first spontaneous bacterial peritonitis in patients with low protein ascites and/or high total bilirubin; however, they concluded that the emergence of infections caused by norfloxacin-resistant bacteria must be weighed carefully against the benefits of long-term prophylaxis (26). In another study by Wade, et al 1995, liver transplanted patients who were treated with protracted therapy with ciprofloxacin before transplantation were shown to be more prone to fungal infections after being transplanted (27).

The possibility of development of resistant bacterial strains with long-term use of prophylactic antibiotics is a major concern in the liver transplant community. Given the conflicting variables, a preventive strategy cannot be definitely recommended. If used, antibiotic prophylaxis should be recommended in selected cases, and the duration should not exceed six months to avoid the development of antibiotic resistance. All patients with cirrhosis and gastrointestinal bleeding should receive antibiotics on admission.

**PREVENTION OF HEPATORENAL SYNDROME**

The hepatorenal syndrome (HRS) is characterized by renal failure in patients with chronic liver disease due to severe vasoconstriction of the renal circulation (28). Renal failure in the setting of advanced liver disease can be due to several conditions like low intravascular volume, shock due to sepsis or hemorrhage, nephrotoxicity of medications used or interstitial renal disease (29). These conditions are usually not related to HRS. The underlying mechanism behind HRS is complex and beyond this manuscript.

AASLD provides five major criteria for the diagnosis of HRS (25). These criteria are shown in Table 1. HRS occurs in up to 10% of patients with advanced cirrhosis and ascites. It normally follows either of two clinical patterns (29). The International Club of Ascites (ICA) defines HRS type-1 as: “a rapidly progressive renal failure defined by a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL or 220 µmol/l in less than two weeks. Although it may appear spontaneously, type-1 HRS often develops with a precipitating event, particularly spontaneous bacterial peritonitis. Type-1 HRS occurs in the setting of an acute deterioration of circulatory function (arterial hypotension and activation of the endogenous vasoconstrictor systems) and is frequently associated to rapid impairment in liver function and encephalopathy.”
median survival with no treatment in these patients is less than one month. On the other hand, Type-2 HRS is defined by ICA as moderate renal failure (serum creatinine of >1.5 mg/dL) with a slowly progressive course and is frequently associated with refractory ascites. Type-2 HRS appears spontaneously in most cases (30). In some patients, HRS develops without any identifiable precipitating factor, whereas in others it occurs in close chronologic relationship with some complications or therapeutic interventions. The two most common situations that have shown correlation with HRS are SBP (the most common precipitating factor) and therapeutic paracentesis without plasma volume expansion. In SBP, about 30% of patients develop an impairment of renal function. This is considering absence of shock and despite treatment with non-nephrotoxic antibiotics. This impairment in renal function is reversible after resolution of infection in about 10% of cases; however, in the remaining patients, this impairment is not reversible and half of them meet the criteria of type-1 HRS (31).

In some patients, HRS develops without any identifiable precipitating factor, whereas in others it occurs in close chronologic relationship with some complications or therapeutic interventions. The two most common situations that have shown correlation with HRS are SBP (the most common precipitating factor) and therapeutic paracentesis without plasma volume expansion. In SBP, about 30% of patients develop an impairment of renal function. This is considering absence of shock and despite treatment with non-nephrotoxic antibiotics. This impairment in renal function is reversible after resolution of infection in about 10% of cases; however, in the remaining patients, this impairment is not reversible and half of them meet the criteria of type-1 HRS (31).

Large volume therapeutic paracentesis (LVTP) has been associated in the development of HRS. The use of colloid replacement during LVTP is a controversial issue in the field of hepatology. Gines, et al in 1988, did a randomized control study regarding this issue showing no change in morbidity or mortality between patients with or without albumin infusion after LVTP. However, they showed changes in plasma renin, serum electrolytes and creatinine levels between the two groups (32). In another study, also by Gines, et al in 1996, it was shown that patients with an increase in serum renin levels after LVTP have a decrease in life expectancy compared to patients with no increase in serum renin levels (33). AASLD guidelines recommend usage of albumin infusion for LVTP (more than five liters at once) with 8–10 grams of albumin per liter of fluid removed (25).

