REVIEW

Management and Treatment of Patients With Cirrhosis and Portal Hypertension: Recommendations From the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program

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Cirrhosis represents the end stage of any chronic liver disease. Hepatitis C and alcohol are currently the main causes of cirrhosis in the United States. Although initially cirrhosis is compensated, it eventually becomes decompensated, as defined by the presence of ascites, variceal hemorrhage, encephalopathy, and/or jaundice. These management recommendations are divided according to the status, compensated or decompensated, of the cirrhotic patient, with a separate section for the screening, diagnosis, and management of hepatocellular carcinoma (HCC), as this applies to patients with both compensated and decompensated cirrhosis. In the compensated patient, the main objective is to prevent variceal hemorrhage and any practice that could lead to decompensation. In the decompensated patient, acute variceal hemorrhage and spontaneous bacterial peritonitis are severe complications that require hospitalization. Hepatorenal syndrome is also a severe complication of cirrhosis but one that usually occurs in patients who are already in the hospital and, as it represents an extreme of the hemodynamic alterations that lead to ascites formation, it is placed under treatment of ascites. Recent advances in the pathophysiology of the complications of cirrhosis have allowed for a more rational management of cirrhosis and also for the stratification of patients into different risk groups that require different management. These recommendations are based on evidence in the literature, mainly from randomized clinical trials and meta-analyses of these trials. When few or no data exist from well-designed prospective trials, emphasis is given to results from large series and consensus conferences with involvement of recognized experts. A rational management of cirrhosis will result in improvements in quality of life, treatment adherence, and, ultimately, in outcomes.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Cirrhosis represents the end stage of any chronic liver disease. Hepatitis C and alcohol are currently the main causes of cirrhosis in the United States. Two major syndromes result from cirrhosis, namely portal hypertension and hepatic insufficiency. In addition, peripheral and splanchnic vasodilatation with the resulting hyperdynamic circulatory state is typical of cirrhosis and portal hypertension. The hyperdynamic circulatory state is characterized by low arterial pressure, high cardiac output, and decreased peripheral vascular resistance.

In a patient with any chronic liver disease, finding a palpable left lobe of the liver (hard and nodular) and a small right lobe span suggests the presence of cirrhosis. Similarly, any sign of portal hypertension detected by physical examination (splenomegaly, caput medusae), laboratory investigation (even a subtle decrease in platelet count, such as a count $<175{,}000/mm^3$), or by imaging studies (colloid shift on the liver–spleen scan; a nodular surface, collaterals, and splenomegaly seen on computed tomography scan or ultrasound) is indicative of the presence of cirrhosis. Moreover, even subtle indicators of liver insufficiency (albumin levels <3.8 mg/dl or INR, international normalized ratio, >1.3) can suggest the presence of cirrhosis.

Cirrhosis can remain compensated for many years before the development of a decompensating event (1). Decompensated cirrhosis is marked by the development of any of the following complications: jaundice, variceal hemorrhage, ascites, or

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encephalopathy (1). Jaundice results from hepatic insufficiency and, other than liver transplantation, there is no specific therapy for this complication. However, it is important to recognize and treat superimposed entities (e.g., alcoholic hepatitis, sepsis, drug hepatotoxicity), which may contribute to the development of jaundice. The other complications of cirrhosis occur mainly as a consequence of portal hypertension and hyperdynamic circulation. Gastroesophageal varices result almost solely from portal hypertension, although 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. Hepatorenal syndrome (HRS) results from severe peripheral vasodilatation, which leads to renal vasoconstriction. Hepatic encephalopathy (HE) is a consequence of shunting of blood through portosystemic collaterals (as a result of portal hypertension), brain edema (cerebral vasodilatation), and hepatic insufficiency.

A simple way of assessing the severity of cirrhosis is by determining the Child–Turcotte–Pugh (CTP) class (**Supplementary Table 1** online). Patients who belong to CTP class A are compensated and those in CTP classes B and C are decompensated.

The development of hepatocellular carcinoma (HCC) can lead to decompensation and, conversely, decompensated cirrhosis is an independent predictor of death in HCC; therefore, HCC should be considered as a prognostic indicator at any disease stage rather than a distinct stage of cirrhosis or as an event defining decompensation (1). Nevertheless, the management of cirrhosis also involves the diagnosis and management of HCC.

A recent consensus conference established that compensated cirrhosis should be considered a separate entity from decompensated cirrhosis with different management, prognosis, and causes of death (2). Therefore, the following treatment recommendations for cirrhosis are divided according to the status–compensated or decompensated–of the cirrhotic patient with a separate section for the screening, diagnosis, and management of HCC, as this applies to both patients with compensated and decompensated cirrhosis.

The recommendations are based on evidence in the literature, mainly from randomized clinical trials (RCTs) and meta-analyses of these trials. When few or no data exist from well-designed prospective trials, emphasis is given to results from large series and consensus conferences with involvement of recognized experts. Clinical considerations may justify a course of action that differs from these recommendations.

Recommendations are summarized in the Cirrhosis and HCC Quicknotes available at http://www.hepatitis.va.gov.

MANAGEMENT OF COMPENSATED CIRRHOSIS

Patients with compensated cirrhosis are not jaundiced and have not yet developed ascites, encephalopathy, or variceal hemorrhage. The median survival of patients with compensated cirrhosis is ~9 years (3), but it is as long as 12 years when patients are censored at the time of decompensation (1).

The two goals in the management of compensated cirrhosis are (i) treatment of the underlying liver disease (e.g., hepatitis C or B, alcohol, non-alcoholic steatohepatitis), and (ii) prevention/early diagnosis of the complications of cirrhosis. The treatment of the underlying liver disease is beyond the scope of these recommendations. The main recommendations specific to patients with newly diagnosed cirrhosis are screening for varices and HCC (see "Screening, diagnosis, and management of HCC").

Screening for gastroesophageal varices and primary prophylaxis of variceal hemorrhage

An esophagogastroduodenoscopy (EGD) should be performed once the diagnosis of cirrhosis is established (4–6). The objective of EGD is to detect the presence/size of varices for determining whether the patient should receive therapy for prevention of first variceal hemorrhage (primary prophylaxis).

Gastroesophageal varices are present in ~50% of cirrhotic patients. Their presence correlates with the severity of liver disease; although only 40% of CTP class A patients have varices, they are present in 85% of CTP class C patients (7). Patients with gastroesophageal varices develop variceal hemorrhage at the rate of 12–15% per year. The mortality rate with each episode of variceal hemorrhage is approximately 15–20%. Therefore, one of the main preventive measures for the patient with compensated cirrhosis is the prevention of first variceal hemorrhage (primary prophylaxis). Recommendations stated below follow recent treatment recommendations endorsed by the AASLD (American Association for the Study of Liver Diseases) and the ACG (American College of Gastroenterology) (5,6).

Candidates for primary prophylaxis of variceal hemorrhage. Three factors identify patients at a high risk of bleeding from varices: large variceal size, red wale marks on the varices (defined as longitudinal dilated venules resembling whip marks on the variceal surface), and advanced liver disease (CTP class B or C) (8). Patients with large varices or patients with high-risk small varices (those with red signs or those occurring in a CTP class C patient) are at the highest risk of bleeding. Other patients with small varices (non-high risk) are at a low risk of bleeding, but are at risk for variceal growth.

Accepted therapies. Two therapies are currently accepted in the prevention of the first episode of variceal hemorrhage, namely nonselective β-blockers (NSBBs) and endoscopic variceal ligation (EVL) (**Supplementary Table 2**).

NSBBs (i.e., propranolol, nadolol) reduce portal pressure by reducing the cardiac output (β1-blockade effect) and, more importantly, by reducing portal blood inflow through splanchnic vasoconstriction (β2-blockade effect). Therefore, selective β1-blockers (e.g., atenolol, metoprolol) are less effective and are not recommended for the primary prophylaxis of variceal hemorrhage. Results from RCTs show that, in patients with varices, NSBBs significantly reduce the incidence of first variceal hemorrhage, from 25 to 15% in a median follow-up of 24 months (9). The effect is more evident in patients with medium/large-sized varices (30% first hemorrhage in controls compared

with 14% in NSBB-treated patients). Mortality is lower in the β-blocker group compared with that in the control group, and this difference has been shown to be statistically significant (10). The incidence of first variceal hemorrhage in patients with small varices, although low, is reduced with β-blockers (from 7 to 2% over a period of 2 years); however, these numbers are too small to show statistical significance. In patients with small varices that are not at a high risk of hemorrhage, NSBBs have been effective in delaying variceal growth, and thereby preventing variceal hemorrhage (11).

EVL is a local therapy that consists of placing rubber bands around varices until obliteration. EVL has been compared with NSBB in several randomized trials in patients with large varices with or without red wale markings. Two meta-analyses show that EVL is associated with a small but significantly lower incidence of first variceal hemorrhage without differences in mortality (12,13). However, a more recent meta-analysis showed that the estimated effect of EVL in some trials may be biased and was associated with the duration of follow-up (the shorter the follow-up, the more positive the estimated effect of EVL (14)) and that both therapies seemed equally effective. EVL is cost-effective when cost per quality-adjusted life year is considered (15) and is preferred over NSBB by both patients and physicians (16). However, NSBBs have other advantages, such as prevention of bleeding from other portal hypertension sources (portal hypertensive gastropathy and gastric varices) and a possible reduction in the incidence of spontaneous bacterial peritonitis (SBP) (17).

After a careful review of the available data, a consensus panel concluded that both NSBB and EVL are effective in preventing first variceal hemorrhage in patients with medium/large varices, and that the choice should be based on patient characteristics and on preferences, local resources, and expertise (2).

In patients with medium/large-sized varices at the highest risk of bleeding (CTP class C, red wale marks) either NSBB or EVL can be used, whereas in patients with medium/large varices that are not at the highest risk, NSBBs are preferred and EVL should be considered in patients with contraindications, intolerance (including those in whom the dose of NSBB cannot be adjusted to achieve target goals), or non-compliance to NSBB (5,6).

In patients with small varices that are at a high risk of bleeding (red wale marks and/or CTP class C), NSBBs are recommended given the technical difficulties in performing EVL.

Patients with gastric fundal varices (with or without esophageal varices) should receive NSBB; prophylactic EVL is not recommended in these patients, given the risk of precipitating hemorrhage.

In patients without varices, treatment is not recommended given the lack of efficacy of NSBB in preventing the development of varices and a higher rate of side effects (18).

Treatment schedule. Given the lack of correlation between decreases in heart rate and decreases in portal pressure (19), the dose of NSBB is adjusted to the maximal tolerated doses to heart rates of 55–60 b.p.m. Propranolol is administered twice a day (b.i.d) and is usually started at a dose of 20 mg b.i.d. Nadolol is administered q.d. (once a day) and is started at a dose of 20–40 mg q.d. The NSBB on the Department of Veterans Affairs (VA) National Formulary is propranolol (10, 20, 40, and 80 mg tablets). On the basis of data showing recurrent bleeding on discontinuation of β-blockers (20), it is recommended that NSBBs be continued indefinitely. Importantly, once NSBBs are initiated and the dose is appropriately adjusted there is no need for repeat EGD.

EVL is performed every 1–2 weeks until the obliteration of varices, with first surveillance EGD performed 1–3 months after obliteration and every 6–12 months thereafter.

Contraindications/side effects. Approximately 15% of patients have contraindications to the use of NSBB, such as asthma, insulin-dependent diabetes (with episodes of hypoglycemia), and peripheral vascular disease. The most common side effects related to NSBB in cirrhosis are lightheadedness, fatigue, and shortness of breath. Some of these side effects disappear with time or after a reduction in the dose of NSBB. In clinical trials, side effects have led to treatment discontinuation in ~15% of patients. The rate of side effects in trials in which nadolol was used (~10%) seems to be lower than in trials in which propranolol was used (~17%); however, direct comparisons have not been made (21).

Side effects of EVL occur in ~14% of cases and are usually minor. The most common complications are transient dysphagia and chest discomfort. Shallow ulcers at the site of each ligation are the rule, and the use of proton pump inhibitors after ligation seems to reduce their size (22). However, there have been reports of bleeding from ligation-induced esophageal ulcers that has resulted in death (23,24), and this risk should be discussed with the patient.

Therapies not recommended for primary prophylaxis. These therapies are summarized in (**Supplementary Table 2**). Nitrates (such as isosorbide mononitrate, ISMN) are ineffective in preventing first variceal hemorrhage in patients with large varices (25,26) and have been associated with a higher mortality in patients older than 50 years (27). ISMN, a potent venodilator, may lead to a higher mortality in these patients by aggravating the vasodilatory state of the cirrhotic patient, as shown in shorter-term hemodynamic trials using other vasodilators, such as losartan (28) and irbesartan (29). Therefore, the use of nitrates alone in patients with cirrhosis should be discouraged, unless there is a clear indication for coronary artery disease.

The combination of a NSBB and ISMN has a synergistic portal pressure-reducing effect and could theoretically be more effective than NSBB alone in preventing first variceal hemorrhage (30). Double-blind, placebo-controlled RCTs have shown a lack of efficacy (31,32) and a greater number of side effects with combination therapy (31). Therefore, the use of a combination of a β-blocker and ISMN cannot be recommended for primary prophylaxis.

The combination of a NSBB and spironolactone (which has been shown to decrease portal pressure by reducing plasma

volume and splanchnic blood flow) has not been shown to increase the efficacy of nadolol in the primary prophylaxis of variceal hemorrhage (33).

