Ascites in adults with cirrhosis: Diuretic-resistant ascites

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INTRODUCTION

Ascites due to cirrhosis can be mobilized in approximately 90 percent of patients with a treatment regimen consisting of dietary sodium restriction (usually 88 mEq [2000 mg] per day) and oral diuretics (usually consisting of spironolactone and furosemide) [1]. (See "Ascites in adults with cirrhosis: Initial therapy".)

Patients with diuretic-resistant ascites have pre-hepatorenal syndrome and a poor prognosis [2]. The two-year survival rate of all patients with cirrhosis after the development of ascites is approximately 50 percent [3,4]. By comparison, survival in patients with diuretic-resistant ascites is 50 percent at six months and 25 percent at one year [5].

This topic will review the approach to the 10 percent of patients who appear to have diuretic-resistant ascites (also referred to as refractory ascites). The diagnosis and evaluation of patients with ascites, the initial therapy of ascites due to cirrhosis, and the management of spontaneous bacterial peritonitis are discussed elsewhere. (See "Evaluation of adults with ascites" and "Ascites in adults with cirrhosis: Initial therapy" and "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis".)

The management of ascites in adults with cirrhosis is also discussed in practice guidance from the American Association for the Study of Liver Diseases [6]. The discussion that follows is consistent with that guidance.

PATHOGENESIS

True diuretic-resistant ascites is usually associated with advanced cirrhosis, marked neurohumoral activation (of the sympathetic and renin-angiotensin-aldosterone systems), and very low urinary excretion of sodium, frequently less than 10 mEq per day despite maximal tolerated doses of diuretics [1,2].

Neurohumoral activation results in renal vasoconstriction and enhanced sodium reabsorption in the proximal tubule (under the influence of angiotensin II and norepinephrine) and collecting tubules (under the influence of aldosterone). Even among patients with nonazotemic cirrhosis, those with a greater degree of neurohumoral activation show diminished diuretic responsiveness [7,8]. (See "Pathogenesis of ascites in patients with cirrhosis".)

The development of diuretic resistance in a previously diuretic-sensitive patient is most often due to progression of the liver disease [3]. However, it can also be due to two other complications of cirrhosis: hepatocellular carcinoma and portal vein thrombosis (either bland clot or metastatic hepatocellular carcinoma). A triple-phase computed tomography (CT) scan can help diagnose or exclude these complications. A liver and spleen ultrasound with Doppler can be performed, but is much less sensitive in detecting tumor than CT. (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Imaging' and "Acute portal vein thrombosis in adults: Clinical manifestations, diagnosis, and management", section on 'Diagnosis'.)

Progression to diuretic-resistance is generally an irreversible process unless there is a reversible component to the liver disease (eg, alcoholic hepatitis, hepatitis B virus infection and decompensated cirrhosis in a patient treated with antiviral therapy, or autoimmune hepatitis treated with glucocorticoids) or the patient undergoes successful liver transplantation, transjugular intrahepatic portosystemic stent shunt (TIPS) placement, or peritoneovenous shunt creation.

It is important to note that diuretics do **not** cause hepatorenal syndrome. This association may be inappropriately suggested because most patients are taking diuretics when hepatorenal syndrome is diagnosed. On the other hand, diuretics can cause azotemia, particularly if fluid is removed too rapidly in patients without peripheral edema. Diuretic-induced azotemia improves with the cessation of therapy and fluid repletion. By comparison, hepatorenal syndrome typically worsens inexorably (unless effective treatment is initiated), even after diuretics are stopped. (See "Hepatorenal syndrome" and "Ascites in adults with cirrhosis: Initial therapy", section on 'Rate of fluid removal'.)

DIAGNOSIS

Diuretic-resistant ascites in patients with cirrhosis is considered to be present if at least one of the following criteria is fulfilled in the absence of therapy with a nonsteroidal antiinflammatory drug (NSAID, which can induce renal vasoconstriction and diminish diuretic responsiveness) or other nephrotoxic medication [2]:

- An inability to mobilize ascites (manifested by minimal to no weight loss) despite confirmed adherence to the dietary sodium restriction (88 mEq [2000 mg] per day) and the administration of maximum tolerable doses of oral diuretics (400 mg per day of spironolactone and 160 mg per day of furosemide) [9]. This dose is only infrequently reached because patients often develop side effects at much lower doses.

- Rapid reaccumulation of fluid after therapeutic paracentesis despite adherence to a sodium-restricted diet.

- The development of diuretic-related complications such as progressive azotemia, hepatic encephalopathy, or progressive electrolyte imbalances.

Many patients who appear to be diuretic-resistant are not following a sodium-restricted diet. Adherence to the sodium restriction must be confirmed with a 24-hour urine collection containing less than 78 mEq of sodium (or a urine sodium <urine potassium) [10]. The 78 mEq of sodium cutoff reflects the recommended 88 mEq intake minus 10 mEq in non-urinary losses. Patients who are diuretic sensitive will excrete ≥78 mEq of sodium per day because of the diuretic. (See "Ascites in adults with cirrhosis: Initial therapy", section on 'Diuretic resistance' and "Patient education: Collection of a 24-hour urine specimen (Beyond the Basics)".)

The results of urine testing for sodium are interpreted as follows:

- Urine sodium excretion ≥78 mEq per day (or a urine sodium >urine potassium) and weight loss: The patient is diuretic sensitive and adherent to the dietary sodium restriction.

- Urine sodium excretion <78 mEq per day (or a urine sodium <urine potassium) and minimal to no weight loss (or weight gain): The patient is diuretic resistant at the current doses.

- Urine sodium excretion ≥78 mEq per day (or a urine sodium >urine potassium) and minimal to no weight loss (or weight gain): The patient is diuretic sensitive but not adherent to the sodium restriction.

