

Uma Mahadevan MD, Series Editor
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Use of Beta-blockers in Patients with Cirrhosis



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Non-selective beta-blockers improve outcomes in patients with cirrhosis and are recommended in (1) compensated cirrhosis and CSPH (to prevent decompensation), (2) decompensated cirrhosis without prior episodes of VH (to prevent first VH), and (3) patients with prior episodes of VH in combination with EVL (to prevent recurrent VH). NSBB should be started as soon as any of the above indications is identified, as progressive hemodynamic changes (hypotension, decreased renal perfusion) may cause the therapeutic window to be missed. Carvedilol is preferred, starting at 3.125 mg daily and titrated to 12.5 mg daily or a maximum dose of 25 mg daily. Trials have used once daily dosing, but a divided twice daily dose may be better tolerated. A specific HR should not be targeted with carvedilol, but blood pressure should be monitored, and dose should be reduced or discontinued in patients with MAP <65, systolic BP <90 or in the presence of AKI.

Pathophysiology of Portal Hypertension in Cirrhosis

In cirrhosis, both increased hepatic vascular resistance and increased blood flow through the portal vein contribute to the development of portal hypertension. The initial mechanism in the pathogenesis of portal hypertension in cirrhosis is the deposition of collagen in the liver parenchyma causing distortion of the normal vascular architecture and impeding blood flow through the liver.¹ In addition to mechanical factors, local imbalance of vasoactive molecules

and myofibroblast contraction in the liver results in increased intrahepatic vasoconstriction that further increases resistance.^{2,3}

The initial increase in portal pressure due to intrahepatic architectural distortion is mild but enough to cause shear stress in splanchnic capillaries that lead to the synthesis of vasodilatory molecules such as nitric oxide and release of inflammatory cytokines such as TNF-alpha that cause splanchnic vasodilation, increasing portal venous flow, which leads to a further increase in portal pressure.^{4,5} These vasodilators also cause systemic vasodilation and lower mean arterial pressure causing activation of neurohormonal

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DISPATCHES FROM THE GUILD CONFERENCE, SERIES #70

Table 1. Dosing of Non-Selective Beta-Blockers

Drug	Initial Dose	Target or Maximal Dose	Comments
Carvedilol	6.25 mg daily or 3.125 mg twice daily	12.5 mg daily or 6.25 mg twice daily. Dose can be increased to 25 mg daily or 12.5 mg twice daily if well tolerated	Preferred agent. Decrease dose if SBP<90 or MAP<65 mmHg
Nadolol	20-40 mg daily	160 mg/day (without ascites) 80 mg/day (with ascites)	Increase dose up to maximum tolerated dose or HR 55-60 BPM Decrease dose if SBP<90 or MAP<65 mmHg
Propranolol	10-20 mg twice daily	320 mg/day (without ascites) 160 mg/day (with ascites)	Increase dose up to maximum tolerated dose or HR 55-60 BPM Decrease dose if SBP<90 or MAP<65 mmHg

MAP: mean arterial pressure; SBP: systolic blood pressure; HR: heart rate; BPM: beats per minute.

systems, such as the renin-angiotensin-aldosterone system and adrenaline, leading to sodium and water retention, increased intravascular volume and increased cardiac output, which in turn lead to an even greater increase in portal venous flow and hence in portal pressure. Additionally, neurohormonal activation also acts at the level of intrahepatic blood vessels causing vasoconstriction and further increasing hepatic resistance to blood flow.^{6,7}

Predicting Decompensation

While cirrhosis refers to the last stage of liver fibrosis caused by any chronic liver disease, patients with cirrhosis have different clinical stages, each with an increasingly worsened prognosis: compensated cirrhosis is a mostly asymptomatic stage where no complications of portal hypertension have occurred and has a median survival greater than 15 years. On the other hand, decompensated cirrhosis is defined by one or more decompensating event (ascites, variceal hemorrhage, or encephalopathy) and carries a high mortality with a median survival of only 1.5 years.^{8,9}