Sort, et al in 1999, did a randomized study in 126 patients with cirrhosis and SBP showing a reduction in renal impairment and death in patients that were treated with antibiotics and intravenous albumin compared to antibiotics alone (34). They explained these findings by correlating the treatment with albumin to preventing circulatory dysfunction and subsequent activation of vasoconstrictor system; therefore, reducing the chances of developing HRS (34).

Akriviadis, et al in 2000, did a randomized control study on a hundred and one patients with severe alcoholic hepatitis by treating with Pentoxifylline (PTX), an inhibitor of tumor Necrosis Factor, versus placebo. This study concluded that a substantial decrease in mortality is achieved by using PTX in severely ill patients with acute alcoholic hepatitis by decreasing the development of HRS (35).

Gastrointestinal bleeding and over-diuresis have been classically considered precipitating factors of HRS. In the case of gastrointestinal bleeding, renal failure is related to hypovolemic shock and ischemic hepatitis which suggests a close relation to acute tubular necrosis (ATN) and not of functional origin (31).

Diuretics have been studied as a treatment of ascites in patients with liver cirrhosis. Spahr, et al (Hepatology 2001) showed that patients with refractory ascites have less natriuretic response to furosemide compared to patients with non-refractory ascites. This is due to higher plasma renin activity of patients with refractory ascites (36). Gines, et al in another study in 1987, demonstrated that patients with refractory ascites on diuretics are more prone to develop reversible renal failure compared to large volume paracentesis. Although the usage of loop diuretics is associated to a rise in renal function tests, these are normally reversible after discontinuation of these drugs (37). Gentillini, et al in 1999, showed that combining diuretics with intravascular-
lar colloid like albumin in hospitalized patients with refractory ascites prevents an increase on serum creatinine due to diuretics suggesting an unchanged intravascular volume and also a possibility of increased delivery of sodium to the ascending loop of henle, thus enhancing natriuresis (38). The use of intravascular colloids in a non-hospitalized patient on long-term diuretics is not practical nor advocated at the present time.

The use of diuretics in patients with refractory ascites has been controversial due to two reasons. The excessive reduction of intravascular volume and the fear of inducing HRS have been considered by caregivers before prescribing diuretics in cirrhotic patients with refractory ascites. Diuretic treatment has been classically described as a precipitating factor of HRS (31). Diuretics, in variable doses, have been studied in detail in patients with heart failure regarding preload reduction. Most of the data available for cirrhotic patients with ascites are derived from cardiovascular studies. The doses recommended in cirrhotics are based on congestive heart failure trials. It should be mentioned that patients with congestive heart failure are not prone to develop HRS, therefore the safety of the doses recommended in patients with liver cirrhosis are questionable. In patients with ascites, the maximum dose of diuretics recommended by many authors are 400 mg/day of spironolactone and 160 mg/day of furosemide. Due to lack of convincing evidence regarding dose safety of diuretics in cirrhotic patients, we consider these doses excessive. A safer combination of diuretics would be furosemide up to 40 mg daily and spironolactone up to 300 mg/day. Using these lower maximum limits will be preventive in HRS development. The use of intravenous diuretics is absolutely contraindicated in these patients in any circumstances due to rapid decrease on the intravascular volume. Patients presenting with severe acute alcoholic hepatitis should be considered for PTX. Cirrhotics presenting with SBP should be treated with antibiotics and albumin infusion, reducing the chances of HRS development (Table 2).

### MISCELLANEOUS PREVENTIVE MEASURES

#### Prevention of Muscle Cramps

Muscle cramps have been associated with LC since 1985 when Konikoff, et al demonstrated this association in 33 patients (39). The pathogenesis of muscle cramps is not clear at present. Angeli, et al in 1996 did a large case control study on 488 patients showing not only a clear evidence of causal relationship rather than simple association between liver cirrhosis and muscle cramps, but also demonstrated that the prevalence of muscle cramps are related to the duration of cirrhosis and the severity of liver damage (40). They hypothesized a correlation between intravascular volume depletion and muscle cramps.

Abrams, et al also, in 1996, did a study on 132 cirrhotic patients and concluded that the increased prevalence of cramps in these patients was related to the severity of liver disease (41). Subjects with cirrhosis had a significantly higher prevalence of muscle cramps (continued on page 40)
compared with patients with chronic hepatitis, suggesting that the presence of cirrhosis is an independent risk factor. Higher total serum bilirubin levels and lower albumin levels were associated with an increased frequency of muscle cramps.