The completeness of the 24-hour urinary collection is an important issue, since inadequate collections can underestimate the urinary excretion of sodium. Measurement of urinary creatinine is usually helpful in estimating the completeness of the collection. Men with cirrhosis and a stable serum creatinine concentration should excrete >15 mg of creatinine per kg of body weight per day, and women should excrete >10 mg/kg per day [2]. However, some patients with advanced cirrhosis have muscle wasting and lower rates of creatinine excretion [11,12]. In such patients, it may be difficult to use creatinine excretion as a marker of the completeness of the collection.

There is evidence that a random urinary sodium/potassium (Na/K) ratio may be almost as good as a 24-hour collection [13,14]. In the absence of diuretic therapy, patients with ascites have a very low urine sodium concentration and a high urine potassium concentration due to secondary hyperaldosteronism. One study found that approximately 90 percent of patients with a urine Na/K ratio >1 in a random specimen excreted more than 78 mEq/day in a 24-hour urine collection [13]. Measurement of spot urine Na/K has essentially replaced collection of 24-hour specimens.

The 10 percent of patients who have true diuretic resistance typically have marked neurohumoral activation, which results in renal vasoconstriction and enhanced sodium reabsorption in the proximal tubule (under the influence of angiotensin II and norepinephrine) and collecting tubules (under the influence of aldosterone) [2]. Even among patients with nonazotemic cirrhosis, those with a greater degree of neurohumoral activation show diminished diuretic responsiveness [7,15]. (See "Pathogenesis of ascites in patients with cirrhosis".)

DIFFERENTIAL DIAGNOSIS

Diuretic-resistant ascites in patients with cirrhosis must be differentiated from malignant ascites due to peritoneal carcinomatosis, Budd-Chiari syndrome (hepatic vein thrombosis), or malignant chylous ascites. These disorders are typically refractory to diuretic therapy because of an inability to mobilize the ascitic fluid [16]. By contrast, massive hepatic metastasis, another cause of malignant ascites, is due to intrahepatic portal hypertension and can be treated in a similar fashion to patients with cirrhosis [16].

To differentiate diuretic-resistant ascites from these other entities, patients should undergo paracentesis with ascitic fluid analysis (assessment of appearance and measurement of triglyceride content if opalescent or milky, fluid cell count and differential, fluid total protein,

and serum-ascites albumin gradient), as well as abdominal ultrasound with Doppler imaging. (See "Evaluation of adults with ascites", section on 'Initial ascitic fluid tests'.)

Another form of diuretic-resistant ascites, called nephrogenic ascites, occurs in patients with end-stage kidney disease who are usually being treated with maintenance dialysis. The pathogenesis of this disorder, which is usually **not** due to liver disease or portal hypertension, may be related to an increase in peritoneal capillary permeability induced in part by inadequate dialysis [17,18]. The serum-ascites albumin gradient is <1.1 g/dL, consistent with the absence of portal hypertension unless the patient has cirrhosis or heart failure in addition to their renal failure. Some patients respond to more intensive dialysis, but definitive therapy is renal transplantation [17].

INITIAL TREATMENTS

The first step in the treatment of patients who appear to have diuretic-resistant ascites is to stop medications that decrease systemic blood pressure (and thus renal perfusion), such as beta blockers, angiotensin converting enzyme inhibitors (ACEIs), and angiotensin receptor II blockers (ARBs). It may be particularly important to discontinue beta blockers because their use in patients with diuretic-resistant ascites has been associated with increased mortality [19]. (See 'Discontinuing beta blockers' below.)

Nonsteroidal anti-inflammatory drugs (NSAIDs) should also be discontinued because they can cause renal vasoconstriction.

In patients who continue to have diuretic resistance despite the interventions, oral midodrine, a vasopressor, may be effective. We start with 5 mg orally three times daily and adjust the dose (by increments of 2.5 mg for each dose) every 24 hours (maximal dose 17.5 mg three times daily) to achieve a mean arterial pressure of >82 mmHg. (See "Hepatorenal syndrome".)

Continuation of sodium restriction and when to discontinue diuretics — Patients with diuretic-resistant ascites should continue to follow a low-sodium diet (88 mEq [2000 mg] per day), though diuretics should be discontinued if the urine sodium is <30 mEq per day [20].

Discontinuing beta blockers — Nonselective beta blockers are used routinely to prevent variceal bleeding in patients with cirrhosis and esophageal varices, but they have the potential to reduce renal perfusion in patients who already have compromised renal perfusion, leading to decreased natriuresis. In addition, some studies suggest they are associated with increased mortality rates in patients with diuretic-resistant ascites and in patients with spontaneous bacterial peritonitis (SBP) [19,21,22]. This increase in mortality may occur because reduced

mean arterial blood pressure is strongly correlated with reduced survival in patients with advanced cirrhosis [23,24]. Based on the available data and our own experience, we do not initiate beta blockers (or we discontinue them if already part of the patient's regimen) in patients with decompensated cirrhosis and/or diuretic-resistant ascites. Preliminary data suggest that it is safe to abruptly discontinue beta blockers, with no adverse effects on the hepatic venous pressure gradient, though there is a slight increase in the cardiac index [25]. If these patients require primary or secondary prophylaxis against variceal bleeding, we prefer variceal banding. (See "Primary prevention of bleeding from esophageal varices in patients with cirrhosis" and "Prevention of recurrent bleeding from esophageal varices in patients with cirrhosis" and "Cirrhosis in adults: Overview of complications, general management, and prognosis", section on 'Decompensated cirrhosis'.)

We also discontinue beta blockers in patients who present with SBP, bleeding, azotemia, severe alcoholic hepatitis, or hypotension. In some patients, if the patient's blood pressure and azotemia improve off the beta blocker, it can be restarted cautiously with careful monitoring of blood pressure (including in home monitoring) and renal function. However, among patients with SBP, we discontinue the beta blocker permanently. To continue it increases risk of death [22]. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Discontinue nonselective beta blockers' and "Management and prognosis of alcoholic hepatitis", section on 'Discontinue nonselective beta blockers'.)

