

a series of articles  
written by medical  
professionals about  
the management  
and treatment of  
hepatitis C

## Management of the Decompensated Cirrhotic Patient with HCV

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**C**irrhosis represents the end-stage of any chronic liver disease. The hepatitis C virus (HCV), along with alcohol, is a leading cause of cirrhosis in the United States. Cirrhosis leads to two major syndromes: **portal hypertension and hepatic insufficiency**. Additionally, peripheral and splanchnic vasodilatation with the resulting hyperdynamic circulatory state is typical of cirrhosis and portal hypertension. Cirrhosis can remain compensated for many years prior to the development of a decompensating event. Decompensated cirrhosis is marked by the development of any of the following complications: **jaundice, variceal hemorrhage, ascites or encephalopathy**. Jaundice results from hepatic insufficiency and, other than liver transplantation, there is no specific therapy for this complication. It is however important to recognize and treat superimposed entities (e.g., alcoholic hepatitis, drug hepatotoxicity) that may contribute to the development of jaundice. The other complications of cirrhosis occur as a consequence of portal hypertension and/or hepatic insufficiency. Gastroesophageal varices result almost solely from portal hypertension, although the hyperdynamic circulation contributes to variceal growth and hemorrhage.

Ascites results from sinusoidal hypertension and sodium retention, which is, in turn, secondary to vasodilatation and activation of neurohumoral systems. The hepatorenal syndrome results from severe peripheral vasodilatation that leads to renal vasoconstriction. Hepatic encephalopathy is a consequence of both portal hypertension (shunting of blood through portosystemic collaterals) and hepatic insufficiency.

### Antiviral Therapy in HCV Decompensated Cirrhosis

There is limited published data regarding antiviral therapy in patients with decompensated HCV cirrhosis. According to the 2002 NIH Consensus Conference Statement, the primary therapy recommended for patients with decompensated liver disease due to hepatitis C should be referral for liver transplantation [1]. Interferon and ribavirin therapy (the standard antiviral therapy for HCV) is potentially dangerous in the setting of decompensated cirrhosis because of the increased risk of life-threatening infections and the concern that treatment might accelerate hepatic decompensation [2]. For these reasons, and due to limited published literature, interferon therapy for patients with decompensated cirrhosis due

to HCV should be considered experimental and within the confines of clinical trials [3]. However, the small percentage of patients with decompensated cirrhosis who achieve a sustained virological response remain virus-free post-transplantation, as opposed to universal recurrence of HCV infection in those who are virus-positive pre-transplantation [4]. Therefore, studies identifying the subgroup of patients with decompensated cirrhosis most likely to benefit from therapy will be essential.

### Management of Decompensating Events of Cirrhosis

Patients with decompensated cirrhosis should be referred for liver transplantation. Until the time of transplant, therapy of the patient with decompensated cirrhosis should focus on the management of each individual decompensating event.

#### Acute variceal hemorrhage

Patients with cirrhosis who present with upper gastrointestinal hemorrhage should have a diagnostic endoscopy performed to investigate the possibility of variceal hemorrhage, as indicated by the presence of: active bleeding from a varix, a "white nipple" overlying a varix, clots overlying a varix, or

varices with no other potential source of bleeding [5]. Bacterial infections occur frequently in cirrhotic patients admitted with gastrointestinal hemorrhage and the use of short-term (7 days) antibiotic prophylaxis has been shown to decrease the rate of infections and to improve survival [6]. Although the recommended

indicated in patients in whom hemorrhage from esophageal varices cannot be controlled or in whom bleeding recurs in spite of two sessions of endoscopic therapy (associated or not with pharmacological therapy) [14]. In patients who bleed from gastric fundal varices, failure of one sclerotherapy session should be

in whom portal pressure (as determined by the hepatic venous pressure) can be reduced significantly with pharmacological therapy have the lowest risk of rebleeding and the greatest survival benefit [16]. In patients who re-bleed on pharmacological therapy or on EVL, the combination of EVL and pharmacological

amoxicillin/clavulanate is not available in the United States and therefore the combination of ampicillin/sulbactam could be used instead. In patients with community-acquired SBP, no encephalopathy and a normal renal function, orally administered quinolones with a high bioavailability (ofloxacin, levofloxacin) are an acceptable alternative [20], provided that the local prevalence of quinolone-resistant organisms is low. In patients with renal dysfunction, either at baseline or during treatment, plasma expansion with albumin should be used as an adjunct to therapy [21]. Treatment should be administered for a minimum of 5 days, preferably for 8 days. A control paracentesis performed 48 hours after starting therapy is generally necessary to assess the response to therapy and the need to modify antibiotic therapy and/or to initiate investigations to rule out secondary peritonitis. In the presence of an obvious clinical improvement, control paracentesis may not be necessary.

