Clinical Scenario

A 56-year-old man with hepatitis C–related cirrhosis is admitted for management of ascites. Despite a 90-mEq sodium–restricted diet and high doses of diuretics (spironolactone 400 mg/day and furosemide 160 mg/day), the ascites has not been well controlled for the past 4 weeks. Physical examination reveals an arterial pressure of 90/70 mm Hg, heart rate of 98 bpm, lower extremity edema, stigmata of cirrhosis with temporal wasting, mild icterus and spider angiomas, tense ascites, splenomegaly, and grade 1 encephalopathy. His hemoglobin level is 12 g/dL, white cell count is 3.8 $10^9$/L, and platelet count is 79 $10^9$/L. Other laboratory test results are AST, 44 U/L; ALT, 57 U/L; serum bilirubin, 3.1 mg/dL; albumin, 3.2 g/dL; international normalized ratio (INR) for prothrombin time, 1.9; serum sodium, 129 mEq/L; potassium, 5.2 mEq/L; blood urea nitrogen, 22 mg/dL; and serum creatinine, 1.7 mg/dL. A diagnostic paracentesis does not reveal evidence of spontaneous bacterial peritonitis. Ultrasound examination of the liver does not show any portal vein thrombosis or liver masses. How should this patient be managed, and what is the role of large volume paracentesis, transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation in this patient?

The Problem

Patients with cirrhosis may develop kidney dysfunction manifested by renal retention of sodium and water, as well as vasoconstriction of the renal circulation. Sodium retention is the first complication and is responsible for fluid accumulation in the form of ascites and edema. With time, patients develop more severe sodium retention and can develop ascites that is refractory to diuretic therapy (Figure 1). Later events include solute-free water retention leading to dilutional hyponatremia and renal vasoconstriction that is responsible for the development of hepatorenal syndrome.

Ascites is the most common complication of cirrhosis and results in poor quality of life, increased risk for infections, renal failure, and ultimately death. Nearly 60% of patients with compensated cirrhosis at initial diagnosis develop ascites within 10 years. The development of ascites in cirrhosis is a poor prognostic feature because it has been estimated that approximately 50% of these patients will die in approximately 2 years without liver transplantation. Ascites was recently defined into 3 groups by the International Ascites Club: in Grade 1, ascites fluid is detected only by ultrasound; in Grade 2, ascites is moderate with symmetrical distention of the abdomen; and in Grade 3, ascites is large or tense with marked abdominal distention. Refractory ascites refers to a condition that occurs in 5%–10% of cirrhotic patients admitted to hospital with Grade 3 ascites. It is defined as ascites that does not respond adequately to diuretics. Typically, lack of response indicates that the decrease in weight on therapy is less than 200 g per day.

The most accepted definition and diagnostic criteria of refractory ascites are those proposed by the International Ascites Club in a consensus conference published in 1996 and revised in 2003. In refractory ascites, a significant increase in sodium excretion cannot be achieved either because patients do not respond to the highest accepted doses of diuretics for ascites resolution (spironolactone 400 mg/day and furosemide 160 mg/day), or because they develop side effects such as hyperkalemia, hyponatremia, hepatic encephalopathy, or renal failure that preclude use of diuretics.

Thus, the term refractory ascites defines 2 subtypes: (1) diuretic-resistant ascites, ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to dietary sodium restriction and intensive diuretic therapy, and (2) diuretic-intractable ascites, ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-resistant or diuretic-intractable ascites.
induced complications that preclude the use of an effective diuretic dosage. The diagnostic criteria of refractory ascites are described in Table 1. Refractory ascites is indicative of progression of liver disease and is usually not reversible except in some patients with alcoholic cirrhosis and superimposed alcoholic hepatitis. Refractory ascites is the usual manifestation of type 2 hepatorenal syndrome, which is defined as serum creatinine \( \geq 1.5 \text{ mg/dL} \) or creatinine clearance \( \leq 40 \text{ mL/min} \).

Patients with refractory ascites usually have advanced liver disease and avid sodium retention (with urinary sodium \( <10 \text{ mEq/L} \)) and, therefore, constitute a subset of patients with ascites with a particularly poor prognosis. The estimated 1-year probability of survival is only 50%.

