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## Management of the Complications of Cirrhosis



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**C**irrhosis is the end result of any chronic liver disease and is an entity that progresses across different prognostic stages, the most important being the compensated (asymptomatic) and the decompensated (symptomatic) stages. These stages are defined by the absence or presence of overt complications of cirrhosis, specifically variceal hemorrhage, ascites and encephalopathy.<sup>1</sup> Each stage has entirely different prognosis, predictors of death and predominant pathogenic mechanisms and therefore should be managed separately both in research and in practice.

Portal hypertension (PH) is the initial and main consequence of cirrhosis and is responsible for most of its complications. Portal pressure increases initially as consequence of increased intrahepatic resistance to portal flow due to a) structural

vascular distortion (e.g. fibrous tissue, regenerative nodules, microthrombi) which account for about 70% of the increased intrahepatic resistance and b) increased intrahepatic vascular tone which is consequence of endothelial dysfunction resulting mostly from reduced nitric oxide bioavailability.<sup>2</sup> As portal pressure increases, there is splanchnic vasodilatation, which leads to increased portal venous inflow that further increases portal pressure. Vasodilatation is due to angiogenic factors and increase in nitric oxide and leads to activation of neuro-humoral systems, sodium and fluid retention, resulting in increased cardiac output, and a hyperdynamic circulatory state.<sup>3</sup>

### Stages of Cirrhosis

Complications of cirrhosis do not occur until there is both increase in resistance and flow. When increased resistance is the sole pathogenic factor, portal hypertension is mild (<10 mmHg as determined by the hepatic venous pressure gradient or HVPG) but when there is both increased

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resistance and flow and the HVPG rises to levels  $\geq 10$  mmHg, the patient is at a higher risk (4x) of developing decompensating events.<sup>4</sup> Therefore, patients with compensated cirrhosis are currently sub-staged into those with mild PH (HVPG  $>5$  but  $<10$  mmHg) and those with clinically significant portal hypertension (CSPH) (HVPG  $\geq 10$  mmHg).<sup>5</sup> Among the latter, roughly half the patients have gastroesophageal varices. Because the HVPG of patients with gastroesophageal varices is of at least 11-12 mmHg, patients with varices have, by definition, CSPH.<sup>6</sup>

Of the decompensating events, ascites is the most common (20-year first event rate of 33%), followed by variceal hemorrhage (15%) and encephalopathy (7%). Jaundice is quite rare as the first decompensating event (3%) because its presence indicates a more advanced disease (further decompensation) or acute-on-chronic liver failure.<sup>7</sup> Prognosis is different depending on the type and number of decompensating events. Patients with gastrointestinal bleeding as the sole decompensating event; those presenting with a non-bleeding complication (mainly ascites) as sole decompensating event and those with two or more concomitant complications have a progressively worse prognosis (20%, 30% and 88%, respectively).<sup>7</sup> Therefore, the prognosis and management of variceal hemorrhage should always be considered in the context of the presence or absence of other decompensating events.

In patients with decompensated cirrhosis, vasodilatation is the main pathogenic mechanisms and is secondary to bacterial translocation (covert infection) or overt bacterial infections, with a main mediator being systemic inflammation.<sup>8</sup>

### Reducing Portal Pressure

While HVPG measurements are useful in patient stratification in compensated cirrhosis, it is not as important in the decompensated stage, where markers of liver and kidney dysfunction (model for end-stage liver disease or MELD score) are of greater prognostic significance.<sup>9</sup> However, both in compensated and decompensated cirrhosis, decreases in portal pressure (induced by non-selective beta-blockers) are associated with improvement in outcomes. Hemodynamic

responders are traditionally defined as those in whom HVPG decreases below 12 mmHg or  $> 20\%$  from baseline. In patients with compensated cirrhosis, a decrease of  $>10\%$  from baseline has been shown to be predictive of a more favorable outcome.<sup>10</sup>

Portal pressure can be decreased by decreasing intrahepatic resistance and/or by decreasing portal vein blood inflow. For over 30 years, treatment of portal hypertension has been based on non-selective beta-blockers (NSBB), drugs that decrease portal pressure by a reduction in splanchnic blood flow. NSBB have been shown to be effective in reducing first and recurrent variceal hemorrhage both in patients with compensated and decompensated cirrhosis.