***Endoscopic therapy, either sclerotherapy or variceal band ligation (VBL) is the therapy of choice in the control of acute variceal hemorrhage [11], although it has recently been suggested that pharmacological therapy (somatostatin, terlipressin, octreotide) is as effective as endoscopic therapy [12].*** ■ ■ ■

antibiotic is norfloxacin administered orally at a dose of 400 mg twice a day [7], equal efficacy has been observed with ciprofloxacin at a dose of 500 mg orally twice a day [8]. In patients in whom it cannot be administered by mouth or by nasogastric tube, systemic quinolones can be administered [9;10]. Endoscopic therapy, either sclerotherapy or variceal band ligation (VBL) is the therapy of choice in the control of acute variceal hemorrhage [11], although it has recently been suggested that pharmacological therapy (somatostatin, terlipressin, octreotide) is as effective as endoscopic therapy [12]. The association of pharmacological therapy, used as soon as the diagnosis is suspected (even prior to endoscopy) and continued for 5 days after the diagnosis is established, may represent the best approach to treatment [13]. However, until the efficacy of somatostatin analogues is confirmed in ongoing trials, the only pharmacological therapy available in the United States in the setting of acute variceal hemorrhage is the combination of vasopressin and nitroglycerin that can only be used for a maximum of 24 hours. Shunt surgery or the transjugular intrahepatic portosystemic shunt (TIPS) is

enough to indicate the performance of shunt therapy. Balloon tamponade should be limited to patients with uncontrollable bleeding in whom a more definitive therapy (e.g., TIPS) is being planned.

### ***Prevention of recurrent variceal hemorrhage***

Patients surviving an episode of acute variceal hemorrhage have a very high risk of rebleeding and death. The median rebleeding rate in untreated individuals is around 60% within one to two years from the index hemorrhage, with a mortality of 33% [15]. Patients who have recovered from an episode of acute variceal hemorrhage and who have had no evidence of hemorrhage for at least 24 hours and in whom pharmacological therapy for the control of acute variceal hemorrhage has been discontinued should be considered candidates for prophylactic therapy. Pharmacological therapy with a combination of b-blockers and nitrates or endoscopic therapy with VBL are effective therapies in the prevention of variceal rebleeding. Both therapies appear to be equivalent and the choice will depend on factors such as expertise, compliance, tolerance and patient preference [16-18]. Notably, patients

therapy should be considered [19]. TIPS is only indicated in patients in whom rebleeding recurs despite combined endoscopic and pharmacological therapy. In patients who are surgical candidates, shunt surgery can be considered even prior to TIPS in centers where the expertise is available.

### ***Management of spontaneous bacterial peritonitis (SBP)***

SBP is an infection of ascites that occurs in the absence of a contiguous source of infection (e.g., intestinal perforation, intra-abdominal abscess). The prevalence of SBP in hospitalized cirrhotic patients ranges between 10-30%. The diagnosis should be suspected in any patient with ascites who develops local or systemic signs of infection, encephalopathy or renal dysfunction and the diagnosis confirmed with the presence of an ascites polymorphonuclear (PMN) count >250/mm<sup>3</sup> [7]. The preferred therapy for SBP is the use of intravenous antibiotics, mainly cefotaxime or another third generation cephalosporin (ceftriaxone, ceftazidime) or the combination of a b-lactam/b-lactamase such as amoxicillin/clavulanic acid [7]. The intravenous preparation of

### ***Prevention of recurrent SBP***

In patients who survive an episode of SBP, the one-year cumulative recurrence rate is high, at about 70%. It is therefore essential that patients who survive an episode of SBP be started on antibiotic prophylaxis to prevent recurrence prior to discharge from the hospital. Long-term prophylaxis with oral norfloxacin at a dose of 400 mg every day (or 250mg/day of ciprofloxacin everyday) has been shown to be very effective in preventing recurrent SBP [22], and is therefore indicated in patients who have recovered from an episode of SBP. The once a week use of quinolones has been shown to be less effective and to have a higher development of quinolone-resistant organisms compared to daily norfloxacin [23] and is therefore not recommended. Prophylaxis should be continuous

until disappearance of ascites (i.e., patients with alcoholic hepatitis) or transplant. In patients intolerant to quinolones (a rare event), prophylactic therapy with trimethoprim/sulfamethoxazole can be recommended. Long-term

furosemide is then added at an initial single daily dose of 40 mg, increased in a stepwise fashion to a maximum of 160 mg/day [24]. In order to minimize the rate of complications, weight loss in patients without edema should

differences in mortality. Therefore, as mentioned in a recent consensus conference, TIPS should be relegated to patients with refractory ascites who require very frequent sessions of LVP (>3 times a month) and in whom a favorable