### Management Strategies and Supporting Evidence

#### General Measures

The first and most important aspect in the management of all patients with cirrhosis and ascites is evaluation for liver transplantation. The priority for allocation of organs for liver transplantation in the United States is based on the Model for End-Stage Liver Disease (MELD) score. This is a mathematically derived score calculated from serum bilirubin, serum creatinine, and the INR for prothrombin time. This scoring system is objective, includes an important parameter of renal function, and predicts survival in patients with cirrhosis. However, its role in predicting prognosis in patients with refractory ascites has not been specifically studied. Although serum creatinine is included in the MELD score, some patients with refractory ascites might have a near-normal serum creatinine (as a result of low endogenous production), despite a low glomerular filtration rate. Unfortunately, some of these patients might have low initial MELD scores, which place them at a low priority for liver transplantation. Modifications in the MELD scoring system incorporating serum sodium might improve the accuracy of the model in predicting survival in patients with cirrhosis.

Diagnostic paracentesis is required in all patients admitted to the hospital with ascites and in those patients with any evidence of clinical deterioration such as fever, abdominal pain, gastrointestinal bleeding, hepatic encephalopathy, or hypotension to rule out spontaneous bacterial peritonitis. Abdominal ultrasonography with Doppler helps to exclude hepatocellular carcinoma and/or portal vein thrombosis. If a patient has had a previous episode of spontaneous bacterial peritonitis and is not receiving prophylaxis, oral quinolones (norfloxacin

![Figure 1. Schematic representation of the temporal relationship of the development of renal function abnormalities in cirrhosis. Refractory ascites occurs after initial ascites formation, is associated with intense sodium retention (urine sodium \( <10 \text{ mEq/L} \)), and usually precedes dilutional hyponatremia and hepatorenal syndrome (HRS).](image)

**Table 1. Definition and Diagnostic Criteria for Refractory Ascites in Cirrhosis**

<table>
<thead>
<tr>
<th>Diuretic-resistant ascites: Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment.</th>
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<tbody>
<tr>
<td>Diuretic-intractable ascites: Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage</td>
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**Requisites:**

1. Treatment duration: Patients must be on intensive diuretic therapy (spironolactone 400 mg/d and furosemide 160 mg/d) for at least 1 week and on a salt-restricted diet of less than 90 mmoles/day.
2. Lack of response: Mean weight loss of \( <0.8 \text{ kg} \) over 4 days and urinary sodium output less than the sodium intake.
3. Early ascites recurrence: Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization.
4. Diuretic-induced complications: Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor. Diuretic-induced renal impairment is an increase of serum creatinine by \( >100\% \) to a value \( >2 \text{ mg/dL} \) in patients with ascites responding to treatment. Diuretic-induced hyponatremia is defined as a decrease of serum sodium by \( >10 \text{ mmol/L} \) to a serum sodium of \( <125 \text{ mmol/L} \). Diuretic-induced hypokalemia or hyperkalemia is defined as a change in serum potassium to \( <3 \text{ mmol/L} \) or \( >6 \text{ mmol/L} \) despite appropriate measures.

400 mg/day or ciprofloxacin 500 mg/day) should be given on a long-term basis. Standard medical care of these patients should also include screening for hepatocellular, colorectal, prostate, breast, and cervical cancer. In addition, patients should be vaccinated against hepatitis A and B, pneumococcal pneumonia, and influenza. If the patient has not already had an upper gastrointestinal endoscopy, one should be performed to establish the presence and size of any gastroesophageal varices to determine whether prophylaxis against variceal bleeding is warranted.

An evaluation by a dietitian is recommended for appropriate education regarding caloric and salt intake. A low-sodium diet with 70–90 mmol/day of sodium (<2 g salt) is recommended to reduce ascites and edema formation. More stringent sodium restriction is not recommended because it renders food unpalatable and might impair the nutritional status of the patient. Improvement of the nutritional status is of key importance, because cirrhotic patients with advanced disease have decreased intake of nutrients, decreased absorption of nutrients, increased energy expenditure, and altered fuel metabolism with an accelerated starvation metabolism. Resolution of refractory ascites might significantly improve the nutritional status of patients as measured by resting energy expenditure, total body nitrogen, body fat, and food intake.

Treatment options after considering liver transplantation include repeated large-volume paracentesis plus plasma expansion or TIPS. Peritoneovenous shunts, although effective, were abandoned because of significant complications and high mortality when compared with paracentesis.