There are limited data on use of beta blockers in patients with diuretic-resistant ascites, and additional studies examining the safety of beta blockers in patients with decompensated cirrhosis are needed. The available studies suggest that beta blocker use in patients with diuretic-resistant ascites may be harmful:

- A prospective observational study of 151 patients with diuretic-resistant ascites found that patients who received nonselective beta blockers had worse survival compared with those who did not [19]. Median survival was significantly longer in patients who did not receive propranolol versus those who did (20 versus 5 months). Independent predictors of mortality were Child-Pugh class C, hyponatremia, refractory ascites due to renal failure, and beta blocker therapy. Whether the beta blockers accounted for the increased mortality is unclear, since the study was not randomized. In particular, patients who did not receive beta blockers appeared to be less likely to have varices and to be sicker [26]. In addition, approximately two-thirds of the deaths in patients taking beta blockers were due to hepatocellular cancer or sepsis.

- A crossover trial looked at 10 patients with diuretic-resistant ascites who were undergoing paracentesis [21]. Paracentesis-induced circulatory dysfunction developed in 8 of 10

patients when propranolol was given prior to paracentesis. However, paracentesis-induced circulatory dysfunction was seen in only 1 of 10 patients when propranolol was not given.

In our experience, patients with diuretic-resistant ascites or other signs of hepatic decompensation (eg, hepatic encephalopathy) do not tolerate beta blockers well. We typically restrict the use of beta blockers to patients with compensated cirrhosis and large esophageal varices who require primary prophylaxis against variceal bleeding and are not being managed with variceal ligation. Occasionally, we will use beta blockers as secondary prophylaxis in combination with variceal banding in patients who have had variceal bleeding (and no other evidence of hepatic decompensation), but we have a low threshold to discontinue them. Our banding approach is aggressive (12 to 16 bands on the first session, 5 to 8 on the second, and 0 to 3 on the third, followed by an upper endoscopy and banding as needed every three to six months). Our impression is that less aggressive banding regimens increase the risk of rebleeding between sessions, though our approach has not been formally compared with other approaches. (See "Major side effects of beta blockers", section on 'Beta blocker withdrawal' and "Primary prevention of bleeding from esophageal varices in patients with cirrhosis" and "Prevention of recurrent bleeding from esophageal varices in patients with cirrhosis".)

Data have suggested that the physiologic mechanisms by which beta blockers could reduce survival in patients with diuretic-resistant ascites were impaired cardiac function and blunted compensatory response for maintaining renal perfusion [27,28]. In a study of 584 patients on the liver transplantation waiting list, patients with refractory ascites on beta blockers had lower heart rates (67 versus 77 beats per minute) and a lower cardiac index (3.2 versus 4.2 L/minute/1.73 m^2) compared with no beta blocker use [27]. Beta blocker use in patients with impaired cardiac function was associated with higher waiting list mortality (subdistribution hazard ratio 1.96, 95% CI 1.32-2.90) [27].

Cirrhosis cures hypertension — As patients with cirrhosis decompensate with accumulation of ascites, their systemic vascular resistance and mean arterial pressure (MAP) silently decrease. Many patients, especially those with obesity and cirrhosis due to nonalcoholic steatohepatitis, are hypertensive before they decompensate (hence the phrase "cirrhosis cures hypertension"). When MAP is ≤82 mmHg, two-year survival is only 20 percent; whereas when MAP >82 mmHg, two-year survival is 70 percent [24]. It has been this author's (BAR) experience that the MAP threshold (82 mmHg) applies to all patients (ie, those with spontaneous or iatrogenic hypotension, resulting from antihypertensive medication use). When MAP is ≤82 mmHg, medications that lower blood pressure must be stopped. If they are continued, worsening hypotension, hyponatremia, and azotemia are expected.

Too often, clinicians who start beta blockers or other antihypertensive medications do not follow these patients for the long term and may not realize that antihypertensive medications are not tolerated once ascites develops, especially diuretic-resistant ascites.

Older practice guidelines regarding variceal bleeding recommended beta blocker therapy without plans for discontinuation (ie, no stopping rules). However, attention has been drawn to the adverse effects of beta blockers in patients with ascites and the need for guidance regarding discontinuing therapy [23]. Updated practice guidance and guidelines have added thresholds for drug discontinuation but chose blood pressure <90/60 mmHg rather than MAP <82 mmHg [29,30]. There are no data to support a threshold <90/60 mmHg, which equates to a MAP of 70 mmHg. For example, MAP <60 mmHg was associated with a higher mortality rate. In a retrospective study including 183 patients with cirrhosis who required intensive care unit (ICU) admission, patients with nadir MAP <60 mmHg during the first hospital day had a higher mortality rate compared with MAP ≥60 mmHg (43 versus 7 percent) [31]. MAP <60 mmHg is dangerously close to 70 mmHg, the threshold used by practice guidelines. Many hospitals may still have local recommendations based on older practice guidelines that lead to excessive use of beta blockers. This can lead to iatrogenic hypotension with resulting hyponatremia, azotemia, and mortality.

Discontinuing other medications — Patients with diuretic-resistant ascites who are taking ACEIs, ARBs, or NSAIDs should stop the medications because they impair renal perfusion.