The development of muscle cramps in cirrhotics is believed to be multifactorial. Prevention of muscle cramps is not an easy task. Several drugs have been recommended but they are only partially effective in most cases. Quinine sulfate is the most commonly prescribed drug in this condition but is only partially effective and has serious adverse reactions including reports of thrombocytopenia (which could be fatal), cinchonism, gastrointestinal symptoms, deafness, and optic atrophy.

In a study done by Koivisto, et al published in Clinical Transplantation, it was shown that chronic cirrhotics suffer from low body magnesium and this is not reflected by spot-sample serum ionized magnesium concentrations (42). In a randomized controlled trial done by Roffe, et al it was shown that patients with chronic persistent leg cramps may benefit from treatment with magnesium (43). Due to these data provided, it is of proven benefit and minimal side effect that patients with liver cirrhosis should be treated with magnesium supplementation for prevention of muscle cramps. We discourage the use of quinine sulfate in the treatment of muscle cramps due to questionable benefits and devastating side effects.

Preventive Measures in End of Life Issues

Patient with decompensated liver cirrhosis should be evaluated for the possibility of liver transplantation. This is an important issue for not only the patient but the care providing team. If the patient is not a candidate for liver transplantation, palliative care should be emphasized and unnecessary and futile measures should be avoided in order to reduce suffering of the patient and the caregivers. A thorough end of life discussion should take place with the patient and his/her family at the earliest convenience.

Prevention of Cellulitis

One of the complications of liver cirrhosis is the development of extravascular volume overload which leads to lower extremities edema of the lower extremities. This has a major effect on the integrity of the skin due to venous stasis and a tendency to develop skin infections related to interrupted barrier. An appropriate care of the lower extremities is required to prevent these infections. The use of antibiotics as a preventive measure for development of cellulitis is not practical and creates antibiotic resistance. Other measures should be used to prevent these complications. One of these methods, apart from proper hygiene, is the usage of moisturizers for protection of skin integrity. In a study done by Loden, in 1996, it was shown that using moisturizers with urea content could help prevent water loss and this would improve the barrier properties of the skin (44). Other studies have shown similar findings (45). This suggests that using Eucerin® or other urea containing moisturizers could have a benefit in preventing skin barrier interruption and therefore development of cellulitis.

Sleep Disorders

Patients with chronic liver disease are prone to have a poor sleep pattern. This has been related, most of the times, to hepatic encephalopathy due to advanced liver disease but in a study done by Cordoba, et al in 1998, it was shown that the disturbance of these patients is related more to circadian abnormalities than hepatic encephalopathy (46).

Cirrhotic patients are sensitive to traditional management of sleep deprivation. Medications with direct effect on depressing the central nervous system (specially benzodiazepines) should be avoided in this type of patients as they enhance development of hepatic encephalopathy which is a severe complication of cirrhosis and is responsible for a substantial proportion of deaths in cirrhotic patients (47). In a meta-analysis done by Golenok, et al in 2002, it was shown that Flumazenil is effective in the treatment of acute hepatic encephalopathy in patients with cirrhosis with improvement of not only clinical symptoms but their electroencephalography (47). This provides enough evidence for avoidance of benzodiazepines in patients with liver cirrhosis.

In a randomized control study done by Spahr, et al in 2007, it was shown that cirrhotic patients with sleep alterations (not related to hepatic encephalopathy) have an improvement of their sleep habits with usage of hydroxazine at bedtime, independent of an effect on cognitive performance (48). This shows that medica-
tions with histamine H₁ blocker activity (like hydroxyzine) can be used in a safer manner for the treatment of sleep disturbances in patients with cirrhosis than benzodiazepines, but also careful screening for hepatic encephalopathy should be done after starting these medications (48).

The above data provides an argument that patients with advanced liver disease should be screened periodically by their primary care providers for abnormalities of sleep patterns and with minimum sign of disturbance, the appropriate steps toward resolution of problems should be taken.

References
4. United Network for organ sharing. The Organ Procurement and Transplantation Network. Website: www.optn.org/latestData/rptData.asp