More recently, attention has been placed on drugs that act by decreasing intrahepatic resistance. Carvedilol, is a unique type of NSBB with additional alpha-adrenergic blocking activity and may therefore also act by vasodilating the intrahepatic circulation. Carvedilol has a larger effect in reducing portal pressure compared to traditional NSBB (nadolol, propranolol) but its vasodilating properties, especially in the decompensated patients, may lead to further vasodilatation and worsening of the already unstable hemodynamic status of the decompensated patient. Statins act by ameliorating endothelial dysfunction and have shown to decrease the HVPG.<sup>11</sup> In retrospective studies, statins have been shown to decrease decompensation and in one prospective study simvastatin improved survival in the setting of secondary prophylaxis of variceal hemorrhage<sup>12</sup> (see below).

### Variceal Hemorrhage

Acute variceal hemorrhage is the cause of approximately 70% of the episodes of upper gastrointestinal bleeding in patients with cirrhosis. The current standard of care has resulted in a major decrease in mortality. However, even in the last published series, it remains above 15%, which places acute variceal hemorrhage (AVH) as one of the most serious medical emergencies. The immediate goal of therapy in these patients is to control bleeding, to prevent early recurrence (within five days) and to prevent six-week mortality (main treatment outcome).

After initial volume replacement, blood transfusion strategy should be conservative, initiating packed red blood cell (PRBC) transfusion when hemoglobin is  $< 7$  g/dL with a goal of maintaining hemoglobin between 7 and 9 g/dL), prophylactic antibiotic (ceftriaxone 1 g/day) and infusion of a safe vasoactive drug (e.g. octreotide). If the patient was on NSBB these should be discontinued, as they will blunt the cardiovascular response to bleeding.

Endoscopy should be ideally performed within 12 hours of admission, following hemodynamic resuscitation. Current evidence supports endoscopic variceal ligation (EVL) as the endoscopic therapy of choice for the initial control of bleeding, as it is associated with less adverse events and less mortality than sclerotherapy.

Once endoscopy and EVL have been performed, high-risk patients (defined in that study as Child C cirrhosis with a score of 10-13 or Child B with active bleeding on endoscopy) who have a transjugular intrahepatic portosystemic shunt (TIPS) placed within 72 hours (“early” or preemptive TIPS) have been shown to have lower failure and mortality rates both at 6 weeks and at 1 year compared to patients that continue on standard therapy.<sup>13</sup> Because Child B patients with active hemorrhage were subsequently shown to be at an intermediate risk of mortality,<sup>14</sup> the recommendation of considering a pre-emptive TIPS in patients with variceal hemorrhage applies mostly to Child C patients (score 10-13).<sup>15</sup>

Patients not receiving TIPS should continue with vasoactive drugs for at least two days and up to five days. Patients without evidence of rebleeding should be then tapered off octreotide, taken off antibiotics and started on NSBB for secondary prophylaxis (see below). Patients with persistent bleeding or severe rebleeding should receive a “rescue” TIPS.

Patients who recover from the first episode of variceal hemorrhage have a high re-bleeding risk (60% in the first year), with a mortality of up to 33%. Therapy to prevent re-bleeding is therefore mandatory in these patients and should be instituted prior to hospital discharge. Patients who presented with variceal hemorrhage and other complications (ascites, encephalopathy, spontaneous bacterial peritonitis) with indications for liver transplant

should be referred for evaluation. Patients in whom TIPS was placed during the acute episode require no further specific therapy for portal hypertension or varices is required. Surveillance for TIPS patency should be instituted (Doppler ultrasound every six months). For all other patients, the first-line therapy for the prevention of re-bleeding is the combination of NSBB (propranolol or nadolol) and EVL, with NSBB being the key component of combination therapy as shown in a recent individual meta-analysis.<sup>16</sup>