Repeated therapeutic paracentesis. Therapeutic paracentesis is defined as the removal of a large amount of ascites. This treatment has been used to manage patients with ascites since the time of the ancient Greeks. Interest in paracentesis decreased in the 1950s when diuretics were introduced as treatment for patients with cirrhosis and ascites. Still, some patients were intolerant to diuretics or just did not respond to this therapy. Therefore, in the mid-1980s an interest in this procedure was renewed as a treatment for patients with large-volume and refractory ascites. The safety and superiority (compared with diuretics) of therapeutic paracentesis were clearly demonstrated in randomized controlled studies. Therapeutic paracentesis is usually performed as the initial treatment for refractory ascites in most patients. After paracentesis, plasma expansion with albumin (6–8 g/L of ascites removed) is recommended in all patients to prevent the post-paracentesis circulatory dys-function. This complication is a circulatory derangement with marked activation of the renin-angiotensin system that occurs 24–48 hours after the procedure. It is clinically silent, not spontaneously reversible, and associated with hyponatremia, renal impairment, rapid reaccumulation of ascites, and decreased survival. Post-paracentesis circulatory dysfunction is preventable to a large extent by the administration of albumin. Patients with refractory ascites, on average, require a paracentesis every 2–4 weeks. The majority of patients might be treated as outpatients. Because therapeutic paracentesis is easy to perform and safe, it is considered the first line of treatment for refractory ascites in most centers.

Although local complications such as bleeding, infection, or intestinal perforation related to paracentesis are always a concern in patients with advanced cirrhosis, they are extremely rare if paracentesis is performed with an appropriate technique and needle. The risk of significant bleeding at the puncture site or hemoperitoneum is extremely low. A recent retrospective study showed that the risk of severe hemorrhage after paracentesis occurred in 0.2% of cases, with an estimated death rate of <0.01%. Interestingly, major risk factors for bleeding were high Child-Pugh and MELD scores, but not operator experience, elevated INR, or low platelet count. Similarly, another study reported that therapeutic paracentesis performed in an outpatient setting was safe and efficient, even in patients with a low platelet count and prolonged prothrombin time.

Transjugular intrahepatic portosystemic shunt. TIPS, which functions like a side-to-side portacaval shunt, was introduced nearly 2 decades ago as an alternative to shunt surgery for refractory variceal bleeding in patients with cirrhosis. Initial experience demonstrated that patients who received TIPS also had resolution of their ascites. This observation, in addition to the fact that ascites formation occurs when portal pressure is ≥12 mm Hg, led to the application of TIPS as therapy for refractory ascites. Portal decompression is carried out by the insertion of an intrahepatic stent between the hepatic vein and the portal vein by using a transjugular approach.

Data from nonrandomized and randomized trials have shown better rates of ascites resolution with TIPS when compared with paracentesis, with complete response after TIPS in 51%–79% of cases versus 3%–24% in the paracentesis groups. In all studies ascites resolution was rapidly achieved with TIPS, and when compared with patients receiving therapeutic paracentesis, a significant decrease was observed in the numbers of paracentesis required by patients randomized to the paracentesis arm.
In addition, it has been reported that quality of life improves after TIPS. The main disadvantage with TIPS is frequent obstruction of the prosthesis (70% in 1 year), which precipitates reaccumulation of ascites in some patients. However, newer polytetrafluoroethylene-covered prostheses improve TIPS patency and decrease the number of clinical relapses and reinterventions without increasing the risk of encephalopathy. Other major side effects associated with TIPS include a 30% chance of hepatic encephalopathy, congestive heart failure in patients with unrecognized cardiac disease, hemolytic anemia, and impairment in liver function.

Selection of patients for transjugular intrahepatic portosystemic shunt. The indications and contraindications of placing TIPS in patients with cirrhosis were recently published by the American Association for the Study of Liver Diseases. For the most part in patients with refractory ascites, advanced age (>65 years), congestive heart failure, severe pulmonary hypertension, unrelieved biliary obstruction, uncontrolled infection or sepsis, severe coagulopathy (INR >5), central hepatocellular carcinoma, grade 3 or 4 (West Haven criteria) hepatic encephalopathy, and Child-Pugh score >12 are considered to be contraindications. Patients with preserved liver function in general do well after TIPS; but those with severe liver failure often deteriorate and might die after the intervention. The prognosis of patients receiving TIPS seems to be related to the severity of the underlying liver disease. Therefore, to better determine which patients are at risk for death after a TIPS placement, 2 prognostic models have been proposed. The most used model is that from which the MELD was created. In this model, INR, total serum bilirubin level, serum creatinine level, and etiology of cirrhosis accurately predicted survival (particularly at 3 months) after TIPS was placed. In this model the best outcomes are seen in patients with a MELD score <14. In the other model, variables including bilirubin level >3.0 mg/dL, ALT level >100 IU/L, pre-TIPS encephalopathy, and urgency of TIPS were independent predictors of survival.