The degree of portal hypertension is the main predictor of decompensation. While portal pressures can't be measured directly, the hepatic venous pressure gradient (HVPG) can be obtained via central venous access of the hepatic vein, by subtracting the free hepatic from the wedge hepatic venous pressures. A HVPG >5 mmHg suggest a diagnosis of cirrhosis, and ≥10 mmHg indicates the presence of clinically significant portal hypertension (CSPH). The development of CSPH is the main predictor of decompensation, and multiple studies have shown that in patients

with compensated cirrhosis, a HVPG ≥10 mmHg predicts the development of decompensated cirrhosis.^{10,11}

To avoid invasive testing in clinical practice, transient elastography (e.g. FibroScan) can be used to measure liver stiffness measurements (LSM). LSM and platelet (PLT) count can be used as an alternative method to diagnose CSPH non-invasively (18). If the LSM is <10 kPa, cirrhosis can be excluded. On the other hand, a patient can be diagnosed with compensated advanced chronic liver disease (cACLD) if the LSM is >15 kPa. The term cACLD is used when liver stiffness measurements are utilized to diagnose advanced liver fibrosis or cirrhosis, given that using the term cirrhosis could be inaccurate as this term implies a histological diagnosis. In clinical practice, patients with cACLD can be usually deemed to have cirrhosis, especially if other ancillary data such as liver nodularity or signs of portal hypertension on imaging, or reduced synthetic function (e.g. hypoalbuminemia, prolonged INR) are present. A LSM of 20-25 kPa with a platelet count <150 or LSM >25 kPa alone can be used to diagnose CSPH non-invasively.¹² Therefore, transient elastography allows clinicians to diagnose severe hepatic fibrosis and severe portal hypertension avoiding the need of invasive biopsies or portal pressure measurements.

Mechanism of Action of Beta-Blockers

Physiologic activation of beta-1 receptors in the heart increases cardiac output (CO) through positive chronotropic and inotropic effects, while beta-2 receptors in blood vessels increase blood flow by causing smooth muscle relaxation and vasodilation. By blocking beta-1 and beta-2 receptors,

non-selective beta blockers (NSBB) lower portal pressures by causing splanchnic vasoconstriction and lowering CO, decreasing portal venous flow, and ameliorating the hyperdynamic circulation that occurs in cirrhosis.¹⁰ Carvedilol is a NSBB that, in addition to blocking beta-1 and beta-2 receptors, also inhibits alpha-1 receptors, further decreasing portal pressures by lowering intrahepatic vascular resistance and CO.¹³

Besides their well-known hemodynamic effects, there is evidence to suggest NSBBs can decrease bacterial translocation from the gut by increasing intestinal transit time, improving mucosal barrier function, and decreasing bacterial virulence. By decreasing bacterial translocation and subsequent inflammation, NSBBs may reduce the synthesis of vasodilators and systemic cytokines such as TNF-alpha that further contribute to the hyperdynamic circulatory state.¹⁴

Indications of Beta-Blockers in Cirrhosis

1. Preventing First Decompensation in Patients with Compensated Cirrhosis and Clinically Significant Portal Hypertension (CSPH)

Preventing decompensating events such as variceal hemorrhage (VH), ascites and hepatic encephalopathy is key in the management of patients with cirrhosis, as the development of decompensated cirrhosis portends a poor prognosis. Of these, ascites is the most common decompensation and is the decompensating event associated with the highest mortality.⁸

NSBBs have shown to decrease the risk of ascites in patients with compensated cirrhosis and CSPH. A randomized clinical trial in patients with compensated cirrhosis and CSPH showed an absolute risk reduction of 11% in the development of a decompensating event or death in patients receiving NSBB compared to placebo, with a number needed to treat (NNT) of 9. The lower risk in patients receiving NSBB was mostly driven by the decreased incidence of ascites, although the progression to high-risk varices was also decreased in patients receiving carvedilol, suggesting that carvedilol likely decreases the risk of variceal hemorrhage in patients with compensated cirrhosis and CSPH.¹⁵