Endoscopic sclerotherapy trials yielded controversial results. Although early studies showed promising results, later studies showed no benefit in decreasing first variceal hemorrhage or mortality from variceal bleeding (34,35). A VA prospective, randomized, cooperative trial that compared prophylactic sclerotherapy with sham therapy was terminated 22.5 months after it began, because the mortality rate was significantly higher in the sclerotherapy group than in the sham-therapy group (36). Therefore, sclerotherapy should not be used for the primary prevention of variceal hemorrhage.

The role of a combination of a NSBB and EVL in the prevention of first variceal hemorrhage is uncertain. In a randomized but not placebo-controlled trial that compared EVL alone with EVL + NSBB in patients with large varices and red signs, no differences were observed in the incidence of bleeding or death between groups (8 and 7%, respectively) (37). In another RCT that compared NSBB alone with NSBB + EVL in CTP class B or C patients with large varices and red signs, first variceal bleeding was lower in patients treated with combination therapy (8%) compared with those treated with NSBB alone (30%, a rate that is too high and comparable with untreated patients) (38). In both studies, side effects were more common in EVL + NSBB groups. Given these conflictive results, combination therapy cannot be currently recommended.

Shunt surgery trials have shown conclusively that, although very effective in preventing first variceal hemorrhage, shunting blood away from the liver is accompanied by more frequent encephalopathy and higher mortality (34). These results can be extrapolated to the transjugular intrahepatic portosystemic shunt (TIPS), because its physiology is the same as that of surgical shunts (i.e., diversion of blood away from the liver) (39). Therefore, shunt therapy (surgery or TIPS) should not be used in the primary prevention of variceal hemorrhage.

Therapies under investigation. Recently, the preliminary results of a RCT comparing carvedilol (a NSBB with vasodilating properties) with EVL in the primary prophylaxis of variceal hemorrhage showed that after 16 months of follow-up, carvedilol was associated with a significantly lower rate of first variceal hemorrhage (9%) compared with EVL (21%) with a tendency for higher rate of adverse events with carvedilol (40). The bleeding rate for EVL is higher than that reported earlier and, until details of this study are available, carvedilol cannot be recommended (**Supplementary Table 2**).

The management strategy after screening endoscopy in patients with newly diagnosed cirrhosis is summarized in **Table 1**.

Over-the-counter medications in compensated cirrhosis

Most drugs are metabolized in the liver and, although they are potentially hepatotoxic, the risk for hepatotoxicity is not necessarily higher in patients with pre-existing liver disease.

However, over-the-counter analgesics, specifically acetaminophen (or paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, ibuprofen, naproxen, and sulindac, can potentially lead to decompensation in a patient with compensated cirrhosis or to further decompensation in an already decompensated patient ("acute-on-chronic" liver failure).

Acetaminophen is an intrinsic hepatotoxin that produces dose-related hepatocellular necrosis, with severe hepatotoxicity resulting from a single acute ingestion of more than 15 g. The at-risk dose is lower in individuals with chronic alcohol use or malnutrition in whom therapeutic doses (4 g/day) can produce significant liver injury (41–43). Patients with alcoholic cirrhosis who are actively drinking and/or are malnourished may be more susceptible to develop acute-on-chronic liver injury from lower doses of acetaminophen (44) and therefore, in these patients acetaminophen should be used at doses lower than those recommended. In all other patients with cirrhosis, acetaminophen can be used at therapeutic doses but for limited periods of time, as recent studies have shown that chronic therapeutic use rather than acute massive ingestion of acetaminophen is a more common cause of acute liver failure in the United States (45,46).

NSAIDs, in addition to having a potential for idiosyncratic liver injury, inhibit prostaglandin synthesis and, by doing so, blunt the response to diuretics in patients with cirrhosis and ascites and promote renal vasoconstriction that will in turn lead to decreased glomerular filtration rate and acute kidney injury (AKI) (47,48). Renal vasoconstriction and renal failure after NSAIDs occur not only in patients with decompensated cirrhosis, but also in those with compensated disease (49). Therefore, NSAIDs should be avoided in patients with cirrhosis.

MANAGEMENT OF DECOMPENSATED CIRRHOSIS

The following sections deal with the management of the specific complications of the patient with cirrhosis who has developed decompensation. The first two complications, acute variceal hemorrhage and SBP, are severe and require hospitalization. HRS is also a severe complication of cirrhosis but usually occurs in the patient who is already in the hospital. As HRS represents the result of extreme hemodynamic alterations that lead to ascites formation, it is placed under treatment of ascites.

Treatment of acute variceal hemorrhage

Acute variceal hemorrhage is associated with a mortality rate of 15–20%. Management should be aimed at providing simultaneous and coordinated attention to effective resuscitation, prompt diagnosis, control of bleeding, and prevention of complications.

Candidates for therapy. Candidates include patients with cirrhosis who present with upper gastrointestinal (GI) hemorrhage and in whom diagnostic endoscopy shows one of the following: active bleeding from a varix, a "white nipple" overlying

Table 1. Management strategy after results of screening endoscopy in patients with cirrhosis

No varices	Repeat endoscopy in 3 years (sooner if decompensation occurs)		
Small varices	In a CTP B/C patient or varices with red signs	Nonselective β-blockers (propranolol or nadolol)	Start propranolol (20 mg b.i.d.) or nadolol (20 mg q.d.) Titrate to maximal tolerable dose or a heart rate of 55–60 b.p.m. No need to repeat EGD
	In a CTP A patient, without red signs	Nonselective β-blockers optional If no β-blockers are given, repeat endoscopy in 2 years (sooner if decompensation occurs)	Same as above
Medium/large varices	All patients independent of CTP class	Nonselective β-blockers (propranolol, nadolol) *or*[a] Endoscopic variceal ligation	Same as above Ligate every 1–2 weeks until variceal obliteration First surveillance endoscopy 1–3 months after obliteration, then every 6–12 months indefinitely

b.i.d., twice a day; b.p.m., beats/min; CTP, Child–Turcotte–Pugh; EGD, esophagogastroduodenoscopy; q.d., once daily.
[a]Choice depends on patient characteristics and preferences, local resources.

a varix, clots overlying a varix, or varices with no other potential source of bleeding (50).

General measures. Volume should be expanded to maintain a systolic blood pressure of 90–100 mm Hg and a heart rate of below 100 b.p.m. (4). Colloids are more effective than crystalloids and packed red blood cells in reaching optimal hemodynamic and oxygen transport goals (51). Transfusion goals are required to maintain a hemoglobin of ~8 g/dl (4) as, in experimental studies, total blood restitution is associated with increases in portal pressure (52), and higher rates of rebleeding and mortality (53). Endotracheal intubation should be performed before EGD in patients with massive bleeding and a decreased consciousness level.

One of the main complications associated with variceal hemorrhage is bacterial infection. Short-term antibiotic prophylaxis not only decreases the rate of bacterial infections but also decreases variceal rebleeding (54) and increases survival (55,56). Therefore, its use is considered a standard practice (57). Although oral norfloxacin at a dose of 400 mg b.i.d. for 7 days was recommended by consensus (57), a recent RCT suggests that intravenous (i.v.) ceftriaxone (1 g/day) is more effective in patients with two or more of the following: malnutrition, ascites, encephalopathy, or serum bilirubin >3 mg/dl (58). However in this study, most of the infections (six of seven) observed in the norfloxacin group were caused by quinolone-resistant organisms suggesting that, norfloxacin would still be optimal in centers with a low prevalence of quinolone resistance.

The transfusion of fresh frozen plasma and platelets can be considered in patients with significant coagulopathy and/or thrombocytopenia. A multicenter placebo-controlled trial of recombinant factor VIIa in cirrhotic patients with GI hemorrhage failed to show a beneficial effect of recombinant factor VIIa over standard therapy (59). Although *post hoc* analysis of a sub-population of CTP classes B and C cirrhotic patients indicated that administration of recombinant factor VIIa significantly decreased the proportion of patients with failure to control variceal bleeding, this was not confirmed in a subsequent RCT (60) and therefore, recombinant factor VIIa is not recommended (**Supplementary Table 3**).

Once the patient is hemodynamically stable, EGD should be performed. Although the Baveno consensus suggests a 12-h time frame for the performance of diagnostic endoscopy (4), it should be performed as soon as possible particularly in patients with more severe bleeding.

Specific measures to control acute hemorrhage and prevent early recurrence. *Accepted therapies*. The most rational approach in the control of acute variceal hemorrhage consists of the combination of pharmacological and endoscopic therapy (**Supplementary Table 3**).

Pharmacological therapy has the advantages of being generally applicable and drugs with a low rate of adverse events, such as somatostatin or analogs (octreotide, vapreotide), can be initiated as soon as a diagnosis of variceal hemorrhage is suspected, before diagnostic EGD. Drugs used in this setting act by producing splanchnic vasoconstriction and, thereby decreasing portal blood inflow. RCTs comparing different pharmacological agents (vasopressin, somatostatin, terlipressin, octreotide, vapreotide), show no differences among them regarding control of hemorrhage and early rebleeding, although vasopressin is associated with more adverse events (9). In practice, the choice of pharmacological agent is usually based on availability and cost. Of the safe vasoconstrictors (somatostatin and analogs, terlipressin), octreotide is currently the only one available in the United States and on the Department of VA National Formulary.

Regarding endoscopic therapy, EVL is more effective than endoscopic variceal sclerotherapy with greater control of hemorrhage, less rebleeding, lower rates of adverse events, but without differences in mortality (13,61). EVL should be performed at the time of diagnostic EGD if and when a variceal source of hemorrhage is confirmed. Sclerotherapy is reserved for cases in which EVL cannot be performed.

Treatment schedule. Octreotide is recommended at an initial bolus dose of 50 μg i.v. followed by a continuous i.v. infusion of 50 μg/h. Although the optimal duration of pharmacological therapy has not been well established in RCTs, considering that ~50% of early recurrent hemorrhage occurs within the first 5 days (62), continuing vasoactive drugs for 5 days seems rational. However, as shorter lengths of treatment have also been successful, shorter duration is acceptable, particularly in patients with a low risk of rebleeding (e.g., CTP class A).

EVL should be performed during diagnostic endoscopy when the possible variceal source of bleeding is confirmed. The process should be started at the gastroesophageal junction by placing ~6 bands particularly on the vessel with stigmata of bleeding. Repeat EVL can be attempted if hemorrhage is not controlled or if the patient has an early recurrence of variceal hemorrhage.

Side effects. Octreotide (and other somatostatin analogs) are safe and can be used continuously for many days (5 days in most trials). Complications of EVL in the acute setting are similar to those described above in the primary prophylaxis of variceal hemorrhage.

Other therapies. Despite an urgent endoscopic and/or pharmacological therapy, variceal bleeding cannot be controlled or recurs early in approximately 10–20% of patients, and other therapies should be implemented. An increased portal pressure, as measured by the hepatic venous pressure gradient (HVPG) within 24 h of presentation, predicts treatment failure (63,64).

Shunt therapy, either shunt surgery (in CTP class A patients) or TIPS, has proven clinical efficacy as salvage therapy for patients who fail to respond to endoscopic or pharmacological therapy (65,66). A surgical group has reported an almost universal control of bleeding and low mortality with the performance of portocaval shunt within 8 h after the onset of bleeding in unselected cirrhotic patients collected over a 30-year period (67). This approach has not been validated by other groups and is not widely practiced.

Balloon tamponade is very effective in controlling bleeding temporarily with immediate control of hemorrhage in >80% of patients (68). However, rebleeding after the balloons are deflated is high and its use is associated with potentially lethal complications, such as aspiration, migration, and necrosis/perforation of the esophagus with mortality rates as high as 20%. Therefore, it should be restricted to patients with uncontrollable bleeding for whom a more definitive therapy (e.g., TIPS) is planned within 24 h of placement. Airway protection is strongly recommended when balloon tamponade is used. Although the Sengstaken–Blakemore tube (with both an esophageal and a gastric balloon) is recommended for esophageal varices, the Linton tube, with a larger gastric balloon (and no esophageal balloon) is preferred for uncontrolled bleeding from fundal gastric varices. The use of self-expandable transient metallic stents to arrest uncontrollable acute variceal bleeding has been reported in a pilot study of 20 patients to be associated with bleeding cessation in all patients, and without complications after its removal 2–14 days later (69).

Compared with endoscopic variceal sclerotherapy or EVL, endoscopic variceal obturation with tissue adhesives, such as N-butyl-cyanoacrylate is more effective in treating acute fundal gastric variceal bleeding, with better control of initial hemorrhage, as well as lower rates of rebleeding (70,71). A relatively large prospective RCT compared endoscopic variceal obturation using N-butyl-cyanoacrylate with EVL in patients with acute gastric variceal hemorrhage and showed that control of active bleeding was similar in both groups, but that rebleeding over a follow-up period of 1.6–1.8 years occurred significantly less frequently in the endoscopic variceal obturation group (23 vs. 47%), with an average of only 1.5 sessions (range 1–3) (72). In an uncontrolled pilot study, 2-octyl cyanoacrylate, an agent approved for skin closure in the United States, has been described to be effective in achieving initial hemostasis and in preventing rebleeding from fundal varices (73).

Therapies under investigation. TIPS is currently considered to be a salvage therapy in the control of acute hemorrhage. However, a small randomized controlled trial of 116 consecutive cirrhotic patients with acute variceal bleeding who received a single session of sclerotherapy injection during urgent endoscopy, suggested that early TIPS placement (within 24 h of hemorrhage) was associated with significantly improved survival in high-risk patients (i.e., those with an HVPG >20 mm Hg) and may play an earlier role in treatment of acute variceal hemorrhage (74). Recently, the preliminary results of a multicenter RCT of early covered TIPS (performed within 72 h) in patients with CTP class B and active hemorrhage at endoscopy or in patients with CTP class C, showed a significant survival benefit in patients randomized to TIPS compared with those who received standard therapy (75). Therefore, it would seem that, in high-risk patients, early TIPS is a reasonable alternative; however, this cannot be recommended until more data are available (**Supplementary Table 3**).