Unfortunately, neither of these 2 models has been specifically validated for patients with refractory ascites. However, results from randomized controlled studies showed that lower Child-Pugh and MELD scores at baseline were associated with a higher survival probability in those randomized to TIPS.

Areas of Uncertainty

Transjugular intrahepatic portosystemic shunt or therapeutic paracentesis. A probable area of wide uncertainty in the management of refractory ascites pertains to which is the best treatment option, because there are conflicting survival data, different opinions from experts in the field, and different patient preferences. Five randomized controlled trials were performed to determine whether TIPS is superior to paracentesis in patients with refractory ascites. These trials of TIPS versus repeated paracentesis showed that TIPS was associated with a lower rate of ascites recurrence but a higher rate of hepatic encephalopathy. In the TIPS group, 62% ± 19% showed improvement in ascites versus 24% ± 19% in the paracentesis group. Hepatic encephalopathy occurred in nearly 40% of patients receiving TIPS versus only 22% in those treated with paracentesis. There is conflicting evidence in regard to survival because some studies have shown survival benefit with TIPS, whereas others have not shown any difference in survival. The transplant-free survival rate at 2 years in 2 studies was similar, ranging from 26%–35% for the TIPS group versus 30%–33% in the paracentesis group. Two recent meta-analyses of these 5 randomized controlled studies similarly concluded that although TIPS was better in controlling ascites in these patients, survival was not different. An important aspect to consider when treating patients is cost. The price of treating patients with refractory ascites with TIPS both in the United States and in Europe is much higher than the cost of repeated paracentesis plus albumin. One study showed that the calculated costs per patient receiving TIPS in the United States were 103% greater than those in the paracentesis group. With these conflicting data it is difficult to recommend strict guidelines; nonetheless, it appears that therapeutic paracentesis with albumin is the initial treatment of choice because of its wider applicability, lower cost, and less side effects when compared with TIPS. However, placement of TIPS should be considered in patients with refractory ascites, and only after evaluating the patient’s preference, clinical status, Child-Pugh and MELD scores, bilirubin levels, cardiac function, and INR, should the decision of placing one be made. TIPS placement must be evaluated on a case-by-case basis and probably should be reserved for patients with preserved liver function (bilirubin <3 mg/dL, INR <2, Child-Pugh score <12, MELD score <18), aged <65 years, without hepatic encephalopathy or cardiopulmonary disease, with loculated fluid, or those requiring more than 3–4 taps per month or unwilling to undergo repeated paracentesis. Patients with MELD scores >24 have limited survival and probably should not receive TIPS.

Use of albumin as a volume expander. Another area of debate that has been ongoing for several years is that of the use of albumin as a plasma expander for prevention of post-paracentesis circulatory dysfunction.
Although albumin is better at preventing this complication than other expanders when more than 5 L is removed, randomized comparative studies have not shown differences in survival of patients treated with albumin compared with that of patients treated with other plasma expanders. Larger trials with a high number of patients would be required to demonstrate that the greater protective efficacy of albumin on circulatory function compared with other plasma expanders results in a survival benefit. Although no significant differences in survival have been demonstrated, preventing hyponatremia and renal failure and diminishing the recurrence of ascites favor use of albumin as a volume expander.

Published Guidelines

The most recent guidelines for the management of ascites as well as those for use of TIPS published by the American Association for the Study of Liver Diseases and a consensus published by the International Ascites Club state that refractory ascites should be initially managed with therapeutic paracentesis and plasma expansion. According to these guidelines, placement of TIPS should be considered in patients intolerant to paracentesis, requiring >3 paracentesis per month, with contraindications to paracentesis and a Child-Pugh score <12. At the time the guidelines were published, not all studies of TIPS versus paracentesis were available, and therefore recommendations were not made favoring one method versus the other. Since the guidelines of the American Association for the Study of Liver Diseases and the International Ascites Club will probably not change with the new studies, the initial management of refractory ascites should still be therapeutic paracentesis.

Recommendations

This patient has advanced liver disease with a Child-Pugh score of 12 and a MELD score of 23. The most important aspect of his management is undoubtedly an evaluation for liver transplantation, which apparently has not taken place. For his refractory ascites we recommend therapy with therapeutic paracentesis with albumin administration (Figure 2). Moreover, his Child-Pugh and MELD scores predict poorer survival, and his underlying hepatic encephalopathy, although mild, is likely to worsen if a TIPS is placed. In this particular case a TIPS, although risky, would be considered only if the patient had loculated ascites or was unwilling to undergo repeated paracentesis. The TIPS procedure is best avoided if the patient is likely to receive a liver transplant in the near future.

Suggested Reading


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