In the past, guidelines recommended either

endoscopic variceal ligation (EVL) or NSBBs for primary prophylaxis of VH in patients with cirrhosis and at-risk varices, but more recent evidence shows that NSBBs, particularly carvedilol, are more effective in preventing VH and in improving survival in patients with compensated cirrhosis with varices. Because of this, EVL (a local therapy that just acts by obliterating varices) is now only a second line therapy after NSBB, preferably carvedilol (a systemic therapy that addresses different aspects of the pathophysiology of PH).¹⁶⁻¹⁸ Therefore, compensated patients with CSPH without prior episodes of VH that are started on NSBBs therapy do not need to undergo screening upper endoscopies, as this will not change their management. On the other hand, patients unable to tolerate NSBB should undergo screening upper endoscopies with EVL of large varices with the aim of preventing a first episode of VH.¹²

While NSBBs are indicated in patients with CSPH to prevent decompensation, they should be avoided in patients with compensated cirrhosis without CSPH, as they offer no substantial benefits, and exposes these patients to potentially significant side-effects.¹⁰

2. Preventing Further Decompensation

a. Preventing First Episode of Variceal Hemorrhage in Decompensated Patients with Ascites

Patients with ascites have already developed decompensated cirrhosis. In this setting, efforts should be focused on preventing further decompensation by preventing the first occurrence of VH. NSBB in patients with ascites and high risk varices reduce the risk of VH and improve overall survival.^{16,18} As in patients with compensated cirrhosis and CSPH, screening endoscopy with EVL is mostly reserved to patients with ascites unable to tolerate NSBB.^{12,17}

b. Preventing Recurrent Episodes of Variceal Hemorrhage

In patients with prior episodes of VH, a combination of EVL and NSBB is recommended to prevent further episodes of bleeding. Combining EVL and NSBBs is superior to either monotherapy in preventing recurrent VH.¹⁹ Furthermore, combination therapy decreases mortality in patients with Child-Pugh class B or C cirrhosis, compared

Figure 1. Equivalent classifications of patients with chronic liver disease based on invasive and non-invasive diagnostic methods.

Invasive diagnostic tests:

HVPG	<5 mmHg	5-10 mmHg	≥10 mmHg
METAVIR fibrosis score on biopsy	F1 or F2	F3 or F4	F3 or F4
Terms based on biopsy and HVPG	No cirrhosis	Advanced fibrosis or cirrhosis (if F4) without CSPH	Advanced fibrosis or cirrhosis (if F4) with CSPH

Non-invasive diagnostic tests:

LSM by TE	<10 kPa	≥15 kPa	≥25 kPa or ≥20 kPa with PLT <150
Terms based on non-invasive tests	No cACLD	cACLD without CSPH	cACLD with CSPH

progression of liver disease →

HVPG: hepatic venous pressure gradient; CSPH: clinically significant portal hypertension; LSM: liver stiffness measurements; cACLD: compensated advanced chronic liver disease.

to EVL alone.²⁰ Some data suggests that the main benefit of combination therapy is mostly driven by NSBB, and not EVL.²¹

The risk of rebleeding is as high as >60% but the risk significant differs depending on factors such as Child-Pugh class and size of esophageal varices.²² The reduction of risk of rebleeding depends on how much HVPG decreases; while it can be as low as <10% when HVPG decreases significantly, patients that fail to achieve an appropriate response in HVPG reduction have a bleeding rate of up to 40% despite receiving adequate therapy.²³

Assessing Response to NSBB

Assessing changes in HVPG should not be used to determine response to NSBB in clinical practice given measurements are highly variable when repeated in the same individual. Heart rate has been traditionally used to assess hemodynamic response to beta-blockers, with the assumption that a lower HR is associated with a lower HVPG. Unfortunately, studies have shown a poor correlation between heart rate and HVPG, making the use of HR as a surrogate of HVPG unreliable.²⁴