### NSBB in Patients with Ascites

NSBB have been shown to prevent first and recurrent variceal hemorrhage in patients with cirrhosis and, in hemodynamic responders, NSBB have also been shown to prevent decompensation and death.<sup>17</sup> The effect appears to be independent of the presence or absence of ascites.<sup>18</sup>

The main pathophysiologic mechanism in patients with cirrhosis and ascites is splanchnic and systemic vasodilatation that leads to activation of neuro-humoral systems, sodium and fluid retention, resulting in increased cardiac output, and a hyperdynamic circulatory state.<sup>3</sup> In patients with refractory ascites, these abnormalities are maximal and a relative decrease in cardiac output can lead to a decrease in renal perfusion and to hepatorenal syndrome.<sup>19</sup> NSBB could precipitate this decrease in cardiac output and lead to renal dysfunction and death. This would be particularly so for carvedilol which, in addition to decreasing cardiac output, can worsen vasodilatation. In fact, retrospective studies have shown that NSBB can lead to renal dysfunction in decompensated patients<sup>20</sup> and to a higher mortality in patients with refractory ascites.<sup>21</sup> Subsequent retrospective studies including larger number of patients with ascites and/or refractory ascites (a collective of over 2,000 patients) have shown that beta-blocker (BB) use is either unrelated to an increased mortality. In fact, a recent meta-analysis including these observational studies and randomized studies of BB in the prevention of AVH, shows that BB use was not associated with increased all-cause mortality in patients with ascites, non-refractory ascites alone or refractory ascites alone.<sup>22</sup>

In studies showing a deleterious effect of NSBB, the mean arterial pressure is significantly

lower in patients in the NSBB group, indicating that this may be the clinical indicator that would lead to NSBB dose reduction or discontinuation.<sup>23</sup> Given the benefit of NSBB, particularly in the prevention of recurrent variceal hemorrhage, the Baveno VI consensus conference recommended that, until further evidence is available, NSBB should be used cautiously in patients with refractory ascites and dose reduced/discontinued in the presence of a systolic blood pressure <90 mmHg, serum sodium <130 mEq/L or development of acute kidney injury.<sup>6</sup> Further, recent guidance have suggested that NSBB in patients with ascites require adjustment to a maximal daily dose of 160 mg of propranolol or 80 mg/day of nadolol.<sup>5</sup>

### Ascites and Complications

The two main mechanisms of ascites formation in cirrhosis are universal: portal (sinusoidal) hypertension and renal retention of sodium. In cirrhosis, fluid extravasates from the hepatic sinusoids rather than from the splanchnic capillaries. Therefore, leakage of fluid into the peritoneal space occurs as a result of sinusoidal hypertension that in turn results from hepatic venous outflow block secondary to regenerative nodules and fibrosis. However, sinusoidal hypertension alone is not sufficient for the continuous formation of ascites. Plasma volume expansion, through sodium and water retention, allows for the replenishment of the intravascular volume and is the other essential factor in the pathogenesis of cirrhotic ascites.

As mentioned above, as portal pressure increases (and collaterals form), there is concomitant arterial splanchnic and systemic vasodilatation that results in a reduction in the effective arterial blood volume.<sup>19</sup> This “underfilling” leads to baroreceptor stimulation and consequent activation of various vasoconstrictor and anti-natriuretic neurohumoral systems (the renin-angiotensin-aldosterone system and sympathetic nervous system) that lead to renal sodium and water retention and to an increase in intravascular volume that maintains ascites formation.<sup>3</sup>

The natural history of cirrhotic ascites progresses from diuretic-responsive (uncomplicated) ascites to the development of dilutional hyponatremia, refractory ascites, and finally, hepatorenal syndrome (HRS).

First line therapies for new onset ascites (diuretics) and refractory ascites (therapeutic paracenteses) act downstream of the pathogenic cascade and are mainly symptomatic and therefore have not resulted in a significant improvement in survival. However, treating ascites is important, not only because it improves quality of life but also because spontaneous bacterial peritonitis (SBP), a lethal complication of cirrhosis, does not occur in the absence of ascites.

Most patients with cirrhosis who first develop ascites will respond to treatment with salt restriction and diuretics. Later on, as the pathophysiological mechanisms leading to ascites formation worsen, ascites no longer responds to diuretics and the patient is then said to have developed refractory ascites. First line therapy for these patients is serial large volume paracenteses, the frequency of which is determined by patient discomfort. TIPS acts on the pathophysiological mechanisms and its earlier placement in patients with refractory ascites should be considered. A recent multicenter trial in a recent randomized study of 62 patients with cirrhosis and at least two large volume paracentesis in the previous three weeks, those randomized to covered TIPS stents (average MELD 12, CTP score 9) had a significantly better one-year survival without transplant than those randomized to LVP (93% vs. 52%, respectively) with no differences in encephalopathy, suggesting that TIPS could be first-line therapy for patients with hard to treat ascites and relatively preserved liver function.<sup>24</sup>

Periodic albumin infusions, by increasing intravascular volume (and perhaps by additional functions that including binding of vasodilators and an anti-inflammatory activity) may play a role in the treatment of ascites. In an open RCT, chronic (weekly or biweekly) albumin infusions were associated with an improved survival in patients with non-refractory ascites.<sup>25</sup> This was a small proof-of-concept study and therefore no firm recommendations can be made regarding this approach.

Management of hyponatremia has also been directed downstream of the pathophysiological cascade by the use of “vaptans” that block renal tubular reabsorption of water. However, as expected, the effect is only transient. In a large

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multicenter randomized trial, tolvaptan used for 30 days in patients with dilutional hyponatraemia (of whom 63 had cirrhosis), was associated with a rapid improvement in serum sodium and significant weight loss compared to placebo, without significant side effects.<sup>26</sup> However, a sub-analysis of patients with cirrhosis and hyponatraemia showed that the effect on serum sodium was not only transient but, in those with severe hyponatremia, the effect was not sustained.<sup>27</sup>

Regarding HRS, vasoconstrictors constitute the current mainstay pharmacological therapy in the treatment of HRS. The rationale for use of these agents is to reverse the intense splanchnic and systemic vasodilatation, the main hemodynamic alteration in HRS. Administration of vasoconstrictors (ornipressin, terlipressin, octreotide with midodrine, noradrenaline) for periods greater than 3 days is associated with significant increases in mean arterial pressure, decreased serum creatinine and plasma renin activity as well as an increase in serum sodium.<sup>28</sup> Additional evidence is the significant correlation between increases in mean arterial pressure and decreases in serum creatinine induced by vasoconstrictors in HRS.<sup>29</sup>

In meta-analyses of randomized controlled trials, vasoconstrictor therapy (most studies used terlipressin) was associated with a significantly greater rate of HRS reversal (46-51% vs. 11-22% in control group) and a lower mortality compared to

control therapy.<sup>30,31</sup> Studies included in these meta-analyses all defined HRS with a creatinine >2.5 mg/dL. With changes in the definition of acute kidney injury,<sup>32</sup> a diagnosis of HRS would be reached with lower creatinine levels and thereby a greater rate of response would be expected.<sup>33</sup> This is important because in all studies survival is significantly better in terlipressin 'responders'.

Alternative vasoconstrictive therapy has included the use of intravenous noradrenaline infusion which has been shown to be as effective as terlipressin,<sup>31</sup> and the use of the combination octreotide/midodrine which, despite having shown efficacy in uncontrolled trials, was recently shown to be significantly inferior to terlipressin in a randomized controlled trial<sup>34</sup> and inferior to norepinephrine.<sup>31</sup> Therefore, the vasoconstrictor of choice in HRS is terlipressin, but in countries like the United States, where terlipressin is not available, the combination of octreotide/midodrine can be initiated, and if there is no decline in serum creatinine within a maximum of 3 days, the patient should be transferred to the ICU intensive care unit for a trial of norepinephrine.<sup>35</sup>

Because patients with refractory ascites and HRS have a higher mortality than those with diuretic-responsive ascites, efforts to avoid diuretic/procedures that will lead to worsening vasodilatation and/or to kidney injury in patients with cirrhosis and ascites are essential. ■

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