The strategy in the diagnosis and management of patients with acute variceal hemorrhage is summarized in **Table 2**.

Prevention of recurrent variceal hemorrhage. Patients who survive an episode of acute variceal hemorrhage have a very high risk of rebleeding and death. The median rebleeding rate in untreated individuals is ~60% within 1–2 years of the index hemorrhage, with a mortality rate of 33% (9). Therefore, it is essential that patients who survive an episode of variceal hemorrhage be started on therapy to reduce the risk of hemorrhage recurrence, before discharge from the hospital. Patients who required shunt surgery/TIPS to control the acute episode do not require further preventive measures.

Table 2. Diagnosis and management strategy of patient with acute variceal hemorrhage

Diagnosis	Any of the following findings on upper endoscopy performed within 12 h of admission: Active bleeding from a varix *or* Stigmata of variceal hemorrhage (white nipple sign) *or* Presence of gastroesophageal varices without another source of hemorrhage
General management	Cautious transfusion of fluids and blood products, aiming to maintain a hemoglobin of ~8 g/dl
	Antibiotic prophylaxis (3–7 days) with: Ciprofloxacin 500 mg b.i.d. (p.o.) or 400 mg b.i.d. (i.v.) *or*
	Ceftriaxone 1 g/day (i.v.) particularly in facilities with known quinolone resistance and in patients with two or more of the following : malnutrition, ascites, encephalopathy, serum bilirubin >3 mg/dl
Specific initial management	Pharmacological therapy initiated as soon as diagnosis is suspected Octreotide 50 mcg i.v. bolus followed by continuous infusion 50 mcg/h (3–5 days) *and*
	Endoscopic therapy (ligation preferable) performed at time of diagnostic endoscopy (performed within 12 h of admission)
Rescue management	Considered in patients with bleeding esophageal varices who have failed pharmacological + endoscopic therapy or in patients with bleeding gastric fundal varices who have failed one endoscopic therapy: TIPS *or* Shunt therapy (CTP A patients where available)

b.i.d., twice a day, CTP, Child–Turcotte–Pugh; i.v., intravenous; p.o., orally; TIPS, transjugular intrahepatic portosystemic shunt.

Candidates. Candidates are patients who have recovered from an episode of acute variceal hemorrhage, have had no evidence of hemorrhage for at least 24 h, and in whom pharmacological therapy for the control of acute variceal hemorrhage has been or is being discontinued.

Accepted therapies. A combination of EVL plus pharmacological therapy is the most rational approach, because NSBBs will protect against rebleeding before variceal obliteration and will delay variceal recurrence. A recent meta-analysis showed that a combination of endoscopic (sclerotherapy or EVL) and drug therapy reduces overall and variceal rebleeding in cirrhosis more than either therapy alone (76). Two randomized trials show the superiority of EVL + NSBB vs. EVL alone (77,78). Rebleeding rates in these 2 trials were 23 and 14%, respectively, for EVL plus nadolol, which was significantly lower compared with 47 and 38%, respectively for the EVL arm alone. These results support the use of the combination of EVL + NSBB in preventing rebleeding (5,6). The combination EVL + NSBB is clearly recommended in patients who develop variceal hemorrhage (first or recurrent) while on EVL or a NSBB alone (**Supplementary Table 4**).

The lowest rate of variceal rebleeding (~10%) occurs in patients for whom portal pressure (assessed by HVPG) decreases significantly; i.e., in patients for whom pharmacological therapy (either a NSBB alone or NSBB plus nitrates) leads to a reduction in HVPG to < 12 mm Hg or a reduction of >20% from baseline (79,80). As suggested recently, perhaps the most rational therapy would be to adapt the different therapies for preventing variceal rebleeding in the context of HVPG response (81,82); however, this would require standardization of the HVPG technique, including the best timing to perform the repeat HVPG measurement (2) and confirmation of studies that suggest that the acute response to i.v. propranolol predicts the recurrence of variceal hemorrhage (83,84).

Treatment schedule. The treatment schedules for NSBB (i.e., propranolol, nadolol) and for EVL are the same as described above (see "Screening for gastroesophageal varices and primary prophylaxis of variceal hemorrhage") in the prevention of first variceal hemorrhage.

Side effects. The side effects of a combination of pharmacological plus endoscopic therapy are those of each therapy separately. However, given the greater risk of recurrent hemorrhage in 1–2 years compared with the risk of first hemorrhage (60 vs. 20%, respectively), a more aggressive therapy with a greater number of side effects is justifiable in the secondary prophylaxis of variceal hemorrhage.

Alternative therapies. The combination of a NSBB and ISMN has a synergistic portal pressure-reducing effect and could theoretically be more effective than NSBB alone. Only one study has performed a direct comparison between the combination of propranolol plus ISMN and propranolol alone (85). This study showed a benefit of combination therapy (33% vs. 41% rebleeding rate), but it was not statistically significant. Data collected from different RCTs showed lower median rebleeding rates (~33%) in patients treated with combined pharmacological therapy compared with rebleeding rates in patients treated with NSBB alone (~50%) (9). However, a recent RCT showed that variceal rebleeding in a group treated with NSBB + ISMN + EVL (18%) was significantly lower than in a group treated with NSBB + ISMN without EVL (32%) (86), but with rates similar to those described for combination NSBB + EVL (14% and 23%). Side effects are more frequent with the combination therapy (NSBB plus nitrates) than with NSBB alone, mostly in terms of headache and weakness (9), and have led to a higher rate of treatment discontinuation than with NSBB alone (85). It would seem reasonable that, if a patient is not a candidate for EVL, one would try to maximize portal pressure reduction by giving combination pharmacological therapy.

Shunt surgery is very effective in preventing rebleeding; however, it markedly increases the risk of HE, without any effect

on survival (34,87). Not surprisingly, recent meta-analyses of 11 trials that compared TIPS with endoscopic therapy showed similar results (88,89). That is, even though rebleeding is significantly less frequent with TIPS, post-treatment encephalopathy occurs significantly more often after TIPS, without differences in mortality. Furthermore, a recent trial showed that, even though TIPS was more effective than pharmacological (propranolol plus nitrates) therapy in preventing rebleeding, it was associated with more encephalopathy, identical survival, and higher costs (90). Therefore, TIPS should not be used as a first-line treatment, but rather as a rescue therapy for patients who have failed to respond to pharmacological plus endoscopic treatment.

Therapies not recommended for secondary prophylaxis. These therapies are summarized in (**Supplementary Table 4**). Although NSBB alone and sclerotherapy reduce variceal rebleeding and death rates in treated controls compared with untreated controls, rebleeding rates of 42–43% with these therapies are still unacceptably high in treated patients (9,34,91) and therefore, these therapies are no longer recommended. The pharmacological therapy of choice in the prevention of variceal rebleeding is the combination of a NSBB and a nitrate.

Even though EVL alone is clearly superior to sclerotherapy (91,92) and equivalent to a combination of β-blockers plus nitrates (93), the combination of EVL plus pharmacological therapy is superior to EVL alone and, as mentioned above, should be preferred in the secondary prophylaxis of variceal hemorrhage.

Trials suggest that EVL is followed by a higher rate of variceal recurrence in comparison with sclerotherapy. Even though meta-analysis shows no significant difference in variceal recurrence between treatments (91), the efficacy of the combination of EVL plus sclerotherapy compared with EVL alone in reducing variceal recurrence has been explored. A recent meta-analysis of seven such trials showed that the combination of EVL and sclerotherapy offers no advantage over EVL alone regarding the prevention of rebleeding or reduction of mortality and is associated with a higher complication rate (94). Therefore, the evidence accumulated so far should discourage the use of the combination of EVL plus sclerotherapy.

The strategy in the prevention of recurrent variceal hemorrhage is summarized in **Table 3**.

Treatment of SBP

The most common infections in cirrhosis are the so-called "spontaneous" infections, namely SBP, spontaneous bacterial empyema, and spontaneous bacteremia, which share pathogenic mechanisms and management. They are called spontaneous because there is no obvious source of bacteria that would explain their spread to ascites, pleural fluid or blood.

SBP occurs in 10–20% of hospitalized patients with cirrhosis and ascites, mainly in those with severe liver disease. When first described, its mortality rate exceeded 80%; however, with early recognition of the disease and prompt and appropriate antibiotic therapy, in-hospital mortality from an episode of SBP has been reduced to approximately 10–20% (95). Early diagnosis is a key issue in the management of SBP. It is recommended that a diagnostic paracentesis should be performed in any patient (i) admitted to the hospital with cirrhosis and ascites; (ii) with cirrhosis and ascites who develops compatible symptoms or signs (abdominal pain or tenderness on palpation, fever, or chills); and (iii) with cirrhosis and ascites and with worsening renal or liver function (57).

The diagnosis is established with an ascites PMN (polymorphonuclear) cell count of $>250/mm^3$. It has been suggested that a faster, inexpensive method for diagnosing SBP is through the use of reagent strips similar to those used in the rapid diagnosis of urinary tract infections; however, this practice cannot be recommended as a recent review showed a false negative rate ranging between 0 and 50% (96). Moreover, in the largest series of patients with SBP, using the Multistix 8 SG (Bayer Pharma SAS, Puteaux, France), the false negative rate was unacceptably high at 55% (97). If a traumatic or bloody tap is suspected (i.e., ascitic red blood cells >10,000), care should be taken to subtract 1 PMN for every 250 red blood cells. Separate and simultaneous blood cultures should be collected, as 50% of all SBP cases are associated with bacteremia. In patients with hepatic hydrothorax in whom an infection is suspected and in whom SBP has been ruled out, a diagnostic thoracentesis should be performed as spontaneous bacterial empyema may occur in the absence of ascites or SBP (98). To increase the sensitivity of the bacteriological culture, ascites and/or pleural fluid should be inoculated at the patient's bedside into blood culture bottles (57,99). Even with these careful measures, 30–50% of the time, the causative organism is not isolated (57,100).

Table 3. Management strategy in the prevention of recurrent variceal hemorrhage (secondary prophylaxis)

First-line therapy	Nonselective β-blockers (propranolol, nadolol)	Start propranolol (20 mg b.i.d.) or nadolol (20 mg q.d.) Titrate to maximum tolerable dosage or a heart rate of 55–60 b.p.m. No need for repeat endoscopy
	and	
	Endoscopic variceal ligation	Ligate every 1–2 weeks until variceal obliteration First surveillance endoscopy 1–3 months after obliteration, then every 6–12 months
Second-line therapy (if combined pharmacologic + endoscopic treatment has failed)	TIPS *or* Shunt surgery (CTP class A patients, where available)	

b.i.d., twice a day; b.p.m., beats/min; CTP, Child–Turcotte–Pugh; TIPS, transjugular intrahepatic portosystemic shunt; q.d., once daily.

The following management for spontaneous infections is based on evidence in the literature and results of a consensus conference on the diagnosis and management of SBP sponsored by the International Ascites Club (57).

Treatment of the acute infection. Therapies are summarized in **Supplementary Table 5**. *Accepted therapies*. Once a diagnosis of SBP is established, antibiotic therapy should be initiated, before obtaining the results of ascites or blood cultures. The antibiotic that has been most widely used is i.v. cefotaxime, which leads to SBP resolution in ~90% of the patients (101–103); although in recent studies, cefotaxime has been successful in only 60–70% of the episodes (104), with a success rate as low as 44% in nosocomial SBP (105) because of the presence of multi-drug-resistant organisms. Other third-generation cephalosporins, such as ceftriaxone, have been shown to be as effective as cefotaxime in uncontrolled studies (106,107). In a RCT, the combination of i.v. amoxicillin and clavulanic acid was shown to be as effective and safe as i.v. cefotaxime in the treatment of SBP (108); however as for cefotaxime, lower efficacy and a high rate of antibiotic resistance has been shown recently (109), particularly in nosocomial infections (105). Patients who develop SBP on prophylactic quinolones respond as well to cefotaxime as patients not on prophylaxis (110).

Cefotaxime is on the VA National Formulary but may be restricted at the facility or VISN (Veterans Integrated Service Network) level. However, other third-generation cephalosporins, such as ceftriaxone, are available and should be equally effective. The i.v. preparation of amoxicillin and clavulanic acid is unavailable in the United States but another β-lactam/β-lactamase combination, such as ampicillin/sulbactam, would have a similar spectrum of activity. The susceptibility patterns of individual practice settings should be taken into consideration when selecting the antibiotic for SBP.

Intravenous albumin has been shown to be an important adjuvant to antibiotic therapy in patients with SBP. A RCT comparing cefotaxime plus albumin with cefotaxime alone showed that patients who received albumin had significantly lower rates of renal dysfunction (10 vs. 3%), in-hospital mortality rate (10 vs. 29%), and a 3-month mortality (22 vs. 41%) (111). The rationale behind albumin administration is to improve the decreased effective arterial blood volume that results from SBP and that leads to renal dysfunction, which is the main cause of death in patients with SBP, although albumin may also act by binding endotoxin and reducing cytokine and nitric oxide levels (112). Albumin should be administered to patients at a high risk of developing renal dysfunction, i.e., those with a serum bilirubin >4 mg/dl and evidence of renal impairment at baseline (blood urea nitrogen >30 mg/dl and/or creatinine >1.0 mg/dl) (111,113,114). In fact, a recent study showed that patients with "low-risk" SBP (i.e., those with serum creatinine < 1 mg/dl and urea < 30 mg/dl), who represent approximately half of the patients with SBP, have a good outcome that does not improve with i.v. albumin administration (115).

Dose and duration. The dose of cefotaxime used in clinical trials ranges between 2 g i.v. every 4 h and 2 g i.v. every 12 h. One randomized study compared two different dose schedules of cefotaxime (2 g every 6 h vs. 2 g every 12 h) and showed similar rates of SBP resolution and patient survival with both schedules (103). Therefore, the recommended dose of cefotaxime is 2 g i.v. every 12 h. Ceftriaxone has been used at a dose of 1–2 g i.v. every 24 h and ceftazidime at a dose of 1 g i.v. every 12–24 h. The only study assessing the combination of amoxicillin–clavulanic acid used a dose of 1–0.2 g i.v. every 8 h (108).

A control paracentesis performed 48 h after starting therapy is recommended to assess the response to therapy (57). If a clinical improvement is obvious, this control paracentesis may not be necessary. If the PMN count has not decreased by at least 25% from baseline, antibiotic coverage should be broadened and investigations to rule out secondary peritonitis may be initiated depending on the microorganism isolated (if any) and clinical status.

Antibiotic treatment can be safely discontinued after the ascites PMN count decreases to below 250/mm^3, which occurs in a mean period of 5 days (116). In a comparative study, a 5-day therapy with cefotaxime was as effective as a 10-day therapy (102) and therefore, it has been recommended that antibiotic therapy should be maintained for a minimum of 5 days (57). However, given that the median time to SBP resolution in controlled trials is 8 days, this latter duration of 8 days is probably preferable (117). It is reasonable to consider switching to an oral antibiotic after 48 h of therapy in patients who show clinical improvement (108,118,119), as this will allow for an early discharge with lower costs (119).

The dose of i.v. albumin as adjuvant to antibiotic therapy that has been used is arbitrary: 1.5 g/kg of body weight during the first 6 h, followed by 1 g/kg on day 3 (111), although it would seem rational to tailor the dose to improvement (or lack of improvement) in serum creatinine.

Side effects. The antibiotics recommended above have been associated with very few side effects and no renal toxicity. Cirrhotic patients have an increased propensity for developing aminoglycoside-induced nephrotoxicity and therefore, aminoglycosides should be considered as a last resort in the therapy of infections in cirrhotic patients (120).

Alternative therapies. In patients with community-acquired, uncomplicated SBP (i.e., no renal dysfunction or encephalopathy), an RCT showed that oral ofloxacin, a fully absorbed quinolone, is a good alternative (121). Although theoretically other widely biovailable quinolones, such as ciprofloxacin and levofloxacin, could be used orally, they have not been investigated in clinical trials and the rising prevalence of quinolone-resistant organisms limits their applicability.

The use of extended spectrum antibiotics (e.g., carbapenems, piperacillin/tazobactam) as initial empirical therapy should be considered in patients with nosocomial SBP (105).

Therapies that should not be used. As mentioned above, aminoglycosides should be avoided in cirrhosis (120). As large volume paracentesis (LVP) can be associated with vasodilata-

Table 4. Diagnosis and management strategy in spontaneous bacterial peritonitis (SBP)

Diagnosis	Consider SBP and perform diagnostic paracentesis if: Symptoms/signs (abdominal pain, fever, chills) Patient is in emergency room or admitted Worsening renal function or encephalopathy SBP present if ascites PMN count >250 cells/μl (if fluid bloody, subtract 1 PMN per 250 RBC/μl)
General management	Avoid therapeutic paracenteses during active infection Intravenous albumin (1 g/kg of body weight) if BUN >30 mg/dl, creatinine >1 mg/dl, bilirubin >4 mg/dl; repeat at day 3 if renal dysfunction persists Avoid aminoglycosides
Specific management	Cefotaxime (2 g i.v. every 12 h) *or*
	Ceftriaxone (2 g every 24 h) *or*
	Ampicillin/sulbactam (2g/1 g i.v. every 6 h)
Follow-up	Continue therapy for 7 days Repeat diagnostic paracentesis at day 2 If ascites PMN count decreases by at least 25% at day 2, intravenous therapy can be switched to oral therapy (quinolone such as ciprofloxacin or levofloxacin 250 mg p.o. b.i.d.) to complete 7 days of therapy

b.i.d., twice a day; BUN, blood urea nitrogen; i.v., intravenous; PMN, polymorphonuclear (neutrophil) cell count; p.o., orally; RBC, red blood cell count.

tion (122) and theoretically can contribute to precipitating renal dysfunction in patients with SBP (who are already predisposed because of the presence of a bacterial infection), the performance of LVP should be delayed until after the resolution of SBP. Similarly, medications that can potentially decrease effective intravascular volume, such as diuretics, should be avoided during acute infection.

The strategy in the diagnosis and management of SBP is summarized in **Table 4**.

Prevention of recurrent SBP. In patients who survive an episode of SBP, the 1-year cumulative recurrence rate is high, at ~70%. Therefore, it is essential that patients who have recovered from an episode of SBP be started on antibiotic prophylaxis to prevent recurrence before they are discharged from the hospital. Therapies are summarized in **Supplementary Table 6.**

Accepted therapies. In a double-blind, placebo-controlled study, continuous oral norfloxacin was shown to significantly decrease the 1-year probability of developing recurrent SBP from 68% (in the placebo group) to 20% (in the norfloxacin group) (123). The reduction in SBP caused by gram-negative organisms was even more dramatic, from 60% to 3%. Prophylactic therapy was discontinued after 6 months of therapy and therefore, the effect on survival was not evaluable. As the median survival of patients who develop SBP is ~9 months (124), antibiotic prophylaxis in this setting does not imply an inordinately prolonged period of administration.

Dose and duration. The dose of norfloxacin used in studies of secondary prophylaxis of SBP is 400 mg by mouth (po) q.d. (123,125). Prophylaxis should be continued until liver transplantation or until the disappearance of ascites (likely to occur in alcoholics who stop alcohol ingestion).

Contraindications/side effects. The development of infections by quinolone-resistant organisms is the main complication of long-term norfloxacin prophylaxis. In a study carried out in a large number of cirrhotic patients hospitalized with an infection, gram-negative bacteria isolated from patients on long-term quinolone prophylaxis were significantly more likely to be not only quinolone-resistant but also trimethoprim/sulfamethoxazole-resistant compared with those of patients not on prophylaxis (100).

Alternative therapies. Norfloxacin is not on the VA National Formulary; however, other quinolones with a similar spectrum, such as ciprofloxacin or levofloxacin, could theoretically be used instead; the latter with the added advantage of gram-positive coverage.

Although a study has described that ciprofloxacin administered weekly (750 mg/week) can prevent SBP (126), it had methodological problems and, additionally, the use of intermittent ciprofloxacin has been related to a higher occurrence of quinolone-resistant organisms in stool specimens (127). In a more recent RCT, daily norfloxacin (400 mg/day) was more effective than weekly rufloxacin (400 mg/week) in preventing recurrent SBP due to *Enterobacteriaceae* (125). Therefore, quinolones administered weekly cannot be recommended (**Supplementary Table 6**). Another trial using oral trimethoprim/sulfamethoxazole (one double-strength tablet daily, 5 days per week) (128) also showed efficacy in preventing SBP. However, this trial included patients with an earlier history of SBP and those who had never experienced an episode of SBP, hindering the interpretation of these results. Nevertheless, in patients who are unable to take quinolones, this alternative is reasonable.

The strategy in the prevention of recurrent SBP is summarized in **Table 5**.

Table 5. Management strategy in the prevention of recurrent SBP

Recommended therapy	Oral norfloxacin 400 mg p.o. q.d. (preferred) *or*
	Oral ciprofloxacin 250–500 mg q.d.[a] *or*
	Oral levofloxacin 250 mg q.d.[a]
Alternative therapy	TMP-SMX 1 double-strength tablet p.o. q.d. (Patients who develop quinolone-resistant organisms may also have resistance to TMP-SMX)
Duration	Prophylaxis should be continued until the disappearance of ascites or until liver transplantation

p.o., orally; SBP, spontaneous bacterial peritonitis; TMP-SMX, trimethoprim-sulfamethoxazole; q.d., once daily.
[a]Empirical doses.

Treatment 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 ~30% (3). Once ascites develops, the 1-year survival rate is ~50% compared with the 1-year survival rate of >90% in patients with compensated cirrhosis (3,129–131). Prognosis is particularly poor in patients who develop refractory ascites (132) or HRS (133).

Treatment of ascites has not resulted in significant improvements in survival. However, treating ascites is important, not only because it improves the quality of life of the cirrhotic patient but also because SBP, a lethal complication of cirrhosis, does not occur in the absence of ascites. Patients go through a sequence of diuretic-responsive ascites, followed by refractory ascites, and then HRS.

General measures. Contrary to the treatment of heart failure, in which achieving a negative sodium and water balance implies a certain urgency given the risk/presence of pulmonary edema, cirrhotic ascites therapy is not an emergency as the risk of death is not implicit unless the fluid becomes infected. Therefore, treatment of patients with cirrhosis and ascites is based on oral (not i.v.) diuretics in a stepwise slow manner and should only be initiated in a "stable" cirrhotic patient, i.e., in a patient for whom complications, such as GI hemorrhage, bacterial infection, and renal dysfunction are absent or have resolved. In a patient with tense ascites who experiences abdominal discomfort and/or respiratory distress, a single LVP can be performed before or concomitant to starting diuretic therapy.

As mentioned above, NSAIDs, including aspirin, blunt the natriuretic effect of diuretics and should be avoided in cirrhotic patients with ascites (47,48). Although selective cyclooxygenase-2 inhibitors have not been shown to impair natriuresis or to induce renal dysfunction in cirrhotic rats (134), preliminary data in patients indicate that celecoxib may be related to a decrease in renal function (135) and therefore, cyclooxygenase-2 inhibitor use should also be avoided until more clinical data become available.

Long-term antibiotic prophylaxis in the prevention of the first episode of SBP (i.e., primary prophylaxis) in patients with cirrhosis and ascites is controversial. Given the risk of developing antibiotic-resistant organisms (100,136), the long-term use of prophylactic antibiotics should be restricted to the sub-population of patients at the highest risk of developing SBP. Low (<1–1.5 g/dl) total protein levels in ascites are useful for determining the susceptibility of developing SBP (137); however, the probability of developing SBP in unselected patients with low ascites protein level is still low (9–14%) in control groups of prospective RCTs (138,139) and does not justify prophylaxis in all of them. In a recent placebo-controlled study that selected patients with low (<1.5 g/l) ascites protein who also had advanced liver failure (CTP score ≥9 and serum bilirubin ≥3 mg/dl) or renal dysfunction (serum creatinine ≥1.2 mg/dl, blood urea nitrogen level ≥25 mg/dl, or serum sodium level ≤130 mEq/l) norfloxacin at a dose of 400 mg p.o. q.d. was associated with a reduction in the 1-year probability of SBP (7 vs. 61%), HRS (28 vs. 41%), and 3-month mortality rate (140). It must be noted that all patients included in the study were initially hospitalized, less than half of the patients with low ascites protein met entry criteria, and the survival benefit did not extend to 1 year. However, it is in this selected sub-population of patients with cirrhosis and ascites, that prophylaxis with norfloxacin (400 mg po q.d.) should be undertaken. Another placebo-controlled study that targeted patients with low ascites protein and low risk of developing SBP (serum bilirubin <3.2, platelet count <98,000) showed a tendency for lower SBP rate (4 vs. 14%, $P=0.16$) and lower mortality (12 vs. 28%, $P=0.08$) in patients treated with oral ciprofloxacin compared with placebo (139); however, the study is underpowered and no firm conclusions can be drawn from it.

Management of uncomplicated ascites. *Candidates*. Candidates are cirrhotic patients with ascites not associated with infection or renal dysfunction (141). Recommendations for uncomplicated cirrhotic ascites apply to patients with uncomplicated hepatic hydrothorax (**Supplementary Table 7**). Diuretics can lead to a reduction in intravascular volume and to renal dysfunction and should not be initiated in patients with rising creatinine. In addition, diuretics should not be initiated in patients with concomitant complications of cirrhosis known to be associated with decreased effective arterial blood volume, such as variceal hemorrhage or SBP.

Accepted therapies. Sodium restriction is recommended for all cirrhotic patients with ascites. Although dietary sodium should be restricted to levels lower than urinary sodium excretion, sodium restriction to 88 mEq/day (i.e., 2 g of sodium per day or 5.2 g of dietary salt per day, considering that 1 mEq of sodium = 23 mg of sodium = 58.5 mg of dietary salt) is a realistic goal, particularly in an outpatient setting. Patients with a baseline urinary sodium excretion >50 mEq/day may respond to salt restriction alone. Most patients will require the addition

of diuretics. Clinicians should be cautious about the nutritional status of patients on sodium restriction, as the non-palatability of a salt-restricted diet may lead to an inadequate food intake. In these cases, liberalizing sodium restriction and adding diuretics is preferable to further impairment of the already compromised nutrition of the cirrhotic patient with ascites.

Spironolactone is the diuretic of choice. Even though loop diuretics, such as furosemide, are more potent natriuretic agents, randomized controlled trials have shown that spironolactone is significantly more effective than furosemide alone in the treatment of cirrhotic ascites (142,143). Diuretic therapy can be initiated with spironolactone alone or with spironolactone plus furosemide. Both therapies are equally effective and can be used; however, dose adjustments are needed more frequently in patients for whom treatment is initiated using combination therapy because of more rapid increases in blood urea nitrogen and/or decreases in serum sodium (142,144). Therefore, it is preferable to initiate therapy with spironolactone alone. In patients who develop renal dysfunction (elevation in creatinine >50% to creatinine >1.5 g/dl), diuretics should be temporarily discontinued and restarted at a lower dose after creatinine returns to baseline. Patients who develop hyponatremia (serum sodium <130 mEq/l) while on diuretics should be managed with fluid restriction and a decrease in the dose of diuretics. There is no evidence that other diuretics, such as metolazone, thiazides, or torsemide, offer an advantage over spironolactone and furosemide.

LVP with i.v. albumin has been shown to be as effective as standard therapy with diuretics but with a significantly faster resolution and the same or a lower rate of complications (145–147). As this therapy is significantly more expensive and requires more resources than the administration of diuretics, it is reserved for patients not responding to diuretics (see below). However, in patients with tense ascites in whom other complications are absent or have been resolved, it is reasonable to initiate therapy with total paracentesis (i.e., removal of the maximal amount of ascites) with concomitant albumin infusion followed by the administration of diuretics (141). This therapy will accelerate the amelioration of symptoms secondary to abdominal distension and, in those hospitalized, will accelerate the patient's discharge from the hospital.

Dose and duration. The preferred diuretic schedule is to initiate therapy with spironolactone alone at a single daily dose of 50–100 mg and to increase it in a stepwise manner to a maximum of 400 mg/day. As the effect of spironolactone takes several days to develop, it can be administered in a single daily dose and the dose should be adjusted only every 3–4 days. If weight loss is not optimal (<2 lb/week) or if hyperkalemia develops, furosemide is then added at an initial single daily dose of 20–40 mg and increased in a stepwise manner to a maximum of 160 mg/day. To minimize complications, the maximal weight loss in patients without edema is 1 lb/day (0.5 kg/day), whereas a weight loss of 2 lb/day (1 kg/day) is allowed in patients with edema.

Side effects. Common complications of diuretic therapy include renal impairment due to intravascular volume depletion (25%), hyponatremia (28%), and HE (26%) (145,146,148). Development of these side effects warrants diuretic dose reduction or discontinuation. Spironolactone is often associated with adverse events related to its anti-androgenic activity, mainly painful gynecomastia.

Alternative therapies. Potassium canrenoate, one of the major metabolites of spironolactone, has a comparable diuretic effect and a lower anti-androgenic activity and could be used in cases in which gynecomastia and mastalgia are side effects of spironolactone therapy. However, this drug is not available in the United States. Amiloride, another potassium-sparing diuretic, does not produce gynecomastia and is recommended in patients with intolerable painful gynecomastia, but it has a significantly lower natriuretic effect than spironolactone (149). Amiloride is used at an initial dose of 20 mg/day and can be increased to 60 mg/day. For patients whose natriuretic response on amiloride is suboptimal, it may be worthwhile to attempt a retreatment with spironolactone.

Therapies that should not be used. Furosemide alone should not be used. Two randomized trials have shown significantly lower efficacy of the loop diuretic furosemide used alone compared with spironolactone alone (143) or with the combination of spironolactone/furosemide (142). When furosemide is used alone, sodium that is not re-absorbed in the loop of Henle is taken up by the distal and collecting tubules because of the hyperaldosteronism present in most cirrhotic patients with ascites. Therefore, furosemide should not be used as the sole agent in the treatment of cirrhotic ascites.

As mentioned earlier, ascites therapy is not an emergency as the risk of death is not implicit unless the fluid becomes infected. Therefore, the use of i.v. diuretics is not warranted as it has the potential to lead to volume depletion and renal dysfunction (**Supplementary Table 7**).

Therapies under investigation. Clonidine is a centrally acting α2-agonist with sympathicolytic activity in cirrhosis. In a single-center randomized double-blind placebo-controlled RCT in patients with uncomplicated ascites and an activated sympathetic nervous system (as defined by serum norepinephrine levels >300 pg/ml), clonidine was associated with a significantly lower number of re-admissions for ascites and a longer time to re-admission, as well as lower requirements of LVP, spironolactone, and furosemide (150). These promising results require further investigation before clonidine can be widely recommended.

In addition to an increasing free water excretion, selective inhibition of arginine vasopressin type 2 receptors (V2 receptor antagonists) have a natriuretic effect (151–153). A phase II study of satavaptan, a V2 receptor antagonist, in 148 patients with cirrhosis and ascites without hyponatremia showed a dose-related increase in urine volume and a dose-related decrease in body weight without changes in serum creatinine (154). Further analysis is required (**Supplementary Table 7**).

Table 6. Management strategy in uncomplicated ascites

General management	Treat ascites once other complications have been treated Avoid NSAIDs Norfloxacin prophylaxis (400 mg p.o. q.d.) in patients with an ascites protein level of <1.5 g/dl, impaired renal function (serum creatinine level ≥1.2 mg/dl, BUN ≥25 mg/dl, serum sodium level ≤130 mEq/l), or severe liver failure (CTP score ≥9 points with serum bilirubin level ≥3 mg/dl)	
Specific management	Salt restriction	1–2 g/day Liberalize if restriction results in poor food intake
	Diuretics	Spironolactone based: Spironolactone alone (start at 50–100 mg q.d., single morning dose) *or* Spironolactone (50–100 mg q.d.) + furosemide (start at 20–40 mg q.d., single morning dose)
	LVP	Use as initial therapy only in patients with tense ascites; administer intravenous albumin (6–8 g/l of ascites removed)
Follow-up and goals	Adjustment of diuretic dosage should be performed every 4–7 days	
	Patient should be weighed at least weekly and BUN, creatinine, and electrolytes measured every 1–2 weeks while adjusting dosage	
	Double dosage of diuretics if: Weight loss <4 lb (2 kg) a week *and* BUN, creatinine, and electrolytes are stable	
	Halve the dosage of diuretics or discontinue if: Weight loss ≥1 lb (0.5 kg/day) *or* if there are abnormalities in BUN, creatinine, or electrolytes	
	Maximum diuretic dosage is spironolactone (400 mg q.d.) and furosemide (160 mg q.d.)	

BUN, blood urea nitrogen; CTP, Child–Turcotte–Pugh; i.v., intravenous; LVP, large volume paracentesis; NSAIDs, nonsteroidal anti-inflammatory drugs; p.o., orally; q.d., once daily.

The strategy in the management of ascites is summarized in **Table 6**.

Treatment of hyponatremia in patients with cirrhosis and ascites. Dilutional hyponatremia, mainly attributable to impaired free water excretion through the non-osmotic release of vasopressin, is a complication that occurs in ~20% of patients with cirrhosis and ascites (155). It is usually asymptomatic because it develops slowly. However, recent data suggest that hyponatremia is a risk factor for the development of HE and is associated with a poor quality of life (156). Hyponatremia is an independent predictor of death in patients with decompensated cirrhosis (157,158).

Candidates. Candidates are patients with cirrhosis and ascites who have a serum sodium level below 130 mEq/l.

Accepted therapies. Besides diuretic discontinuation, the most commonly accepted method for the management of hyponatremia is fluid restriction of approximately 1–1.5 l/day; however, the efficacy of this approach is limited (**Supplementary Table 8**).

Therapies that should not be used. Hypertonic saline solution should not be used in these patients as hyponatremia is chronic and is dilutional, and administration of sodium will only worsen ascites and peripheral edema (**Supplementary Table 8**).

Therapies under investigation. Anti-diuretic hormone release in cirrhosis results from a decrease in effective arterial blood volume; therefore, volume expansion with albumin is a reasonable alternative. In small series and a small RCT (159), serum sodium improved significantly in patients who received i.v. albumin. Thus, it seems that albumin may be useful in the short term, although long-term use would seem impractical and expensive.

Several randomized controlled trials suggest that selective inhibition of arginine vasopressin type 2 receptors (V2 receptor antagonists), which increase water re-absorption in the distal renal nephron, are useful in ameliorating hyponatremia. Short-term placebo-controlled trials of VPA-985 (lixivaptan) showed a dose-dependent improvement in serum sodium (153,160), with the main complication being dehydration with the highest dose (250 mg b.i.d.) (160). Similarly, a large multicenter trial in which patients were randomly assigned to placebo ($n = 223$) or oral tolvaptan ($n = 225$) at a dose of 15 mg daily showed that tolvaptan, used for 30 days in patients with euvolemic or hypervolemic hyponatremia (of whom 63 had cirrhosis), was associated with a rapid improvement in serum sodium and significant weight loss compared with placebo (161). Finally, data from a large multicenter trial of satavaptan in patients with cirrhosis, ascites, and hyponatremia indicated that short-term (14 days) use was effective in correcting serum sodium levels in >80% of the patients who received 25 mg/day (162). V2 receptor antagonists are not yet approved in the United States for patients with cirrhosis and ascites, and their efficacy and safety should be further evaluated in long-term studies. An i.v. V1–V2 receptor

antagonist, conivaptan, is approved by the US FDA (Food and Drug Administration) for the treatment of euvolemic hyponatremia in hospitalized patients; however, V1-receptor antagonism may have a deleterious hemodynamic effect in cirrhosis (**Supplementary Table 8**).

Treatment of refractory ascites. In a prospective study, refractory ascites developed in 17% of patients with cirrhosis and ascites at 5 years (163). Refractory ascites assumes either diuretic-resistant ascites (ascites that is not eliminated even with maximal diuretic therapy) or diuretic-intractable ascites (ascites that is not eliminated because maximal doses of diuretics cannot be attained given the development of diuretic-induced complications, such as HE, renal dysfunction, and/or electrolyte abnormalities) (164). However, before diagnosing refractory ascites, it is necessary to ascertain whether the patient has adhered to the prescribed sodium-restricted diet and has refrained from using NASIDs, which blunt the response to diuretics. Non-adherence to dietary sodium restriction and/or diuretics should be suspected if patients fail to lose weight despite an adequate 24-h urine sodium excretion (>50 mEq/l or greater than daily sodium intake).

Candidates. Candidates are cirrhotic patients with ascites who fail to respond to diuretics (despite adherence to diet and drugs) or who present complications, which preclude the administration of adequate doses of these drugs. Recommendations for patients with refractory ascites apply to patients with refractory hepatic hydrothorax, although these patients should undergo an in-hospital careful diuretic therapy before the hydrothorax is considered refractory (**Supplementary Table 9**).

Accepted therapy. Presently, serial LVPs are the first-line therapies used for patients with refractory ascites, adding albumin if >5 l are removed at once. To increase the time between paracenteses, patients should continue on maximally tolerated diuretic dose provided that the urinary sodium is >30 mEq/l. Otherwise, diuretics can be discontinued (141).

Although a single 5-l LVP without albumin replacement causes no disturbances in systemic and renal hemodynamics (165), daily LVP without i.v. albumin is associated with hyponatremia and renal impairment, complications that can be prevented with the concomitant use of i.v. albumin (166), The need for concomitant administration of i.v. albumin was further shown in a trial comparing albumin with synthetic plasma volume expanders. In this trial, albumin was shown to be associated with a lower incidence of post-paracentesis circulatory dysfunction (PCD) (18%) compared with synthetic plasma expanders (38% for polygeline and 34% for dextran-70) (167). PCD is defined as an increase in plasma-renin activity on the sixth day after paracentesis (indicating a decreased effective arterial blood volume). PCD is associated with a faster re-accumulation of ascites and a significantly shorter median survival time (10 vs. 17 months in patients without PCD).

Recommended treatment schedule. As LVP is a local therapy that does not act on any of the mechanisms that lead to the formation of ascites, recurrence of ascites is the rule rather than the exception. The frequency of LVPs is determined by the rate of ascites re-accumulation and, ultimately, by the need to relieve the patient's discomfort. In turn, the rate of ascites re-accumulation depends largely on the patient's compliance with salt restriction and use of diuretics.

In patients in whom daily LVPs are being performed or in whom >5 l LVPs are removed, albumin should be administered at a dose of 6–8 g of albumin i.v. per liter of ascites removed (141).

Contraindications/side effects. As mentioned above, a complication of LVP, particularly without the concomitant administration of albumin, is PCD, which is characterized by a significant increase in plasma-renin activity after paracentesis. PCD seems to be secondary to a worsening in the vasodilatory state (122). Therefore, LVP should not be performed in the setting of conditions that could potentially worsen the vasodilatory state of cirrhosis, such as SBP.

Alternative therapies. TIPS is considered to be a second-line therapy for refractory ascites. This recommendation is based on the results of two meta-analyses of five studies comparing LVP plus albumin with TIPS (168,169), which showed that, as expected, recurrence of ascites after LVP was significantly greater in patients randomized to LVP plus albumin, but no differences in mortality were observed. However, there was a higher rate of severe encephalopathy and a higher cost in the group randomized to TIPS. However, a subsequent meta-analysis of four randomized controlled trials, including individual patient data indicated a significantly higher transplant-free survival rate in the TIPS group vs. the LVP group ($P=0.035$), without differences in encephalopathy (170). Although LVP is still a reasonable initial approach to the patient with refractory ascites, TIPS should be considered earlier on than recommended earlier (141), e.g., in those who require >1–2 LVP/month. TIPS should also be considered in patients in whom ascites is loculated. Although studies on TIPS for refractory ascites were carried out using uncovered stents, the use of covered stents is recommended currently, because of the lower rate of shunt dysfunction and a potentially lower risk of encephalopathy and mortality (171). Patients with serum bilirubin >3 mg/dl, a CTP score >11, age >70 years, and/or evidence of heart failure are at a high risk of death or shunt dysfunction, and TIPS should be avoided in these patients (141,172) (**Supplementary Table 9**).

Peritoneo-venous shunting (PVS) (e.g., LeVeen or Denver shunts) is an alternative to LVP plus albumin. In two randomized trials comparing LVP plus albumin with PVS, both procedures were shown to be equally effective, to have a similar rate of complications, and to have a comparable survival rate (166,173). Owing to its high obstruction rate, PVS required longer admissions for shunt revision or for the management of other more serious complications. The use of PVS had been practically abandoned, because it was considered that it would complicate liver transplant surgery given its ability to produce peritoneal adhesions. However, a recent case series of pre-transplant patients showed that

Table 7. Management strategy for refractory ascites

Definitions	Ascites that is not eliminated even with maximum diuretic therapy
	Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic-induced complications
Recommended therapy	Total paracentesis + i.v. albumin (6–8 g/l of ascites removed)
	If <5 l of ascites is removed, a synthetic plasma volume expander may be used instead of albumin
	Continue with salt restriction and diuretic therapy as tolerated
Alternative therapy	TIPS for patients who require frequent paracenteses (every 1–2 weeks) and whose CTP score is ≤11
	Peritoneovenous shunt for patients who are not TIPS or transplant candidates

CTP, Child–Turcotte–Pugh; i.v., intravenous; TIPS, transjugular intrahepatic portosystemic shunt.

PVS is not associated with additional surgical complications (174) and could therefore, be considered in non-TIPS transplant candidates.

Therapies that should not be used. In patients with refractory hepatic hydrothorax, the insertion of a chest tube should be avoided as it will lead to massive fluid losses, a further depletion of the intravascular effective volume and to renal dysfunction and has also been associated with infection and high mortality (175).

Therapies under investigation. These therapies are summarized in (**Supplementary Table 9**). Clonidine is a centrally acting α2-agonist with sympathicolytic activity in cirrhosis. In a small pilot RCT, the administration of clonidine, at a dose of 0.075 mg po b.i.d., plus spironolactone to patients with refractory ascites increased natriuresis and significantly decreased plasma norepinephrine and aldosterone levels, as well as plasma-renin activity. In a mean follow-up of 10.5 months and compared with patients who were treated with LVP plus albumin ($n = 10$), patients who received clonidine plus spironolactone ($n = 10$) had less re-admissions for ascites, a longer time to ascites re-accumulation, and decreased spironolactone requirements (176).

As mentioned earlier, V2 receptor antagonists have a natriuretic effect, and in a randomized double-blind placebo-controlled study in 151 patients treated with LVP plus spironolactone, satavaptan was associated with a longer time to recurrence of ascites requiring LVP and a significantly lower number of paracenteses (177).

Vasodilatation is one of the main mechanisms in the pathogenesis of ascites. In small studies that were carried out in non-azotemic patients with cirrhosis and ascites, the short-term oral administration of midodrine, an α-adrenergic vasoconstrictor, is associated with a significant improvement in systemic hemodynamics and consequently with decreases in plasma-renin activity and plasma aldosterone levels and increases in urinary sodium and creatinine clearance (178,179). Similar beneficial systemic hemodynamic and renal effects have been observed with the acute administration of terlipressin to patients with cirrhosis and ascites (180). The longer-term (4 week) administration of midodrine plus octreotide in small numbers of patients with refractory ascites has been associated with decreased plasma-renin activity and decreased ascites accumulation (181,182). The efficacy of vasoconstrictors in the treatment of ascites remains to be confirmed in larger randomized trials, particularly given the potential deleterious effects on liver function observed with the combination midodrine plus octreotide (182).

Vasodilatation has also been implicated in the pathogenesis of PCD (122). Two small randomized studies have compared terlipressin with albumin in the prevention of PCD with similar values of plasma-renin activity 4–6 days after LVP (183,184). However, two more recent RCTs comparing midodrine with albumin have shown contradictory results with one study showing similar effects on 6-day levels of plasma-renin activity (185) and another showing significantly higher rate of PCD with midodrine compared with albumin (186). Therefore, results on the use of vasoconstrictors to prevent PCD are also inconclusive.

The management strategy for patients with refractory ascites is summarized in **Table 7**.

Treatment of HRS. HRS is a type of renal failure that occurs in patients with cirrhosis and severe liver dysfunction and has been defined as serum creatinine >1.5 mg/dl (164,187), although it has recently been suggested that it be defined as per the Acute Kidney Injury Network as an increase in serum creatinine of ≥0.3 mg/dl or increase of ≥150 to 200% (1.5- to 2-fold) from baseline (188). HRS is considered to be a part of the clinical spectrum of the cirrhotic patient with ascites and therefore, it usually occurs in patients with refractory ascites with or without hyponatremia. HRS has been divided into two types; HRS-1 is a rapidly progressive type of acute renal failure and usually occurs in hospitalized patients, whereas HRS-2 is a slower type of renal failure and mostly occurs in outpatients with refractory ascites. The prognosis of type 1 HRS is very poor, with a median survival of ~2 weeks (133), whereas HRS-2 has a relatively longer median survival of ~6 months (189).

Acute renal failure, recently renamed AKI (190), occurs in ~19% of hospitalized patients with cirrhosis (188). The most common cause of AKI in cirrhosis is pre-renal AKI, accounting for ~68% of the cases, followed by intra-renal causes,

such as acute tubular necrosis (ATN) and glomerulonephritis (32%), with post-renal causes accounting for < 1% of the cases (188). HRS itself is a form of pre-renal failure, as it results from vasodilatation and a marked reduction in effective arterial blood volume leading to renal vasoconstriction (189,191). Compared with other forms of pre-renal AKI, HRS is not volume-responsive and constitutes ~33% of the cases of pre-renal AKI; i.e., it accounts for only ~20% of cases of AKI in hospitalized patients with cirrhosis (188).

Presently, specific therapy is only recommended for patients with type 1 HRS, i.e., for patients with AKI that occurs rapidly over a period of < 2 weeks. Although consensus conferences have required that serum creatinine levels double to a level >2.5 mg/dl in this period (164,187), waiting until these levels are reached may decrease the response to specific therapy (192–194) and therefore, it has been suggested that treatment for HRS-1 should be initiated earlier, with only 1.5-fold increases in creatinine.

Candidates. Candidates are patients with cirrhosis and ascites who develop AKI and in whom other more common causes of have been excluded. In a patient with cirrhosis who presents with sudden deterioration of renal function, one of the first steps is to discontinue diuretics (or other medications that could potentially decrease effective blood volume, such as lactulose or vasodilators) and to expand the intravascular volume with i.v. albumin at a dose of 1 g/kg of body weight up to a maximum of 100 g (187) or with saline solution in cases in which fluid loss from overdiuresis is suspected (164). Second, factors known to precipitate renal failure in cirrhosis (infection, fluid, or blood loss) need to be investigated, and if present, they should be treated (187). If serum creatinine does not improve or continues to worsen despite these measures, the differential diagnosis is between intrinsic renal failure, HRS, and post-renal failure. To rule out post-renal failure, a renal ultrasound should be obtained, although this is a rare cause of AKI in cirrhosis. To rule out intrinsic renal failure, urinary sediment should be analyzed. Finding significant proteinuria or hematuria suggests glomerulonephritis, and finding granular or epithelial casts suggests ATN but these findings are not definitive. The differentiation between ATN and HRS is the most difficult, as urine indices and response to volume expansion may be equivocal (188). A history of septic or hypovolemic shock, as well as a recent history of nephrotoxins or contrast dye suggests ATN (188). It has been suggested that the response to vasoconstrictors plus albumin may also be used to establish this differential (195).

Accepted therapy. The first and only choice for definitive therapy for HRS is liver transplantation, as it is the only therapy that will provide a long-term survival (**Supplementary Table 10**). With the implementation of the MELD (model for end-stage liver disease) score in the allocation of organs in the United States, priority for transplant is given to patients with high creatinine (196). Patients with HRS who are transplanted have more complications and a higher in-hospital mortality rate than those without HRS (197–200). However, patients who respond to vasoconstrictor therapy (see below) have a similar outcome than those transplanted without HRS (201). A recent study, carried out in the MELD era, shows that pre-operative serum creatinine is an independent predictor of post-transplant survival (200). Therefore, it is important to have therapies that will reduce serum creatinine and "bridge" the patient-to-liver transplantation.

Bridging therapies to liver transplantation. As the mechanism that drives HRS is extreme splanchnic and systemic vasodilatation, vasoconstrictors have been used as a bridge to transplantation (**Supplementary Table 10**). Until recently, data using arteriolar vasoconstrictors in HRS were mostly derived from small uncontrolled studies using ornipressin, terlipressin, noradrenaline, the combination of octreotide plus midodrine, or vasopressin. These studies have been summarized recently and showed promise in the treatment of type 1 HRS (188).

The best evidence supports the use of terlipressin for HRS and it is widely used in Europe and Asia, but it is not approved by the US FDA. Four RCTs (193,194,202,203) have shown that HRS reversal is higher with terlipressin (46%) compared with the control group (11%). In the only placebo-controlled, double-blind multicenter trial that included the largest number of patients (193), HRS reversal occurred in 34% of the patients, a rate significantly greater than in placebo-treated patients (13%). Overall survival was not improved in the two largest RCTs (193,194). However, survival is significantly improved in patients who respond to terlipressin (193,194,204,205). Two recent small, open-label RCTs that compared noradrenaline with terlipressin showed that neither HRS reversal nor the rate of side effects was different between groups (206). The combination of midodrine plus octreotide has the advantage of oral/subcutaneous administration (192,207) but has not been tested against terlipressin. In the United States, off-label use of the combination of midodrine plus octreotide associated with i.v. albumin, remains a commonly used regimen for HRS (208), and is supported by the AASLD treatment recommendations (209).

Dose and duration. Terlipressin has been used at different doses in different studies. It should be started at a dose 0.5–1 mg i.v. (slow push) every 4–6 h. If there is no early response (>25% decrease in creatinine levels after 2 days), the dose can be doubled every 2 days up to a maximum of 12 mg/day (i.e., 2 mg i.v. every 4 h). Treatment can be stopped if serum creatinine does not decrease by at least 50% after 7 days at the highest dose. In patients with early response, treatment should be extended until reversal of HRS (decrease in creatinine below 1.5 mg/dl) or for a maximum of 14 days (187).

A more rational method for adjusting the dose of vasoconstrictors is by monitoring mean arterial blood pressure (an indirect indicator of vasodilatation). This method has been used for adjusting the dose of midodrine plus octreotide (207,208). The doses of octreotide and midodrine are titrated to obtain an increase in the mean arterial pressure of at least 15 mm Hg. Midodrine is administered orally at an initial dose of 5–7.5 mg thrice daily and, if necessary, increased to 12.5–15 mg thrice daily. Octreotide is administered subcutaneously at an initial

Table 8. Diagnosis and management strategy of hepatorenal syndrome

Diagnosis	Consider HRS in a patient with cirrhosis and ascites and a creatinine level of >1.5 mg/dl It is a diagnosis of exclusion; before making the diagnosis, the following need to be ruled out and treated: Sepsis (patient needs to be pancultured) Volume depletion (hemorrhage, diarrhea, overdiuresis) Vasodilators Organic renal failure (urine sediment, kidney ultrasound) Diuretics should be discontinued and intravascular volume expanded with i.v. albumin If renal dysfunction persists despite above, diagnose HRS			
Recommended therapy	Liver transplant (priority dependent on MELD score) If patient is on transplant list, MELD score should be updated daily and communicated to transplant center; if patient is not on transplant list, packet should be prepared urgently			
Alternative (bridging therapy)	Vasoconstrictors	Octreotide PLUS Midodrine *or* Terlipressin[a]	100–200 mcg s.c. t.i.d. 5–15 mg p.o. t.i.d. 0.5–2.0 mg i.v. every 4–6 h	Goal to increase MAP by 15 mm Hg
	and			
	Intravenous albumin (both for at least 7 days)		50–100 g i.v. q.d.	

i.v., intravenous; HRS, hepatorenal syndrome; MAP, mean arterial pressure; MELD, model for end-stage liver disease; t.i.d.; thrice a day; s.c., subcutaneously; p.o., orally [a]Not available in the United States.

dose of 100 μg thrice daily and, if necessary, increased to 200 μg thrice daily (207).

Therapies under investigation. Small uncontrolled studies suggest that the TIPS may be useful in the treatment of type 1 and type 2 HRS (210,211); however, the majority of patients in these trials had alcoholic cirrhosis and many were actively drinking and therefore, the improvement observed could have resulted from an improvement in the underlying liver disease. Interestingly, a recent uncontrolled trial of TIPS placed in five patients with HRS-1 who had responded to octreodide/midodrine, showed that TIPS was associated with long-term success with increased glomerular filtration rate and sodium excretion (192). TIPS should be used as a treatment of type I HRS only in the setting of prospective randomized controlled trials (**Supplementary Table 10**).

In a small, randomized study, the molecular adsorbent recirculating system (MARS), a modified dialysis method using an albumin-containing dialysate, was shown to improve the 30-day survival in 8 patients with HRS-1 compared with 5 patients treated with intermittent venovenous hemofiltration alone (212). As MARS incorporates a standard dialysis machine or a continuous venovenous hemofiltration monitor and glomerular filtration rate was not measured, the decrease in serum creatinine observed in most patients could be related to the dialysis process. However, clear beneficial effects on systemic hemodynamics and on HE were observed. MARS is still considered to be an experimental therapy and its use in patients with type-1 HRS cannot be recommended outside prospective pathophysiological or therapeutic investigations (**Supplementary Table 10**).

Therapies of proven inefficacy. Renal venodilators, such as prostaglandins and dopamine (at non-pressor doses), have been used in patients with HRS in an attempt to reduce intra-renal vascular resistance, without an obvious benefit (213–217). The combination of peripheral vasoconstrictors plus renal vasodilators has also failed to improve renal function in patients with HRS (218).

A recent trial compared the effects of i.v. octreotide infusion (50 μg/h) plus albumin with placebo using a randomized, double-blind, cross-over design (219). After 4 days of continuous infusion (octreotide or placebo) plus albumin, there was no improvement in renal function, urinary sodium, or plasma-renin activity, leading to the conclusion that octreotide alone is ineffective in the treatment of HRS in cirrhotic patients (**Supplementary Table 10**).

The strategy in the diagnosis and management of HRS is summarized in **Table 8**.

Treatment of HE

HE reflects a spectrum of neuropsychiatric and psychometric test performance abnormalities occurring in patients with significant liver dysfunction after exclusion of other known neuropsychiatric diseases. HE represents a continuum from minimal (sub-clinical) to overt HE with varying degrees of severity (220). In a consensus conference, HE was further divided into episodic HE defined as acute episodes with or without (spontaneous) an identifiable precipitating factor; recurrent HE when 2 episodes of episodic HE occur within 1 year; persistent HE that includes persistent cognitive deficits that affect negatively on social and occupational functioning, or HE that recurs promptly after discontinuing medication. Minimal HE (that used to be referred to as "sub-clinical" encephalopathy) is the asymptomatic phase that is diagnosed on the bases of abnormal psychometric testing (220) and will not be discussed in this section.

The diagnosis of HE is established most frequently on clinical grounds by the identification of compatible symptoms after excluding alternative causes, but may rarely involve

formal psychometric testing, electroencephalograms, or neuroimaging.

Treatment of HE is based on several leading hypotheses on the underlying pathophysiology of HE (221). The ammonia hypothesis is the prevalent hypothesis based on the observations that increased serum ammonia levels are observed in 60–80% of patients with HE, and that reducing ammonia through decreased production or increased removal leads to clinical improvement. The accumulation of glutamine in brain astrocytes induced by hyperammonemia produces osmotic stress and causes astrocytes to swell and malfunction. Hyponatremia, a finding common in advanced cirrhosis, seems to aggravate this swelling and may be a factor that aggravates HE (222). Normally, portal vein ammonia produced by small bowel enterocytes or through colonic bacterial catabolism of nitrogen sources (e.g., ingested protein), is metabolized and cleared by the liver. In cirrhosis, ammonia is not cleared by the liver as it escapes through the portosystemic shunts and because an impaired liver fails to perform this function. The gamma-amino butyric acid (GABA) hypothesis suggests that the GABA-receptor complex (GABA-binding site, chloride channel, and barbiturate and benzodiazepine receptor sites) is an important neuronal inhibitor, and that GABA-ergic transmission interacts with ammonia in the pathogenesis of HE. The false neurotransmitter hypothesis suggests that HE may stem from an increased ratio of plasma aromatic amino acids to branched-chain amino acids that lead to increased levels of monoamine neurotransmitters, which contribute to altered neuronal excitability.

The approach to HE therapy varies according to the clinical setting, e.g., episodic vs. persistent (220). As the development of HE is not lethal by itself, management is focused on the treatment of overt HE rather than its prophylaxis; although HE can be prevented by limiting exposure to common precipitants (e.g., sedatives).

Episodic HE. The major goals of treatment include the identification and correction of precipitating factors, as well as measures aimed at reducing the brain concentration of ammonia (223,224). Protein-restricted diets are usually prescribed. However, their efficacy was recently evaluated in a trial carried out in cirrhotic patients admitted to the hospital owing to an episode of acute encephalopathy ($n = 30$), which randomized patients to receive a low-protein diet with progressive increments or a normal protein diet for 14 days, in addition to standard measures for treating HE. The outcome of HE was not significantly different between both study groups. Protein synthesis was similar for low and normal protein diet, but those of the low-protein diet group showed higher protein breakdown (225). As mentioned in an accompanying editorial, the rationale for a low-protein diet in the short- and long-term management of HE seems questionable as it is of no benefit and could be detrimental to the patient with cirrhosis (226).

Accepted therapy. The most important facts to be recognized are that (i) HE is reversible, and (ii) a precipitant cause can be identified in the majority of patients.

In a landmark study, Fessel and Conn (227)showed that of 100 patients with (episodic) HE, 80% of the cases were precipitated by factors, such as GI hemorrhage, increased protein intake, infection (including SBP), pre-renal azotemia, hypokalemic alkalosis, hyponatremia, constipation, hypoxia, or the use of sedatives and tranquilizers. Accordingly, the first step in the treatment of episodic HE is the identification and treatment of the precipitant cause (**Supplementary Table 11**).

Regarding specific therapy for HE, lactulose is the treatment of choice given its established safety and effectiveness. Lactulose is a non-absorbable disaccharide that reduces ammonia by acidifying the colon and reducing colonic transit time. A large systematic review showed that lactulose or lactilol was more effective than placebo in treating HE (relative risk 0.62, 95% CI: 0.46–0.84) without differences in mortality (228). Oral administration is preferred, although lactulose enemas may be used in patients who are unable to consume it orally (**Supplementary Table 11**).

Dose and duration. Lactulose should be administered initially at a dose of 30 ml every 1–2 h until a bowel movement occurs. After catharsis begins, the oral dose should be adjusted to obtain 2–3 soft bowel movements per day (15–30 ml b.i.d.). Lactulose enemas (300 ml in 1 l of water) should be administered every 6–8 h until the patient is awake enough to start oral intake. Lactulose can be discontinued once HE is resolved in patients in whom a precipitant was identified and treated and in patients without an obvious precipitant but who do not have an earlier history of HE. Lactulose should be continued in patients with recurrent or persistent HE (see below).

Side effects. The common side effects of lactulose therapy include unpleasant taste, bloating, abdominal cramps, and diarrhea. Lactulose should be withheld when diarrhea occurs, and restarted at a lower dose once it resolves. It should be emphasized that diarrhea itself may be more harmful than HE, as it may result in a decreased effective arterial volume and precipitate renal dysfunction. Another harmful consequence of lactulose-induced diarrhea is hypernatremia that has recently been associated with a high mortality in cirrhosis (158).

Alternative therapies. Antibiotics reduce ammonia load by eliminating colonic bacteria. Neomycin, a poorly absorbed aminoglycoside, has been used in the treatment of HE, combined with sorbitol or milk of magnesia (to accelerate intestinal transit and to cleanse the bowel), and has been shown to be as effective as lactulose (229). However, long-term use has been associated with nephrotoxicity and ototoxicity, limiting its use. Metronidazole dosed at 200 mg four times a day (q.i.d.) has also been shown to be as effective as neomycin dosed at 1 g q.i.d., but may be associated with peripheral neuropathy. Rifaximin is a non-absorbed derivative of rifamycin with a broad-spectrum antibiotic activity against gram-positive and gram-negative organisms. It has been approved by the FDA for the treatment of travelers' diarrhea due to non-invasive *Escherichia coli*, and has been given orphan status for HE. Two RCTs performed outside the United States have shown that rifaximin, at a dose of 400 mg po thrice daily, is as effective as lactitol (230) or lactulose (231)

in episodic HE. A recent meta-analysis showed that rifaximin is not superior to non-absorbable disaccharides in the treatment of episodic or persistent HE, except that it may be better tolerated (232). Results were the same in a sensitivity analysis, including only patients with acute (episodic) encephalopathy. Therefore, and until the results of ongoing larger trials are available, rifaximin should be restricted to patients who have not responded to lactulose or in patients who cannot tolerate even the minimal dose of lactulose (**Supplementary Table 11**). There is no evidence to suggest that combining rifaximin and lactulose will be of further benefit and it could be potentially detrimental, as rifaximin will eliminate bacteria that metabolize lactulose and acidify the colon.

Therapies under investigation. Various therapies directed at reversing alterations of various neurotransmitters postulated in the pathogenesis of HE (such as bromocriptine and flumazenil), or in the urea cycle (such as ornithine aspartate and benzoate) have been investigated and shown in limited trials to be useful in the treatment of HE (221,223). Regarding flumazenil, a benzodiazepine receptor antagonist, two recent meta-analyses showed a beneficial effect on HE. One of them showed a significant clinical and electroencephalographic improvement of HE in patients treated with flumazenil from 5 min to 3 days (233). The other showed that, although flumazenil had no significant effect on recovery or survival from HE, it was associated with a significant improvement in HE at the end of the treatment (234). Until further evidence is available, flumazenil may be considered for patients with chronic liver disease and HE, particularly for those in whom sedatives play a role or in whom there is no clear precipitant (**Supplementary Table 11**).

A non-conventional way of reducing ammonia is by the use of the MARS. In contrast to the regular methods of hemofiltration, this system is designed to remove both low- and middle-molecular-weight water-soluble substances (such as ammonia) and albumin-bound molecules. In a multicenter RCT comparing MARS with standard medical therapy in patients with severe cirrhosis and grades 3–4 HE, MARS was associated with earlier and more frequent improvement of HE (235).

The strategy in the management of episodic HE is summarized in **Table 9**.

Recurrent or persistent HE. As mentioned above, recurrent HE is when 2 episodes of episodic HE occur within 1 year; persistent HE is defined by persistent cognitive deficits that affect negatively on social and occupational functioning, or HE that recurs promptly after discontinuing medication. These patients require chronic therapy. One of the most common causes of persistent HE is TIPS placement. Persistent and intractable post-TIPS HE can be treated by occluding the shunt or by reducing its diameter.

Accepted therapy. Lactulose is the treatment of choice, given its established safety and effectiveness (**Supplementary Table 12**).

Dose and duration. Lactulose should be administered orally at a dose adjusted to obtain 2–3 soft bowel movements per day (starting at 15 ml po b.i.d.).

Table 9. Management strategy of episodic hepatic encephalopathy (HE)

General management	Identify and treat precipitating factor (GI hemorrhage, infection, pre-renal azotemia, constipation, sedatives) Short-term (<72 h) protein restriction may be considered in severe HE
Specific therapy	Lactulose enemas (300 cm^3 in 1l of water) in patients who are unable to take it p.o. *or* Lactulose 30 cm^3 p.o. every 1–2 h until bowel evacuation, then adjust to a dosage that will result in 2–3 formed bowel movements per day (usually 15–30 cm^3 p.o. b.i.d.) Lactulose can be discontinued once the precipitating factor has resolved

b.i.d., twice a day; GI, gastrointestinal; p.o., orally.

Side effects. The common side effects of lactulose therapy include unpleasant taste, bloating, abdominal cramps, and diarrhea. Lactulose should be withheld when diarrhea occurs, and restarted at a lower dose once it resolves. It should be emphasized that diarrhea itself may be more harmful than HE, as it may result in decreased effective arterial volume with consequent hypernatremia and/or renal dysfunction.

Therapies that should not be used. In the past, prolonged dietary protein restriction was recommended in HE, but the supporting data for this recommendation are unclear. Protein and energy malnutrition is common in patients with cirrhosis. Protein restriction can promote protein degradation, and if maintained for long periods, worsens the nutritional status and decreases muscle mass. Skeletal muscle is capable of decreasing blood ammonia by metabolizing ammonia to glutamine; therefore, measures that decrease muscle mass in a patient with cirrhosis should be avoided. Recent guidelines from nutritionists no longer recommend protein restriction in any patient with HE (236) (**Supplementary Table 12**). The suggested protein intake in cirrhotics (with or without HE) is 1–1.5 g/kg/day. It has been suggested that proteins from vegetables and dairy products give a higher calorie per nitrogen ratio and hence, produce less ammonia than animal proteins. Diet supplementation with amino acids (mainly branched-chain amino acids) and trace elements may improve the nutritional status and HE (237).

Cirrhotic patients are highly susceptible to the sedative effect of benzodiazepines and doses considered therapeutic are able to precipitate stages of prolonged or near coma. Therefore, benzodiazepines and other sedative drugs (anti-histamines, narcotics, and anti-depressants with sedative effects) should be avoided or administered very carefully and at lower doses in cirrhotic patients. Eradication of *Helicobacter pylori*, a urease-producing bacteria found in the upper GI tract, has not been shown to be helpful in the treatment of HE.

A randomized, but not blinded, study that compared lactitol 60 g/day ($n=25$), rifaximin 1,200 mg/day, and no-treatment in the prevention of post-TIPS HE showed no differences in the

Table 10. Management strategy of persistent hepatic encephalopathy (HE)

General management	No long-term protein restriction Protein from dairy or vegetable sources is preferable to animal protein Avoid sedatives and tranquilizers Avoid constipation
Specific therapy	Lactulose dosage that produces 2–3 soft, formed bowel movements per day, starting at 15–30 cm^3 p.o. b.i.d.
Alternative therapy	Rifaximin 400 mg p.o. t.i.d. in patients who cannot tolerate lactulose

b.i.d., twice a day; p.o., orally; t.i.d., thrice a day.

1-month incidence of HE (36, 32, and 32%, respectively) (238) and therefore, prophylactic therapy in patients in whom TIPS is performed is not warranted.

Therapies under investigation. Recently, there has been an increase in the use of rifaximin because it seems to be safer than neomycin and was shown to be as effective as lactitol in episodic HE (230); however, rifaximin is costly. In fact, a cost-effective study showed that rifaximin monotherapy was not cost-effective in the treatment of persistent HE, although a strategy using rifaximin in patients who are lactulose-refractory may be highly cost-effective (239). A recent meta-analysis showed that rifaximin is not superior to non-absorbable disaccharides in the treatment of episodic or persistent HE, except that it may be better tolerated (232). Results were the same in a sensitivity analysis, including only patients with chronic (persistent) encephalopathy. Therefore, and until the results of ongoing trials are available, rifaximin should be restricted to patients who have not responded to lactulose or in patients who cannot tolerate even the minimal dose of lactulose. There is no evidence to suggest that combining rifaximin and lactulose will be of further benefit and it could be potentially detrimental as rifaximin will eliminate bacteria, which metabolize lactulose and acidify the colon (**Supplementary Table 12**).

Other novel therapies for HE that require further investigation are synbiotic therapy (combination pro- and pre-biotic), which has been shown to improve minimal HE (240,241) (**Supplementary Table 12**).

The strategy in the management of recurrent/persistent HE is summarized in **Table 10**.

SCREENING, DIAGNOSIS, AND MANAGEMENT OF HCC

HCC is an increasingly common complication of chronic liver disease in the United States. Population studies suggest a rising incidence of HCC from 1.4 per 100,000 between 1975 and 1977 to 3.0 per 100,000 between 1996 and 1998 (242), which will likely peak in the next decade. A corresponding increase in the number of cases being diagnosed and treated in the VA system has been reported (243). Recommendations stated below follow recent treatment recommendations endorsed by the AASLD (244).

Surveillance

Surveillance for HCC is indicated for all patients with a diagnosis of cirrhosis, particularly those due to hepatitis C infection or alcohol, which are the most common risk factors in the United States, and selected non-cirrhotic patients with hepatitis B, including Asian females aged ≥50 years (males aged ≥40 years), Africans over the age of 20 years, and those with a family history of HCC (**Supplementary Table 13**). A combination of serum α-fetoprotein plus abdominal ultrasound every 6–12 months is the recommended approach for HCC surveillance, based on average doubling times that average 6 months, and studies showing improved survival, such as a large RCT of surveillance with α-fetoprotein and ultrasound every 6 months vs. no surveillance in a cohort of 18,816 patients in China that showed a 37% reduction in HCC-related mortality (245) and a small study in US veterans showing that screened patients were 10 times more likely to have received potentially curative treatment which in turn led to an improvement in survival (243).

Diagnosis

The diagnosis of HCC is based primarily on abdominal imaging studies, and may be supported by serum tumor markers or pathology. As per the recent AASLD recommendations (244), small mass lesions (< 1 cm) identified on ultrasound should be followed by a surveillance ultrasound every 3 months, and if stable over 1–2 years, surveillance should return to every 6–12 months. If mass lesions measuring 1–2 cm in diameter on ultrasound are found, two dynamic imaging studies (computed tomography and magnetic resonance imaging) should be carried out. If both show a typical vascular pattern (arterial phase enhancement with venous phase washout), the lesion should be treated as HCC. If one or both show an atypical vascular pattern, imaging-guided biopsy can be considered to confirm HCC, and close surveillance every 3 months is maintained if biopsy is non-diagnostic. If mass lesions measuring >2 cm are found on ultrasound, one dynamic study (computed tomography or magnetic resonance imaging) should be obtained, and the mass should be treated as HCC if a typical vascular pattern is observed. However, if the serum α-fetoprotein is >200 ng/ml, biopsy is not required. A careful consideration of local expertise in imaging techniques, imaging-guided biopsy, and histopathologic examination is important for clinicians in determining the best approaches needed to diagnose HCC. Although core biopsy specimens are preferred, imaging-guided or endoscopic ultrasound-guided fine needle aspiration cytology may be considered as an alternative approach on the basis of local expertise (246,247).

The diagnostic workup of a liver mass in a patient with chronic liver disease is summarized in **Table 11**.

Table 11. Diagnostic workup of a liver mass in a patient with chronic liver disease

Mass <1 cm	Diagnosis	Low likelihood of being HCC, therefore no specific diagnostic tests		
	Follow-up	Repeat imaging study every 3 months If no growth in 1–2 years, no HCC; continue screening every 6 months If growth, treat as HCC		
Mass 1–2 cm	Diagnosis	Two dynamic imaging studies (US, CAT scan, or MRI)	Both with typical vascular pattern	Treat as HCC
			One typical and the other atypical	Consider biopsy of mass
			Both atypical	Consider biopsy of mass vs. close follow-up
	Follow-up after biopsy	Biopsy confirms HCC	Treat as HCC	
		Non-diagnostic	Repeat imaging study every 3 months: If no growth in 1–2 years → no HCC If growth, treat as HCC	
Mass >2 cm	Diagnosis	One dynamic imaging study (US, CAT scan, or MRI)	Typical vascular pattern	Treat as HCC
			Atypical vascular pattern	Biopsy of mass
	Follow-up after biopsy	Biopsy confirms HCC	Treat as HCC	
		Non-diagnostic	Repeat imaging study every 3 months: If no growth in 1–2 years → no HCC If growth, treat as HCC	

CAT, computerized axial tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound.

Staging

Once a diagnosis of HCC is established, tumor staging is important in guiding treatment decisions. The BCLC (Barcelona Clinic Liver Cancer) system is the most commonly used staging system in clinical practice, and incorporates three clinical parameters (248): (i) tumor staging based on the American Liver Tumor Study Group's modified TNM (tumor-node-metastasis) staging system; (ii) liver function and disease severity based on CTP and MELD scores; and (iii) performance status based on World Health Organization (WHO) criteria. A careful consideration of the effect of HCC treatment on quality of life and life expectancy should be incorporated into the treatment approach.

Treatment

Several approaches to the treatment of HCC are commonly used and therefore, specific treatment decisions should be based on local or regional expertise, and where available, should involve a multidisciplinary team of specialists in hepatology, surgery, liver transplantation, interventional radiology, oncology, and pathology. Treatment options include surgical resection, liver transplantation, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and systemic chemotherapy, or combinations of these. For patients with decompensated cirrhosis, liver transplantation represents the treatment of choice for solitary HCC <5 cm or early multifocal HCC (up to 3 lesions of ≤3 cm each). A comparative assessment of treatment efficacy between HCC therapies in cirrhotic patients should be performed on the basis of survival.

Approved, potentially curative therapies. Surgical resection is the optimal therapy for solitary HCC in non-cirrhotic patients. Non-cirrhotic HCC is less common in the United States, but is more frequently seen in Asia where chronic hepatitis B is the leading etiology. Owing to the advances in selection criteria and surgical techniques, surgical mortality is <1–3% and a 5-year survival after resection may exceed 50%. Inclusion of patients with normal serum bilirubin and the absence of clinically significant portal hypertension (HVPG <10 mm Hg) results in excellent surgical outcomes without post-operative decompensation and an improved 5-year survival of >70%, whereas patients with increased bilirubin and clinically significant portal hypertension (HVPG ≥10 mm Hg) have a 5-year survival of <30% (249,250). Despite the authors' conclusions, a recent study confirms that in patients with CTP class A and a single tumor, indirect evidence of clinically significant portal hypertension (esophageal varices, platelet count of <100,000/mm^3 + splenomegaly) is associated with a poor post-resection 5-year survival (56%) compared with patients without evidence of portal hypertension (71%) (251). As such, assessment of clinically significant portal hypertension is important in determining the eligibility for tumor resection. Therefore, resection is typically reserved for CTP class A or B patients with normal bilirubin and absence of clinically significant portal hypertension with solitary HCC <5 cm in diameter in a favorable anatomic location. Post-resection tumor recurrence is common, occurring in ~70% of individuals at 5 years, primarily because of true recurrence (50–70%) or owing to the development of *de novo* tumors (30–50%). Pre- or

post-resection adjuvant chemotherapy has not been shown to be effective in reducing recurrence rates and therefore, is not routinely recommended.

Liver transplantation is the preferred treatment for patients with decompensated cirrhosis who have solitary HCC <5 cm or up to 3 lesions of ≤3 cm each, without evidence of vascular invasion or extrahepatic spread, based on Milan criteria. These individuals show an excellent 5-year survival of >70% (252). Transplant-eligible patients in the United States who meet the Milan criteria are given a bonus MELD score of 22, which may increase by 10% for every 3 months on the wait list (253). Unfortunately, because of limited liver donor supply, many individuals may drop out from new contraindications to transplantation (e.g., tumor growth, vascular invasion), while on the waiting list and therefore, much enthusiasm has been generated by efforts to use pre-transplant HCC therapy (e.g., RFA, TACE) to treat or "downstage" tumors, or to extend transplant listing for tumors beyond the Milan criteria. However, existing data are inadequate to make a recommendation for or against these strategies and therefore, these should be carefully considered in consultation with an experienced transplant center. Living donor liver transplantation may represent one strategy to reduce the drop-out rate on the wait list, and early studies suggest 5-year survival rates as high as 68% in patients with HCC, with a markedly decreased waiting time of 83 days when compared with 414 days for deceased-donor transplantation (254). Although this is an attractive alternative, additional evidence is needed before formal recommendations on its role in HCC therapy can be established.

Percutaneous ablation is the preferred treatment for patients with early stage HCC who are not eligible for tumor resection. There are two approaches that are frequently used, including percutaneous ethanol injection (PEI) and RFA. PEI is a highly effective, safe, and inexpensive approach for small HCC, which achieves necrosis rates of 90–100% for tumors of <2 cm, and in patients with compensated cirrhosis results in a 5-year survival of 50%, comparable with surgical resection. However, success rates are lower for larger tumors, with necrosis rates of 70% for tumors of 2–3 cm, and 50% for tumors of 3–5 cm (255–257). PEI is limited primarily by its inability to achieve complete necrosis in tumors of ≥3 cm, and the need for multiple injection sessions due to an inability to access the entire tumor volume. RFA involves the insertion of single or multiple electrodes that deliver heat to tumor in a directed manner, inducing a wider and more predictable span of tumor necrosis than PEI. As such, RFA is equally effective as PEI for small tumors of <2 cm, but is more effective than PEI for larger tumors, for which randomized controlled trials have shown better tumor necrosis and improved survival (255,257). RFA is limited primarily by a small but higher rate of complications (e.g., pleural effusions and peritoneal bleeding) and by a significantly higher cost.

Approved, non-curative therapies. TACE is the preferred non-curative treatment for patients with large or multifocal HCC who are not eligible for resection or percutaneous ablation, and who do not have an extrahepatic tumor spread. HCC is characterized by profound neo-angiogenic activity, which is dependent on the hepatic artery for its blood supply. Selective arterial obstruction of targeted lobar and segmental branches of the hepatic artery using chemotherapeutic agents (e.g., cisplatin or adriamycin) mixed with lipiodol and other agents (e.g., gelfoam) result in ischemic tumor necrosis. Although TACE results in significant tumor necrosis in >50% of patients, as measured by intra-tumoral necrotic "bubbles," and has been shown to improve survival compared with no therapy in patients with advanced HCC and compensated liver disease, complete responses are uncommon. Therefore, repeat TACE sessions are frequently required (257). TACE is contraindicated in patients with decompensated cirrhosis, or with portal vein obstruction. Post-embolization syndrome represents a unique complication of TACE occurring in ~50% of patients following the procedure and is typically marked by a self-limited 24–48 h period of fever, abdominal pain, and ileus.

Systemic chemotherapy is a non-curative treatment strategy generally reserved for patients with advanced, unresectable HCC who are not eligible for percutaneous ablation or TACE. Due in part to frequent expression of drug resistance genes, HCC is poorly responsive to traditional chemotherapy agents (e.g., gemcitabine, cisplatin, doxorubicin, oxaliplatin) and does not respond to systemic hormonal therapy (e.g., tamoxifen). Therefore, this type of chemotherapy should not be used in these patients.

Molecularly targeted therapy has emerged as an important new treatment approach based on an enhanced understanding of the role of vascular endothelial growth factors (such as VEGF) and their pathways in the regulation and tumorigenesis of HCC. Sorafenib is an oral multi-targeted tyrosine kinase inhibitor, which blocks HCC angiogenesis through the inhibition of both VEGF and the Raf kinase pathway. Sorafenib represents the only FDA-approved chemotherapy agent for advanced HCC, on the basis of a large randomized controlled multicenter trial involving 602 patients who were randomized to a daily oral intake of sorafenib 400 mg or to placebo (258). Nearly all patients had preserved liver function (95% CTP class A) and most had advanced HCC (37.8% TNM stage 3 and 50.8% TNM stage 4). Compared with placebo, patients on sorafenib experienced a significantly longer median survival (10.7 vs. 7.9 months) and a delayed time to radiological progression. Major side effects observed included diarrhea (11 vs. 2%), hand–foot skin reaction (8 vs. 1%), and fatigue (15 vs. 10%). These results were recently confirmed in a similar group of 266 patients with HCC from the Asia–Pacific region, in whom sorafenib was associated with a significantly longer survival (2.8 vs. 1.4 months) and a decreased time to progression (259). Therefore, sorafenib is recommended in patients with advanced HCC not eligible for locoregional therapy and who have preserved liver function and performance status. The strategy in the management of HCC is summarized in **Table 12**.

Table 12. Management strategy of HCC based on CTP class, size, and performance status

CTP A, PS 0	Single HCC <2 cm	HVPG <10 mm Hg and bilirubin <1.5 mg/dl	Surgical resection
		Varices/collaterals or HVPG >10 mm Hg or bilirubin >1.5 mg/dl	Liver transplant evaluation RFA/PEI
CTP A–B, PS 0–2	Single HCC 2–5 cm	HVPG <10 mm Hg and bilirubin <1.5 mg/dl	Surgical resection
		Varices/collaterals or HVPG >10 mm Hg or bilirubin >1.5 mg/dl	Liver transplant evaluation RFA/PEI
	2 or 3 HCC masses <3 cm (the largest)		Liver transplant evaluation Radiofrequency ablation
	Intermediate stage (multinodular , PS 0)		Transarterial chemoembolization
	Advanced stage (portal invasion, metastases)		Sorafenib
CTP C, PS >2	Terminal stage		Symptomatic treatment

CTP, Child–Turcotte–Pugh; HCC, hepatocellular carcinoma, HVPG; hepatic venous pressure gradient; PEI, percutaneous ethanol injection; PS, performance status; RFA, radiofrequency ablation.

CONFLICT OF INTEREST

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REVIEW

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