Studies have shown that less than half of patients achieve a hemodynamic response with traditional NSBB, but most recently, the concept of NSBB “non-responders” has been brought into question, with a recent study suggesting all patients respond to NSBB, and that “non-responders” may represent inaccurate HVPG measurements.²⁵

Carvedilol has shown to be effective in

preventing hepatic decompensation and liver-related death even when not monitoring HVPG or HR changes, and to achieve a lower HVPG compared to other NSBB.^{15,26} The Baveno VII expert consensus and current clinical guidelines recommends carvedilol as the preferred NSBB in patients with cirrhosis given it is more effective in reducing portal pressures and improving clinical outcomes.^{12,17,27}

When Should Beta-Blockers be Used Cautiously?

Observational studies raised the concern that beta-blockers may cause harm in patients that already have ascites, mainly by causing acute kidney injury (AKI) and worsening mortality.^{28,29} Since then, further studies demonstrated that the deleterious effects of NSBBs occur mostly in patients with refractory ascites, mainly by altering the compensatory mechanisms that maintain renal perfusion in these patients.^{30,31} This is likely reflective of the worsening hemodynamic changes that occur as decompensation progresses; patients with refractory ascites have lower MAP and higher CO compared to patients with diuretic-responsive ascites, indicative of a more pronounced hyperdynamic circulation.⁶

More recent studies have demonstrated improved survival with NSBBs even in patients with refractory ascites if adequate blood pressures (systolic BP >90 mmHg or MAP >65 mmHg) are maintained. Therefore, NSBB improve survival even in patients with refractory ascites, if the

Figure 2. Indications and Goals of Therapy with NSBB in Patients with Cirrhosis.

progression of liver disease →

Stage of cirrhosis	Compensated without CSPH	Compensated with CSPH	Decompensated
NSBB indicated	No	Yes	Yes*
Goals of therapy		Prevent decompensation	Prevent further decompensation

NSBB: non-selective beta-blockers; CSPH: clinically significant portal hypertension; VH: variceal hemorrhage; HE: hepatic encephalopathy.
 *In patients with ascites or HE and high-risk varices (to prevent first episode of VH) or patients with prior VH (to prevent recurrent VH).

blood pressures are adequate to maintain renal perfusion.^{30,32} In addition, the recommended maximal dose in patients with ascites is lower than in those without ascites, and the dose should be further reduced or discontinued if patients develop AKI, or a systolic blood pressures <90 mmHg or MAP <60 mmHg.^{12,17}

Case Examples: Are NSBB Recommended?

1. Patient with cirrhosis diagnosed by transient elastography (TE) with a LSM of 16 kPa and a PLT count of 190. The patient has never had ascites, VH or hepatic encephalopathy. A prior endoscopy was normal, there were no esophageal varices.

The patient has compensated cirrhosis without CSPH based on non-invasive tests (LSM >15kPa but <20 kPa and with PLT >150). NSBB are not recommended as they have not shown to be beneficial in patients without CSPH and would likely only expose this patient to undesired side effects.

2. Patient with cirrhosis evidenced by a LSM (by TE) of 23 kPa and a PLT count of 130. The patient has never had an upper endoscopy and has never had ascites, gastrointestinal hemorrhage or encephalopathy.

The patient has compensated cirrhosis with CSPH based on non-invasive tests (LSM >20 kPa and PLT <150). Carvedilol is recommended without the need for an upper endoscopy, with the main goal of preventing decompensation, mainly ascites (the complication of cirrhosis associated with the highest mortality) and possibly a first episode of VH. An endoscopy to screen for varices is not recommended if the patient is able to tolerate NSBBs, as the presence or absence of high-risk varices will not change management at this time.

3. Patient with compensated cirrhosis who undergoes an upper endoscopy for dyspepsia that shows large varices. The patient has no prior TE, and PLT count has fluctuated between 130 and 180. A recent abdominal US showed mild splenomegaly and a patent portal vein.