Systemic blood pressure tends to progressively fall with increasing severity of cirrhosis, particularly in patients with decompensated liver disease. Survival in patients with cirrhosis and ascites is dependent on mean arterial pressure (MAP) with a cut-point of 82 mm Hg; those with MAP >82 mm Hg have a 70 percent chance of surviving two years, whereas those with a MAP <82 mm Hg have only a 20 percent 2-year-survival [24]. The progressive decrease in systemic blood pressure is associated with reductions in renal perfusion and glomerular filtration rate and increases in the activity of the renin-angiotensin system [20]. This leads to elevated serum levels of vasoconstrictors such as vasopressin, angiotensin, and aldosterone. The use of medications such as ACEIs and ARBs blocks the production of these vasoconstrictors that are needed to compensate for the vasodilatory effects of nitric oxide. (See "Ascites in adults with cirrhosis: Initial therapy", section on 'Avoidance of angiotensin inhibition'.)

NSAIDs inhibit the synthesis of renal prostaglandins, leading to renal vasoconstriction, a lesser response to diuretics, and the possible precipitation of acute renal failure [32].

Oral midodrine — Midodrine is an oral vasopressor that will usually increase blood pressure in advanced cirrhosis, resulting in improved renal perfusion. We use midodrine in patients with

hypotension and/or diuretic-resistant ascites who do not respond to dietary modifications, education, discontinuation of beta blockers, and appropriately-prescribed diuretics. We start with 5 mg orally three times daily and adjust the dose every 24 hours (by increments of 2.5 mg for each dose; maximal dose 17.5 mg three times daily) to achieve a MAP >82 mm Hg.

Midodrine has been shown to be effective in combination with parenteral octreotide in reversing type I hepatorenal syndrome. There is also accumulating evidence that midodrine may be useful in treatment of diuretic-resistant ascites without the use of octreotide [33,34]. Midodrine is an attractive option because patients with diuretic-resistant ascites may be severely hypotensive, with systolic pressures in the 70s and 80s. Healthcare providers may be reluctant to give diuretics to these patients. The addition of midodrine can improve renal perfusion, increase renal sodium excretion, reduce ascites, and improve survival [33-35].

Midodrine has also been studied as an alternative to colloid replacement in patients undergoing large-volume paracentesis. (See 'Midodrine as an alternative to albumin' below.)

OPTIONS IF INITIAL TREATMENTS FAIL

Patients who do not respond to initial noninvasive treatments for diuretic-resistant ascites in the setting of cirrhosis, or who respond at first but subsequently lose their response, will require more invasive treatment. Patients should continue to follow a low-sodium diet, though diuretics should be discontinued if the urine sodium is <30 mEq per day or if diuretics induce intolerable side effects [20]. (See 'Initial treatments' above.)

Therapeutic options for patients who fail noninvasive treatments include:

- Liver transplantation
- Serial therapeutic paracenteses (approximately every two weeks)
- Transjugular intrahepatic portosystemic stent shunt (TIPS) placement

Other modalities such as peritoneovenous (LeVeen or Denver) shunts or surgical portasystemic shunts have very limited indications, and other new therapeutic options such as low-flow ascites pumps require further evaluation [36]. (See 'Other invasive treatments' below.)

Liver transplantation — The development of ascites in a patient with previously compensated cirrhosis is an accepted indication for listing for liver transplantation, provided that there are no contraindications, such as active alcohol use. (See "Liver transplantation in adults: Patient selection and pretransplantation evaluation".)

Patients usually progress from diuretic-sensitive to diuretic-resistant ascites over a period of months to years if they do not die from other complications of cirrhosis [3]. Patients developing diuretic-resistant ascites should ideally already be listed for and awaiting liver transplantation. While liver transplantation is definitive therapy for refractory ascites, patients often have a long waiting time until an organ becomes available. While the patient awaits transplantation, other therapeutic approaches will be required.

Therapeutic paracentesis — Serial large-volume paracenteses (LVPs) are mainstays in the treatment of diuretic-resistant ascites, both for patients awaiting liver transplantation and for those who are not transplantation candidates. LVP ameliorates the shortness of breath and early satiety that patients experience. It also may be associated with collateral advantages, such as reductions in the hepatic venous pressure gradient [37], intravariceal pressure, and variceal wall tension [37-39]. These parameters are considered important predictors of variceal bleeding, and the improvement after LVP may decrease the risk of bleeding. Serial LVP can be continued until liver transplantation, another treatment option is chosen (eg, TIPS), or death. (See "Diagnostic and therapeutic abdominal paracentesis" and "Pathogenesis of variceal bleeding in patients with cirrhosis".)

Contrary to old dogma based upon anecdotal observations of hemodynamic deterioration after therapeutic paracentesis, the safety of this approach in patients with cirrhosis and tense ascites has been proven in randomized trials [40-42]. Retrospective studies have suggested a risk of deterioration in hospitalized patients following LVP [43]. However, the risk attributable to the paracentesis is unclear given the difficulty in adjusting for underlying severity of illness and comorbidities in these patients and in knowing whether they were truly diuretic resistant.

Limited data have suggested that the incidence of acute kidney injury (AKI) in patients with cirrhosis who undergo paracentesis is low. In a cohort of 102 patients with cirrhosis who underwent a total of 258 paracenteses, AKI without an alternative etiology (defined as an increase in creatinine ≥0.3 mg/dl or ≥50 percent within 48 hours) was observed after four of 258 paracenteses (1.6 percent) [44]. Conversely, an improvement in renal function was observed following 25 of 258 paracenteses (10 percent).

Volume and frequency of paracentesis — Generally, the goal with LVP is to remove as much fluid as possible without excessive manipulation of the patient. The frequency with which LVP is required and the volume of fluid removed provide insight into patient dietary adherence. Patients who are consuming 88 mEq (2000 mg) of sodium per day and are excreting no sodium in the urine should require paracentesis of approximately 8 liters every two weeks (table 1) [2]. (See "Diagnostic and therapeutic abdominal paracentesis".)

Scheduling two-week returns to the clinic works well in our experience, and the typically flaccid, compliant abdominal walls in these patients permit the accumulation of 8 liters of fluid without the development of "tenseness." Patients with some sodium excretion in the urine should require the removal of less fluid, while those requiring the removal of more than 8 liters every two weeks **are likely nonadherent to their diet** and should receive more diet education, rather than more frequent LVP.

Need for routine testing of ascites — The prevalence of occult ascitic fluid infection in asymptomatic outpatients undergoing LVP for diuretic-resistant ascites is low [45,46]. As a result, the routine culture of fluid during paracentesis in such patients is probably not warranted. Our policy is to obtain a cell count and differential on all samples of ascitic fluid in the paracentesis clinic setting, while obtaining cultures only in symptomatic patients or if the fluid is cloudy. (See "Evaluation of adults with ascites", section on 'Cell count and differential'.)

Colloid replacement — The need for colloid replacement to prevent effective hypovolemia after LVP remains controversial [41,42,47]. It is likely not necessary for paracenteses of 5 liters or less [47,48]. For larger paracenteses, albumin solution (6 to 8 g/L of fluid removed) can be administered.

There are several formulations of albumin solution available. In Europe, only a 20 percent solution is available. In the United States, two formulations are available, a 25 and a 5 percent solution. The 25 percent solution is used most commonly in the United States. Both solutions are isotonic, with sodium concentrations of 130 to 160 mEq/L (mmol/L). The 5 percent solution provides five times the sodium load of the 25 percent solution. The 25 percent solution is typically given if the patient is hypervolemic, whereas the 5 percent solution is given if dehydration is suspected. (See 'Summary and recommendations' below.)

The optimal dose of albumin solution has not been well studied. Typically, patients are given 6 to 8 g of albumin for every liter of fluid removed. The only dose-finding study compared 4 g/L of fluid removed with 8 g/L found no difference in plasma renin or renal function at six days and no survival difference at six months [49].

The efficacy of albumin solution administration following LVP has been examined in studies using endpoints such as effective hypovolemia and survival. One marker of effective hypovolemia is an increase in plasma renin activity after paracentesis [42,50], which is referred to as postparacentesis circulatory dysfunction (PCD) [42]. In addition, studies have evaluated whether the need for albumin depends on the volume of fluid removed.

- In a widely quoted study, 105 patients with tense ascites undergoing LVP were randomly assigned to receive albumin solution (10 g/L of ascites removed) or no albumin [41].

Patients not receiving albumin were more likely to show signs of hemodynamic deterioration, including an increase in the plasma renin activity; these patients were also much more likely to develop worsening renal function and/or severe hyponatremia (21 versus 3.8 percent in those receiving albumin). However, a limitation of the study was that almost one-third of the patients had not received diuretics prior to entry into the study, and thus may not have been diuretic resistant.

- There is evidence that PCD only develops when larger volumes of fluid are removed. In a study involving a single 5-liter paracentesis in patients with truly diuretic-resistant ascites, plasma renin did not increase [48].

- In a randomized trial, PCD was less common in patients undergoing total paracentesis who received albumin solution compared with those who received dextran 70 or polygeline (19 versus 34 and 38 percent, respectively) [42]. However, the benefit was limited to patients who had at least 5 liters of ascitic fluid removed. Survival was significantly shorter in patients who developed PCD, but there were no differences in survival among the three treatment groups.

Although no high-quality trial has shown a direct survival advantage of one volume expander over another or compared with no volume expander, a meta-analysis demonstrated a survival advantage with albumin solution infusion compared with alternate volume expanders (eg, dextran, gelatin, hydroxyethyl starch, and hypertonic saline) [51].

More studies with careful selection of truly diuretic-resistant patients are needed. Based on the available data, it is reasonable to forego albumin after paracenteses of 5 liters or less [47,48]. For larger paracenteses, albumin (6 to 8 g/L of fluid removed) can be administered [20].

Midodrine as an alternative to albumin — Prophylactic use of midodrine (an oral alpha-adrenergic agonist) has been suggested as a less expensive alternative to albumin. In a trial with 40 patients undergoing LVP, patients were assigned to midodrine or albumin [52]. There was no difference in plasma renin activity between the groups. However, more studies are needed to establish the role of midodrine in LVP.

Paracentesis for patients who are not diuretic resistant — Some patients with tense ascites in the setting of nonadherence to a sodium restricted diet and diuretics prefer to come to the clinic frequently to have their ascites removed rather than follow the diet and take their medications. The problem with this approach is that repeated LVP causes protein and complement depletion. In theory, this may indirectly predispose to ascitic fluid infection [53], though no definitive data are available [54]. Thus, we prefer to treat diuretic-sensitive patients with diet and diuretics and to reserve serial LVP for patients who are truly diuretic resistant.

Other less invasive treatments — For patients with decompensated cirrhosis, administration of albumin has been studied in the inpatient and outpatient setting in Europe, although data have been mixed [55-58]. In a randomized trial including 777 hospitalized patients with decompensated cirrhosis who had a serum albumin level less than 3.0 g/dL (30 g/L), the risk of reaching a composite endpoint (new infection, kidney dysfunction, or death) was not significantly different for patients given albumin (increasing serum albumin level to ≥3.0 g/dL [30 g/L]) for 14 days or until discharge compared with standard care (albumin infusion if needed for an established indication) (30 versus 30 percent; adjusted odds ratio 0.98, 95% CI 0.71-1.33) [55]. In addition, patients in the albumin group had higher rates of pulmonary edema (4 versus 1 percent), although statistical analysis was not provided. In another trial including 440 patients with cirrhosis and uncomplicated ascites, transplant-free survival rates at 18 months were higher in patients given albumin infusions (40 grams twice weekly for two weeks, then weekly) in addition to standard care (diuretics and large volume paracentesis, as needed) compared with patients receiving standard care alone (77 versus 66 percent; HR 0.62, 95% 0.40-0.95) [57]. Additional trials are needed to determine if albumin infusion is beneficial for treating decompensated cirrhosis and if the potential benefits outweigh the risks and barriers to its use (eg, availability, cost) [58].

The use of albumin for established indications (eg, spontaneous bacterial peritonitis) is discussed separately. (See "Spontaneous bacterial peritonitis in adults: Treatment and prophylaxis", section on 'Special treatment considerations' and "Hepatorenal syndrome".)

Transjugular intrahepatic portosystemic stent-shunt — The prerequisite for the development of cirrhotic ascites is portal hypertension. Thus, measures directed at the reduction of portal pressure could decrease or eliminate ascites formation. One option to decrease portal pressures in carefully selected patients who are diuretic resistant is to create a transjugular intrahepatic portosystemic shunt (TIPS). A guideline from the American Association for the Study of Liver Diseases recommends that TIPS should be considered only in patients who are intolerant of repeated large volume paracentesis [59]. (See "Pathogenesis of ascites in patients with cirrhosis" and "Overview of transjugular intrahepatic portosystemic shunts (TIPS)".)

We consider referring a patient for TIPS if the following conditions are met:

- The patient has diuretic-resistant ascites
- The patient is intolerant of paracentesis or is requiring very frequent paracentesis (eg, weekly).
- The patient has Child-Pugh class A or B cirrhosis (calculator 1 and calculator 2)

- The patient has a Model for End-stage Liver Disease (MELD) score <18 (calculator 3 and calculator 4)
- The patient is <65 years of age
- A caregiver is present in the home
- The patient does not have alcoholic hepatitis
- The patient's cardiac ejection fraction is >60 percent
- The patient does not have a history of severe, spontaneous (ie, in the absence of gut bleeding, infection, or dehydration) hepatic encephalopathy or other injury to the central nervous system (eg, prior subdural bleeding, brain abscess, or cerebrovascular accident)

Patients who are **not** good candidates for TIPS include those with Child-Pugh class C cirrhosis (score >12), a high MELD score (>18) (calculator 3 and calculator 4), heart failure, or severe spontaneous hepatic encephalopathy (ie, encephalopathy in the absence of gastrointestinal bleeding, infection, or dehydration). The MELD score was developed to predict mortality following TIPS. (See "Model for End-stage Liver Disease (MELD)".)

Echocardiograms are typically performed to screen for subtle heart failure prior to TIPS placement. Patients with cirrhosis and ascites usually have ejection fractions of 70 to 75 percent [60]. Central pressure usually increases [61] and cardiac function can deteriorate after TIPS, so a baseline ejection fraction of >60 percent may be the minimum for candidates for TIPS.

TIPS is a side-to-side portacaval shunt, usually placed through the right internal jugular vein under local anesthesia by an interventional radiologist. In two observational studies with 75 patients, compared with the patients' baseline, TIPS led to an increase in urine output, a marked or complete reduction in ascites, and lower diuretic doses or cessation of diuretics in approximately 75 percent of patients [62,63]. After TIPS placement, liver enzymes may transiently deteriorate [64], and there may be a delayed improvement in renal function, including a lower plasma creatinine concentration and improved sodium excretion [62,65]. In one study, for example, the average plasma creatinine concentration was 1.5 mg/dL (132 micromol/L) at baseline, was unchanged at one week, and fell to 0.9 mg/dL (80 micromol/L) by six months [62]. Other potential benefits include improvements in the patient's nutritional status and quality of life [66].

Although the results from individual studies are heterogeneous, increasing evidence suggests that TIPS is more effective than LVP in controlling ascites in carefully selected patients and may be associated with a survival advantage [67-71]. At least three meta-analyses comparing TIPS with LVP have been published [72-74]. The most recent examined individual patient data (149 allocated to TIPS and 156 to LVP) [74]. TIPS was more effective than LVP in preventing recurrent tense ascites (42 versus 89 percent). In addition, transplant-free survival was better in the TIPS

group (75 versus 65 percent at 6 months, 63 versus 53 percent at 12 months, 49 versus 35 percent at 24 months, and 38 versus 29 percent at 36 months). The average number of hepatic encephalopathy episodes was greater in the TIPS groups (1.1 versus 0.6), although the probability of developing a first episode of hepatic encephalopathy was similar.

While TIPS may lead to better ascites control, complications of TIPS must also be considered. Hepatic encephalopathy occurs in approximately 30 percent of patients [75,76] and in a subset of patients is incapacitating [62]. The encephalopathy can usually be managed by lactulose therapy; in resistant cases of hepatic encephalopathy, the stent blood flow can be reduced by revising the shunt. (See "Transjugular intrahepatic portosystemic shunts: Postprocedure care and complications" and "Hepatic encephalopathy in adults: Treatment", section on 'Lactulose and lactitol'.)

Another significant problem after TIPS placement is the development of early thrombosis or delayed shunt stenosis. These problems occurred in 22 to 50 percent of patients who underwent TIPS prior to the development of polytetrafluoroethylene (Gore-Tex)-covered stents [62,66,67,75]. Coated stents have had excellent patency rates in a randomized trial and may be a breakthrough in technology that will substantially reduce the need for redilatation of the stent [77]. Coated stents, rather than the uncoated stents, are now standard of care. (See "Transjugular intrahepatic portosystemic shunts: Postprocedure care and complications", section on 'TIPS dysfunction'.)

Other invasive treatments — Other invasive treatments, such peritoneovenous shunts or surgical portasystemic shunts, have very limited indications.

Peritoneovenous shunt — A peritoneovenous shunt (Denver shunt) drains ascitic fluid into the internal jugular vein, returning the ascites into the vascular space. This technique was popularized as a "physiologic" treatment of diuretic-resistant ascites (and of the hepatorenal syndrome). However, it has been virtually abandoned due to an excessive rate of complications [78-80].

The only remaining indication for a peritoneovenous shunt is the rare patient with diuretic-resistant ascites who is not a candidate for transplantation or TIPS and is too obese or has too many abdominal surgical scars to permit safe, successful paracentesis [81]. Denver shunt placement can mitigate sarcopenia, as the LeVeen shunt did decades ago [82].

Surgical portosystemic shunts — As with TIPS placement, surgical portosystemic shunts (eg, a distal splenorenal shunt) significantly reduce the hepatic venous pressure gradient, the development of ascites, and the frequency of spontaneous bacterial peritonitis [83,84]. Shunt surgery has traditionally been associated with a high morbidity and mortality, and its use in the

treatment of ascites is only of historic interest, though it still has a minor role in patients with recurrent variceal hemorrhage, especially in those unusual patients whose cause is portal thrombosis without underlying cirrhosis. (See "Prevention of recurrent bleeding from esophageal varices in patients with cirrhosis".)

EXPERIMENTAL TREATMENTS

Drug therapies — Drug therapies that have been studied for managing patients with ascites include:

- Vasopressin receptor antagonists – Multiple vasopressin antagonists (vaptans) are primarily used in the treatment of heart failure. However, they have been studied in cirrhosis, though their efficacy in the treatment of diuretic-resistant ascites is unclear. One of the largest trials included 1200 patients with uncomplicated ascites as well as difficult-to-treat ascites. Patients treated with a vasopressin antagonist (satavaptan) had higher mortality rates than those who received placebo, and there was no clinical benefit with regard to the ascites [85]. (See "Hyponatremia in patients with cirrhosis", section on 'Vasopressin receptor antagonists'.)

  Another vasopressin antagonist, tolvaptan, has been associated with liver injury and should not be used in patients with liver disease [86].

  A potential problem with these agents is that they cause thirst, which may lead to complications in patients with hyponatremia. Patients with hyponatremia are usually asymptomatic until the serum sodium is <120 mEq/L (mmol/L). In such patients, treatment with a vasopressin antagonist may result in increased water consumption, leading to osmotic demyelination syndrome if the serum sodium rises too rapidly [87]. (See "Osmotic demyelination syndrome (ODS) and overly rapid correction of hyponatremia".)

  In addition, these agents are very expensive ($10,000 to $15,000 per month).

- Clonidine – Clonidine is an alpha-2-adrenergic receptor agonist that suppresses the renin-aldosterone system. Since the renin-aldosterone system is activated in patients with diuretic-resistant ascites, studies have looked at the use of clonidine in the management of diuretic-resistant ascites [35,88]. However, in this setting, the renin-aldosterone system is activated to support blood pressure, so suppression of the renin-aldosterone system could have detrimental effects.

In a randomized trial, 60 patients with diuretic-resistant or recurrent ascites were assigned to one of four groups: standard medical care plus clonidine, midodrine, or both, or standard medical care alone [35]. Patients who received midodrine or midodrine plus clonidine had better control of ascites compared with those who received standard medical care alone, and there was a trend toward better ascites control in patients who received clonidine alone. However, there was no difference in ascites control between the two midodrine groups. Until there are larger scale trials that prove the safety of clonidine in patients with cirrhosis and ascites, using midodrine to support blood pressure in hypotensive patients with ascites (without clonidine) seems appropriate.

- Sodium-glucose co-transporter 2 inhibitors – Sodium-glucose co-transporter 2 (SGLT2) inhibitors are used for treating hyperglycemia in patients with type 2 diabetes mellitus. Preliminary data in patients with cirrhosis, diabetes mellitus, and fluid retention have suggested that SGLT2 inhibitors were associated with reduction in ascites and peripheral edema [89,90]. Clinical trials are needed to explore the use of SGLT2 inhibitors in patients with diuretic-resistant ascites or in those intolerant/allergic to diuretics. (See "Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus" and "Ascites in adults with cirrhosis: Initial therapy", section on 'Other treatments'.)

Splenic artery embolization — Case reports have described splenic artery embolization for management of bleeding gastric varices or cytopenias associated with portal hypertension [91-96]. The resulting decrease in splenic blood inflow reduces flow through the splenic vein and subsequently decreases portal pressure. The use of this procedure for treatment of refractory ascites awaits more study.

Hypertonic saline plus a loop diuretic — The potential efficacy of hypertonic saline in combination with loop diuretics was evaluated in a study involving 84 patients with cirrhosis and diuretic-resistant ascites who were randomly assigned to either high-dose intravenous furosemide plus small-volume hypertonic saline or to repeated paracentesis plus a standard diuretic regimen [97]. Those assigned to hypertonic saline had significantly better control of ascites, pleural effusions, and leg edema.

The extent to which patients were compliant with a diuretic regimen and sodium restriction (and hence truly diuretic resistant) was unclear. In addition, why hypertonic saline would cause patients to become more responsive to diuretics is uncertain. Thus, more studies are needed before this approach should be considered.

Low-flow ascites pump — A pump that moves ascitic fluid from the peritoneal cavity into the urinary bladder has been developed in Europe (Automated Low-Flow Ascites pump). In a study of 40 patients with cirrhosis, the pump decreased the median number of large volume paracenteses per month from 3.4 to 0.2 [36]. Adverse events included problems related to the bladder catheter, bleeding, and infection. In a multicenter trial including 60 patients with refractory ascites, patients with an ascites pump (alfapump) had longer paracentesis-free intervals compared with standard of care (ie, large volume paracentesis as needed) [98,99]. However, use of the automated pump was associated with a higher rate of serious adverse events (85 versus 45 percent); thus, the potential benefits of the pump are offset by activation of endogenous vasoconstrictor systems and subsequent kidney impairment [98,100]. Daily removal of >1.5 L may increase risk of hyponatremia and AKI [101]. Multidisciplinary expertise in managing patients with advanced liver disease is needed when evaluating patients who may be candidates for this device.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cirrhosis" and "Society guideline links: Portal hypertension and ascites".)

SUMMARY AND RECOMMENDATIONS

- **Diagnosis** – Diuretic-resistant ascites in patients with cirrhosis is considered to be present when at least one of the following criteria is present in the absence of therapy with a nonsteroidal antiinflammatory drug (NSAID), which can induce renal vasoconstriction and diminish diuretic responsiveness (see 'Diagnosis' above):
  - An inability to mobilize ascites despite confirmed adherence to the dietary sodium restriction (88 mEq [2000 mg] per day) and the administration of maximum tolerable doses of oral diuretics (400 mg per day of spironolactone and 160 mg per day of furosemide).
  - Rapid reaccumulation of fluid after therapeutic paracentesis.
  - The development of diuretic-related complications such as progressive azotemia, hepatic encephalopathy, or progressive electrolyte imbalances.

Ascites is truly diuretic resistant in approximately 10 percent of patients with cirrhosis and ascites. (See 'Introduction' above.)

- **Initial therapy**

  - Patients who are diuretic resistant should continue to follow a low-sodium diet (88 mEq [2000 mg] per day). Diuretics should be discontinued if the urine sodium is <30 mEq per day. (See 'Continuation of sodium restriction and when to discontinue diuretics' above.)

  - We suggest beta blockers **not** be initiated in patients with diuretic-resistant ascites or, if the patient is already taking a beta blocker, that it be discontinued (**Grade 2C**). Beta blockers appear to reduce survival in patients with refractory ascites or spontaneous bacterial peritonitis (SBP). In addition, we discontinue beta blockers in patients who present with SBP, bleeding, azotemia, severe alcoholic hepatitis, or hypotension. If the patient's blood pressure and azotemia improve off the beta blocker, it can be restarted cautiously with careful monitoring of blood pressure (including in home monitoring) and renal function. However, among patients with SBP, we discontinue the beta blocker permanently. Other medications to avoid include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and NSAIDS. (See 'Discontinuing beta blockers' above and 'Discontinuing other medications' above.)

  - We suggest that patients with cirrhosis who have hypotension and/or diuretic-resistant ascites and who do not respond to dietary modifications, education, discontinuation of beta blockers, and appropriately-prescribed diuretics be treated with oral midodrine (**Grade 2C**). Midodrine is an oral vasopressor that will usually increase blood pressure in advanced cirrhosis, resulting in improved renal perfusion. We start with 5 mg orally three times daily and adjust the dose every 24 hours (maximal dose 17.5 mg three times daily) to achieve a mean arterial pressure >82 mm Hg mmHg. (See 'Oral midodrine' above.)

- **Subsequent therapy** – For patients who do not improve with initial therapy, therapeutic options include (see 'Options if initial treatments fail' above):

  - Therapeutic paracentesis – We suggest that patients with diuretic-resistant ascites who do not adequately respond to noninvasive treatments undergo serial large-volume paracentesis rather than transjugular intrahepatic portosystemic shunt (TIPS) placement as initial therapy (**Grade 2B**). Large-volume paracentesis is generally well tolerated, whereas TIPS placement frequently results in hepatic encephalopathy. (See 'Therapeutic paracentesis' above.)

The necessity of plasma expansion after large-volume paracentesis remains controversial. We suggest albumin solution be given (6 to 8 grams of albumin/liter of fluid removed) when ≥5 liters of ascites are removed (**Grade 2B**). We sugge**st against** using albumin if <5 liters are removed (**Grade 2C**). (See 'Colloid replacement' above.)

- TIPS – TIPS may be more effective than serial paracenteses in carefully selected patients, but the effectiveness of TIPS in heterogeneous patient populations and centers with varying experience with TIPS has yet to be established. (See 'Transjugular intrahepatic portosystemic stent-shunt' above.)

  We consider referring a patient for TIPS if the following conditions are met:

  - The patient has diuretic-resistant ascites.
  - The patient is intolerant of paracentesis or is requiring very frequent paracentesis (eg, weekly).
  - The patient has Child-Pugh class A or B cirrhosis (calculator 1 and calculator 2).
  - The patient has a Model for End-stage Liver Disease score <18 (calculator 3 and calculator 4).
  - The patient is <65 years of age.
  - A caregiver is present in the home.
  - The patient does not have alcoholic hepatitis.
  - The patient's cardiac ejection fraction is >60 percent.
  - The patient does not have a history of severe, spontaneous (ie, in the absence of gut bleeding, infection, or dehydration) hepatic encephalopathy or other injury to the central nervous system (eg, prior subdural bleeding, brain abscess, or cerebrovascular accident).

- Liver transplantation – Liver transplantation is the only definitive therapeutic option for patients with diuretic-resistant ascites, but patients who are awaiting transplantation or who are not transplantation candidates need to have their ascites managed. (See 'Liver transplantation' above.)

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GRAPHICS

Estimation of sodium balance in patients with cirrhosis and ascites

The following calculations can be used to estimate sodium balance in a patient with ascites and advanced cirrhosis
Mean serum sodium concentration = ascitic fluid sodium concentration = 130 meq/L
Daily net positive balance is 78 meq if intake is 88 meq, excretion is close to zero, and nonurinary losses are 10 meq
Total sodium accumulation over 14 days is 1092 meq (78 x 14)
Increase in extracellular fluid volume (most of which will accumulate as ascites) is 8.4 liters (1092 meq ÷ 130 meq/L)
Thus, if a patient is complying with dietary sodium excretion, an 8.4 liter paracentesis will remove 14 days of accumulated sodium. Paracentesis can be performed less often in compliant patients who still have some urinary sodium excretion.

Graphic 53969 Version 1.0

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