spectrum of neuropsychiatric and psychometric test performance abnormalities occurring in patients with significant liver dysfunction after exclusion of other known brain diseases. The initial management of acute, episodic, HE involves two steps. The first and primary step is the identification and correction of precipitating causes [31]. Careful evaluation should be performed to determine the presence of hypovolemia, gastrointestinal bleeding, infections, including SBP, intake of sedatives or tranquilizers. The second step is the administration of lactulose (orally or by enema). Patients with chronic HE should be treated with oral lactulose at a dose adjusted to obtain 2-3 soft bowel movements/day. In patients with chronic HE who are not tolerant or do not respond to lactulose, the addition of neomycin (starting at 1-3 g per day in 3 doses) or metronidazole (starting at 250 mg PO BID) may be of benefit. Long-term protein restriction should be avoided and a protein content of 1-1.5 g/kg/day protein diet is recommended. Protein from dairy or vegetable sources may be preferable to animal-derived protein.

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## ***Patients with new onset ascites and normal renal function, in whom spontaneous bacterial peritonitis has been ruled out, should receive treatment with sodium restriction and/or diuretics.*** ■ ■ ■

prophylaxis is currently not recommended in patients with ascites who have never had SBP, independent of the presence or not of refractory ascites and/or a low ascites protein content [7].

### **Management of ascites**

Ascites is one of the most frequent complications of cirrhosis. In compensated cirrhotic patients, ascites develops at a 5-year cumulative rate of about 30%. Patients with new onset ascites and normal renal function, in whom spontaneous bacterial peritonitis has been ruled out, should receive treatment with sodium restriction and/or diuretics. Patients with a small amount of ascites and a reasonable urinary sodium excretion (>50 mEq/24 hours) can be started on salt restriction alone. Patients with moderate/tense ascites and avid sodium retention should be treated with sodium restriction and diuretics. In patients who decrease food intake because of the non-palatable salt-restricted diet, it is preferable to liberalize sodium intake and implement measures to increase sodium excretion through the use of diuretics, rather than to compromise nutrition. The preferred diuretic schedule is to initiate therapy with spironolactone alone at a single daily dose of 100 mg and to increase it in a stepwise fashion to a maximum of 400 mg/day. If weight loss is not optimal or if hyperkalemia develops,

be maintained at a maximum of 1 lb/day (0.5 Kg/day), while in patients with edema a weight loss of 2 lb/day (1 Kg/day) is allowable. In a hospitalized patient with moderate/tense ascites in whom other complications have been resolved, it is reasonable to initiate therapy with total paracentesis with concomitant albumin infusion followed by the administration of diuretics, as this will accelerate discharge from the hospital. Serial monitoring of urinary sodium is unnecessary in patients who are responding adequately to diuretics, as assessed by daily weights.

In cirrhotic patients with ascites who fail to respond to diuretics or who present complications that preclude the administration of adequate doses of these drugs (refractory ascites), repeated large volume paracenteses plus intravenous albumin (LVP+A) is first choice. Albumin is infused at a dose of 6-8 g per liter of ascites removed. In patients in whom <5L are being removed, synthetic plasma expanders can be used instead of albumin [25] and it has been suggested that plasma volume expansion may not be necessary in this situation. Sodium restriction and diuretics should be used concomitant to LVP. TIPS has been compared to LVP+A in two large multicenter trials [26;27] and, although associated with a slower recurrence of ascites, TIPS is associated with higher rates of severe encephalopathy and no

post-TIPS evolution can be predicted, i.e., patients with a Child score of <12 points [28].

### **Treatment of hepatorenal syndrome (HRS)**

HRS is the result of extreme vasodilatation with an extreme decrease in effective blood volume that leads to maximal activation of vasoconstrictive systems, renal vasoconstriction and renal failure. HRS has been divided into type 1 and type 2. Type 1 HRS is characterized by rapidly progressive renal failure with a doubling of serum creatinine to a level greater than 2.5 mg/dl or a halving of creatinine clearance to less than 20 ml/min in less than two weeks. The prognosis of type 1 HRS is extremely poor with a median survival of about 2 weeks [29]. In type 2 HRS serum creatinine is greater than 1.5 mg/dl and/or creatinine clearance is less than 40 ml/min but renal failure is more slowly progressive and it has a better prognosis. The definitive treatment for HRS in patients with cirrhosis is likely to remain liver transplantation. Anecdotal studies show that vasoconstrictors together with albumin or TIPS may be useful in reversing HRS but this remains to be confirmed in randomized controlled trials.

### **Treatment of hepatic encephalopathy (HE)**

As recently defined in a consensus conference [30], HE reflects a

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