The patient has compensated cirrhosis with CSPH based on the presence of high-risk varices, independent of LSM or PLT count. Carvedilol is recommended with the goal of preventing ascites and a first episode of VH. If the patient is unable to tolerate carvedilol, endoscopic variceal ligation should be performed with the goal of preventing first VH.

4. Patient with ascites, well controlled on diuretics with no prior episodes of VH.

The patient has decompensated cirrhosis based on the presence of ascites. Therefore, the only complication of cirrhosis that can be prevented at this point is VH. The main predictor of variceal hemorrhage is the presence of high-risk varices and therefore an upper endoscopy should be performed. If endoscopy shows high-risk varices (large varices or small varices with red wale signs), preference is given to NSBBs (including carvedilol) because of benefits beyond prevention of VH. If patient will be placed on NSBB, blood pressure and renal function should be monitored closely after initiating NSBB and the dose should be decreased or discontinued if patient develops systolic BP <90 or severe adverse effects (e.g. acute kidney injury). Another NSBB such as propranolol or nadolol can be considered if the patient is unable to tolerate carvedilol due to low BP.

5. Patient with ascites requiring weekly large volume paracentesis (LVP) with no prior episodes of VH.

The patient has further decompensated cirrhosis based on the presence of refractory ascites. The only complication of cirrhosis that can be prevented at this point is VH. The main predictor of variceal hemorrhage is the presence of high-risk varices and therefore an upper endoscopy should be performed. If endoscopy shows high-risk varices (large varices or varices with red wale signs) preference would be given to NSBB to prevent VH. Refractory ascites may be associated with lower blood pressure and systolic function that could decrease renal perfusion and lead to AKI and could worsen on NSBB. If patient will be placed on NSBB, blood pressure and renal function should be monitored closely after initiating NSBB and the dose should be decreased or discontinued if patient develops systolic BP <90 or severe adverse effects such as AKI. In these patients, particularly if BP is borderline low, another NSBB such as propranolol or nadolol would be more appropriate than carvedilol.

6. Patient with an episode of VH that occurred one year ago, with no history of ascites or hepatic encephalopathy. The acute episode of VH was treated successfully but the patient was then lost to follow up and has not had any other decompensating event.

The patient has decompensated cirrhosis based on a prior episode of VH. Carvedilol in combination with serial surveillance endoscopies and EVL of high-risk varices is recommended to prevent recurrent episodes of VH. The combination of EVL and NSBB is superior to either therapy alone in preventing recurrent VH. ■

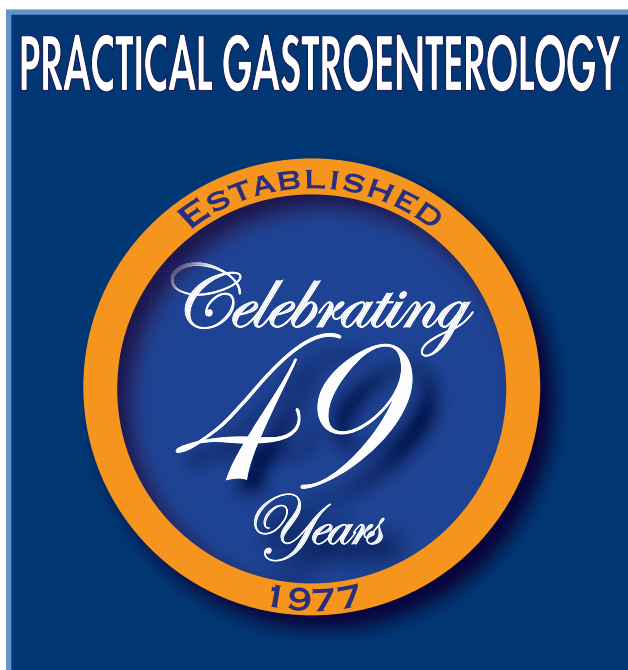
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Answers to this month's crossword puzzle:

