Diagnosis and Management of Ascites

Evaluation of Ascites

Ascites is defined as an abnormal accumulation of fluid in the abdominal cavity. Ascites is the most common complication of cirrhosis, with approximately 50% of patients with compensated cirrhosis developing ascites over the course of 10 years. After developing ascites that necessitates hospitalization, the risk of mortality increases to 15% at 1 year and nearly 50% at 5 years. Complications following the development of ascites include spontaneous bacterial peritonitis, dilutional hyponatremia, refractory ascites, and hepatorenal syndrome. Development of these complications markedly decreases the likelihood of survival. Once ascites develops, patients should be referred for consideration of liver transplantation.

History and Physical Examination

In the United States, in approximately 85% of patients with ascites, cirrhosis is the cause, but 15% have a non-hepatic cause of fluid accumulation. Approximately 5% of patients have “mixed” ascites or have two or more causes for the ascites, typically cirrhosis plus another reason. In addition to assessing for risk factors for liver disease, history or risk factors for malignancy, heart failure, nephrotic syndrome, thyroid myxedema, recent abdominal surgery, and tuberculosis should be elicited. The presence of bulging flanks suggests the presence of ascites. In order for the flank dullness to be appreciated on physical exam, at least 1500 mL of ascites needs to be present. The shifting dullness test improves the diagnostic sensitivity of physical examination for detecting the presence of ascites; this test has 83% sensitivity and 56% specificity in detecting ascites. An abdominal ultrasound can be done to confirm the presence of ascites when suspected on history and physical examination.

Diagnostic and Therapeutic Paracentesis

The evaluation for the etiology of clinically apparent ascites should begin with an abdominal paracentesis with appropriate ascitic fluid analysis. In addition, at time of any hospital admission, a diagnostic paracentesis should be done to assess for infection. Patients do not need to be fasting for this procedure. Prophylactic blood products, including fresh frozen plasma and platelets, do not routinely need to be given prior to a paracentesis in patients with cirrhosis with associated thrombocytopenia and coagulopathy. The tests for coagulation do not reflect the true bleeding risk in these patients, as there is diminished production of both procoagulants and anticoagulants. There are no threshold criteria for coagulation parameters or platelet count for a paracentesis. This procedure, however, should be avoided in the setting of clinically evident hyperfibrinolysis or disseminated intravascular coagulation. Epsilon aminocaproic acid can be given to treat hyperfibrinolysis. Desmopressin may be used in patients with renal failure. The following summarizes the key steps in performing an abdominal paracentesis.
• **Patient Position and Site for Paracentesis:** The procedure is usually performed with the patient lying supine. As described in the most recent practice guidelines from the American Association for the Study of Liver Diseases, the left lower quadrant of the abdomen is the preferred site for the paracentesis and the exact insertion site should be located 2 fingerbreadths (3 cm) cephalad and 2 fingerbreadths (3 cm) medial to the anterior superior iliac spine (Figure 5). Some experts choose the midline of the abdomen midway between the pubis and umbilicus, but this site is considered less preferable in obese patients (due to the increase in midline wall thickness) and in patients with lower volume-ascites (a smaller pool of fluid in the midline than in the lateral quadrant). The right lower quadrant may be complicated by a dilated cecum or appendectomy scar. Extreme care should be taken to avoid the inferior epigastric arteries (Figure 6), which are located halfway between the pubis and anterior superior iliac spines and run cephalad in the rectus sheath, as well as visible collaterals in the abdominal wall. In addition, caution is needed in patients who have a palpable spleen, as it could be ruptured with the left lower quadrant approach. If the ascitic fluid is difficult to find on physical examination or if there is significant bowel dilatation, ultrasonography can be used to help locate the fluid pocket and visualize the spleen and other structures to guide this procedure. Paracentesis sites should be chosen distant from abdominal surgical scars or under image guidance.

• **Choosing Needle for Insertion:** A 1.0 or 1.5 inch 21 or 22 gauge single hole needle (or 3.5 inch 22 gauge needle for obese patients) can be used for a diagnostic paracentesis, whereas a 15 or 16 gauge multihole two-piece needle set can be used for therapeutic paracentesis, involving the removal of more than 5 L of ascites for symptomatic relief from abdominal pain, early satiety, and/or dyspnea.

• **Preparation and Insertion Technique:** The site should be cleansed with iodine or chlorhexidine solution and the skin should be anesthetized using 1% lidocaine solution via a 25 or 27 gauge needle. Sterile gloves should be worn to avoid contamination of samples. After raising a wheal in the superficial skin, 3 to 5 mL of lidocaine is used to anesthetize the soft tissue tract using the Z-track technique (the skin is pulled downward with the non-dominant hand, while inserting the needle with the other hand (Figure 7), to decrease the risk of ascitic fluid leak. The skin is not released until the needle enters the peritoneal cavity, indicated by the aspiration of ascitic fluid. The paracentesis needle is inserted along the same line using the Z-track technique. A scalpel can be used to create a skin nick to facilitate the entry of the larger gauge needle if therapeutic paracentesis is needed. After entry into the peritoneum, the angle and depth of the paracentesis needle should be stabilized. The suction applied should be intermittent rather than continuous to avoid pulling in omentum or bowel into the needle tip and obstructing flow. If the flow of liquid stops, the patient can be slowly repositioned in an effort to pool more fluid near the needle tip.

• **Fluid Collection and Samples:** For a diagnostic tap, a minimum of 25 mL of fluid should be collected. One to two mL of ascitic fluid should be injected into a purple top (EDTA) tube for the cell count and differential tests. Three to four mL of fluid should be directed into a red top tube for chemical analysis. Fluid should be directly inoculated into blood culture bottles at the bedside, typically 10 mL into each bottle. If needed, an additional 50 mL of fluid can be sent in a sterile syringe or cup for cytology or other tests. Vacuum bottles are used to assist the speed of fluid removal in a therapeutic paracentesis.

• **Paracentesis Complications:** The paracentesis procedure is generally very safe, with only a 1% risk of abdominal wall hematoma and a less than 0.5% risk of mortality, even in patients with coagulopathy related to liver disease. Post-paracentesis ascitic fluid leak can occur in 5% of patients, especially when larger needles are used. More serious complications such as hemoperitoneum and bowel perforation are extremely rare, reported in less than 1 in 1000 cases. Infections due to this procedure are rare, most often occurring in cases of bowel injury.
Analysis of Ascitic Fluid

The following includes a summary of major laboratory tests to consider performing with diagnostic paracentesis. Other tests not discussed can be ordered if there is suspicion for alternative or additional causes of ascites. For any initial diagnostic paracentesis to evaluate ascites, it is important to determine whether portal hypertension is present and whether the ascitic fluid is infected.

- **Albumin and Protein**: Routinely, an ascitic fluid sample should be sent for albumin and total protein. The serum-ascites albumin gradient (SAAG) is calculated by subtracting the ascitic fluid albumin value from the serum albumin value obtained on the same day. A SAAG value greater than or equal to 1.1 g/dL is indicative of portal hypertension, but does not exclude additional causes of ascites in a patient with portal hypertension.[9] An ascitic fluid total protein value less than 2.5 g/dL is consistent with ascites from cirrhosis or nephrotic syndrome, whereas a high ascitic fluid protein value greater than 2.5 g/dL is seen in patients with a cardiac cause of ascites.

- **Cell Count and Cultures**: Routinely, a cell count and differential should be performed on ascitic fluid. With any concern for infection, the fluid should be directly inoculated into aerobic and anaerobic blood culture bottles at the bedside prior to the administration of antibiotics, as it increases the yield of bacterial growth in culture from 50% to around 80% when the polymorphonuclear leukocyte (PMN) count is greater than or equal to 250 cells/mm³.[10,11] The yield on Gram’s staining of ascitic fluid is very low, except in the setting of bowel perforation into the ascites. Fungal cultures should be obtained if indicated.

- **Mycobacterial Smear and Culture**: Ascitic fluid smear and culture for mycobacteria should be reserved for patients at high risk for tuberculous peritonitis as the sensitivity of the smear is poor and the sensitivity of the fluid culture for mycobacteria is only approximately 50%. The 4 to 6 weeks needed before culture results are available delays diagnosis. Ascitic fluid polymerase chain reaction (PCR) assays can be done but the utility of these tests has not been well established. The gold standard for the diagnosis of tuberculous peritonitis remains directed peritoneal biopsy via laparoscopy or mini laparotomy and mycobacterial culture.

- **Carcinoembryonic Antigen and Alkaline Phosphatase**: Ascitic fluid carcinoembryonic antigen greater than 5 ng/mL or ascitic fluid alkaline phosphatase greater than 240 units/L is consistent with secondary bacterial peritonitis due to gut perforation.[12] Additional labs that support secondary bacterial peritonitis from gastrointestinal perforation include ascitic fluid total protein greater than 1 g/dL, glucose less than 50 mg/dL, and lactate dehydrogenase (LDH) greater than 225 mU/mL.[13]

- **Cytology**: Ascitic fluid cytology is expensive and is only revealing in the setting of peritoneal carcinomatosis, typically in patients with a history of breast, colon, gastric or pancreatic carcinoma. At least 50 mL of fresh warm ascitic fluid needs to be immediately processed for optimal yield, with a sensitivity of 82.8% with one sample sent, improving to 96.7% when 3 samples are sent from different paracenteses.[14]

- **Cancer Antigen 125**: Serum cancer antigen 125 (CA125) can be elevated in any patient with ascites or pleural effusion of any cause, as the level rises when mesothelial cells are under pressure in the presence of fluid, so it does not necessarily indicate ovarian malignancy in this setting. Thus, CA125 is not routinely ordered as a diagnostic test when evaluating ascitic fluid.

**Persistent Ascites due to Cirrhosis**

Patients undergoing serial outpatient therapeutic paracenteses only need to have the fluid routinely sent for cell count and differential. At time of any hospital admission, before initiation of antibiotics, patients should undergo diagnostic paracentesis for cell count and differential and bacterial culture to assess for spontaneous bacterial peritonitis (SBP). The diagnosis of SBP requires an elevated ascitic fluid absolute PMN count of greater than or equal to 250 cells/mm³ without an obvious treatable intraabdominal source of infection, which should prompt empiric antibiotic therapy.[15,16]
Basic Management of Ascites

Sodium restriction and diuretics are the mainstays of treatment for patients with ascites due to portal hypertension, but patients with low SAAG (less than 1.1 g/dL) ascites do not respond well to these measures, with the exception of those with nephrotic syndrome (Figure 8).[2]

Treatment of the Underlying Disorder

Cessation of alcohol use is vital to the management of ascites due to alcoholic liver disease. In one study of hospitalized patients with Child-Turcotte-Pugh class C cirrhosis due to severe alcoholic liver disease, 75% of those who remained abstinent were still alive at 3 years whereas most who continued to drink alcohol were not.[17] Treatment of autoimmune hepatitis and chronic hepatitis B can also lead to significant clinical improvement and resolution of ascites in some cases. Similar to the management of liver-related ascites, treatment of ascites in non-hepatic cases should focus on treatment of the underlying disorder (e.g. treatment of tuberculosis, treatment of secondary bacterial peritonitis, or surgical resection of benign ovarian tumor).

Dietary Sodium Restriction

Patients with portal hypertension-associated ascites should restrict their daily dietary sodium intake to less than 2000 mg (88 mmol).[2] Any further restriction risks malnutrition due to poor palatability of foods. Twenty-four hour urinary sodium excretion can be measured to assess the adequacy of fluid loss and dietary sodium restriction. Completeness of the 24-hour collection is estimated by measurement of 24-hour urinary creatinine; accounting for some anticipated loss of body mass in the setting of cirrhosis, daily excretion of creatinine should exceed 15 mg/kg body weight in cirrhotic men and 10 mg/kg body weight in cirrhotic women. The goal of treatment is to increase the daily urinary excretion of sodium to a value above 78 mmol per day, so that in conjunction with daily nonurinary sodium excretion, the daily sodium excretion should exceed the allowed daily dietary intake of sodium.[2] Random urinary sodium concentration is not useful because of the variable sodium excretion and total urine volume throughout the day, but a random “spot” urine sodium/potassium ratio correlates with 24-hour urinary sodium excretion, with higher ratios indicating greater urinary excretion. Thus, a ratio of greater than one is desired. Patients who are excreting a sufficient amount of urinary sodium (24-hour urinary sodium greater than 78 mmol per day or spot urine sodium/potassium ratio greater than one) and are not losing weight are likely consuming more than 2000 mg of sodium daily and need further education and adherence counseling. On the other hand, the diuretic dose should be increased in patients not excreting a sufficient amount of urinary sodium, unless they are diuretic resistant.

Fluid Restriction

Dietary sodium restriction is more important than fluid restriction in the management of cirrhosis. Fluid restriction is not necessary unless the serum sodium concentration is less than 120 mmol/L or mental status changes attributed to hyponatremia develop. Rapid correction of chronic hyponatremia (with hypertonic saline or other means) should be avoided due to risk of osmotic demyelination syndrome.

Diuretics

In patients with portal hypertension, the combination of spironolactone and furosemide, starting at doses of 100 mg daily and 40 mg daily, respectively, is recommended.[2] Single agent spironolactone can be used and is superior to single agent furosemide,[18] but combination therapy leads to more rapid fluid loss in patients with moderate ascites and decreases the risk of hyperkalemia. If weight loss is insufficient, maintaining the 100 mg:40 mg ratio, the doses of the diuretics may be increased simultaneously every 3 to 5 days to maximum daily doses of 400 mg of
spironolactone and 160 mg of furosemide. The combined single morning dosing improves compliance, optimizes diuresis, and avoids nocturia. A ratio less than 100 mg:40 mg of spironolactone and furosemide may be used for patients with parenchymal renal disease with concern for hyperkalemia. Furosemide can be temporarily held or reduced for those with hypokalemia.

**Option if Intolerant to Spironolactone**

For patients unable to tolerate spironolactone due to painful gynecomastia, amiloride (10 to 40 mg daily) can be substituted, although it has a lower natriuretic effect than spironolactone.[19] Eplerenone is a newer aldosterone antagonist used to treat heart failure and is not associated with gynecomastia but has not been extensively studied yet for the management of ascites.[20] Hydrochlorothiazide in combination with furosemide is not recommended due to combined hypokalemia. Torsemide and bumetanide have also been used in combination with spironolactone in the management of ascites, but they have not demonstrated superiority over furosemide.

**Daily Limit for Weight Loss**

In patients with significant peripheral edema, there is no limit for daily weight loss, but in those without peripheral edema, daily weight loss should be restricted to 0.5 kg maximum. Diuretics may need to be held in the setting of significant volume loss such as active gastrointestinal hemorrhage or diarrhea, uncontrolled or recurrent hepatic encephalopathy, significant hyponatremia (serum sodium less than 120 mmol/L) despite fluid restriction, or renal dysfunction (e.g. serum creatinine greater than 2.0 mg/dL).

**Medications to Avoid**

The use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers should be avoided in patients with cirrhosis, due to concerns of renal failure and increased mortality for those who develop hypotension. Hypotension (mean arterial pressure less than or equal to 82 mmHg) independently predicts increased one-year mortality in patients with cirrhosis. In patients with refractory ascites, propranolol is associated with decreased survival perhaps due to the increased risk of paracentesis-induced circulatory dysfunction, so, the risks and benefits of its use should be considered individually for each patient.[21] Nonsteroidal anti-inflammatory drugs (NSAIDS), including aspirin, should also be avoided due to the risk of reduced urinary sodium excretion and renal failure. Although vaptans can improve hyponatremia, there are significant risks associated with use of these types of agents in patients with cirrhosis. For example, tolvaptan, a selective oral vasopressin V2-receptor antagonist used to treat hypervolemic and euvolemic hyponatremia, has been shown to be effective in patients with refractory ascites, but is contraindicated for use in persons with underlying liver disease, including those with cirrhosis, due to risk of causing severe hepatotoxicity.[22,23] Moreover, hyponatremia recurs upon discontinuation of the medication.[24] Satavaptan was evaluated for the management of ascites in patients with cirrhosis and was potentially associated with a higher risk of mortality.[25]

**Management of Tense Ascites**

A single large volume paracentesis followed by dietary sodium restriction and initiation of diuretics is appropriate as initial therapy for new onset large volume ascites.[26] Up to 5 liters can be removed without significant disturbances in systemic and renal hemodynamics,[27] but if more than 5 liters of ascitic fluid is removed, then intravenous albumin (8 g/L of fluid removed) should be given.[28]
Management of Refractory Ascites

Among patients with cirrhosis and ascites, fewer than 10% will develop refractory ascites, which is defined as ascites that is unresponsive to dietary sodium restriction and maximal diuretic dosing (typically, spironolactone 400 mg daily and furosemide 160 mg daily), or that which recurs rapidly after therapeutic paracentesis. There are two different subtypes: diuretic-resistant ascites (lack of response to dietary sodium restriction and intensive diuretic treatment) and diuretic-intractable ascites (diuretic-induced complications such as hepatic encephalopathy, renal insufficiency, hyponatremia, or hyperkalemia that prevent optimization of diuretic dosing). Once refractory ascites develops, one-year mortality is approximately 50%. Options for treatment include optimization of medical management, serial large volume paracenteses, transjugular intrahepatic portosystemic shunt (TIPS), peritoneovenous shunt, and liver transplantation.

Medical Treatment

As mentioned previously, propranolol has been shown to be associated with decreased survival in the setting of refractory ascites and discontinuation should be considered. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be avoided. Oral midodrine, an agent used to treat hypotension, was shown to increase mean arterial pressure and improve survival in a pilot study in cirrhotic patients with refractory or recurrent ascites. The dose is typically initiated at 5 mg orally three times daily and titrated upward in 2.5 mg increments for each dose daily, with a maximum dose of 17.5 mg three times daily to achieve an increase in systolic blood pressure of 10 to 15 mmHg. A favorable clinical response to midodrine may allow for reinitiation of diuretic therapy.

Serial Large Volume Therapeutic Paracenteses

Once a patient is deemed diuretic resistant, diuretics should be discontinued, and management may rely upon serial large volume therapeutic paracenteses alone. Typically, a large volume paracentesis (up to 10 L removed) performed every 2 weeks should control ascites in a patient who is compliant with dietary sodium restriction. Need for more frequent paracenteses suggests dietary non-compliance. The use of indwelling intraabdominal catheters is reserved for patients with malignancy-associated ascites and is not recommended in this situation. Long-term serial paracenteses can lead to significant loss of protein and worsen malnutrition, but placement of a percutaneous endoscopic gastrostomy (PEG) tube in an effort to provide nutrition should be avoided in these patients due to the high risk of mortality associated with performing the procedure.

Albumin Infusions with Therapeutic Paracentesis

In one randomized study, the use of intravenous albumin (10 grams administered per liter of fluid removed) in the setting of therapeutic paracentesis decreased the risk of negative changes in plasma renin and serum creatinine levels. A meta-analysis of 17 trials demonstrated a reduction in risk of post-paracentesis circulatory dysfunction, hyponatremia, and mortality in the albumin group (odds ratio of death 0.64, 95% CI, 0.41-0.98); study protocols typically used a 20% or higher concentration of albumin solution, and administered 5 to 10 g of albumin per liter of fluid removed. With a large volume paracentesis (5 liters or more removed), some experts recommend giving 6 to 8 g of intravenous albumin for every liter of ascitic fluid removed, with the albumin infused during or immediately following the paracentesis. In the United States, both 5% and 25% concentrations of intravenous albumin are available but the 25% solution is preferred since the 5% solution contains 5 times the amount of sodium.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS, which is a side-to-side portocaval shunt placed by Interventional Radiology, has been shown in multiple multicenter randomized controlled trials to be superior to serial large volume paracenteses
in the control of ascites, but with varying results on the impact on overall transplant-free survival and the potential risk of inducing or worsening hepatic encephalopathy.\[34,35,36,37,38,39\] Polytetrafluoroethylene-covered stents are preferred over uncovered stents due to decreased rates of TIPS occlusion.

- **Absolute Contraindications**: The absolute contraindications to placement of TIPS include congestive heart failure (particularly right-sided heart failure), severe tricuspid regurgitation, severe pulmonary hypertension (mean pulmonary pressure greater than 45 mmHg), extensive polycystic liver disease, and uncontrolled infection or biliary obstruction (Figure 9).\[34\]

- **Relative Contraindications**: The relative contraindications for performing TIPS include obstruction of all hepatic veins, complete portal vein thrombosis, hepatocellular carcinoma (especially if centrally located), severe coagulopathy (international normalized ratio [INR] greater than 5) or thrombocytopenia (platelet count less than 20,000/cm\(^3\)), moderate pulmonary hypertension, recurrent or persistent severe spontaneous hepatic encephalopathy, advanced liver failure (bilirubin greater than 5 mg/dL or Model for End-stage Liver Disease [MELD] score greater than 17), cardiac dysfunction (ejection fraction less than 60%), cardiac diastolic dysfunction, and advanced age (e.g. greater than 69 years) (Figure 10).\[34\]

- **Outcome after TIPS**: Short- and long-term mortality rates following TIPS can be estimated using MELD and Child-Turcotte-Pugh scoring systems. Clinical improvement in ascites following TIPS is seen in 74% of patients.\[40\] Diuretics may need to be continued even after placement of TIPS. Approximately 30% of patients develop hepatic encephalopathy after TIPS, though most can be managed medically (e.g. lactulose). Risk factors for the development of hepatic encephalopathy after TIPS include older age and history of pre-TIPS hepatic encephalopathy.\[41\] Narrowing or occluding the TIPS can treat severe debilitating hepatic encephalopathy resistant to medical therapy, which, fortunately, is rare. Those with renal dysfunction, especially those on dialysis, may have a reduced response to TIPS.

**Peritoneovenous Shunts**

The use of peritoneovenous shunts for management of ascites has fallen out of favor due to limited long-term patency (less than 20% at 2 years), risk of complications, and no improvement in survival compared to medical therapy.\[42,43,44\] It is reserved as palliative treatment in select patients who are not candidates for transplantation, TIPS, or serial therapeutic paracenteses.\[2\]
Complications Associated with Ascites

Spontaneous Bacterial Peritonitis (SBP)

Diagnosis of SBP requires an ascitic fluid absolute polymorphonuclear count greater than or equal to 250 cells/mm$^3$ without an obvious intraabdominal, surgically-treatable source and should prompt empiric antibiotic treatment with an intravenous third-generation cephalosporin, preferably cefotaxime 2 g every 8 hours, for 5 days.\cite{45,46} Patients with serum creatinine greater than 1 mg/dL, blood urea nitrogen greater than 30 mg/dL, or total bilirubin greater than 4 mg/dL should receive intravenous albumin 1.5 g per kg body weight upon diagnosis and 1.0 g per kg body weight on day 3 after diagnosis.\cite{47,48} After an episode of SBP, patients should receive long-term prophylaxis with daily norfloxacin or trimethoprim-sulfamethoxazole.\cite{49} More detailed information regarding diagnosis, treatment, and prevention of SBP is provided in Lesson 2 of this Module.

Dilutional Hyponatremia

Vasodilatation in cirrhosis triggers activation of the renin-angiotensin system and sympathetic nervous system, leading to avid sodium and water retention with increased antidiuretic hormone release, resulting in dilutional hyponatremia. Up to 50% of patients with cirrhosis and ascites have a serum sodium concentration less than 135 mmol/L. Hyponatremia is an independent risk factor for morbidity and mortality in patients with cirrhosis and has been proposed as an addition to the MELD score for liver transplant prioritization.\cite{1,19,50}

- **Indication for the Treatment of Hyponatremia**: Treatment specifically for hyponatremia is not necessary unless the serum sodium concentration drops below 120 mmol/L, which occurs in only 1% of patients, or if there are neurologic symptoms attributed to hyponatremia. If treated, the rate of correction should not exceed an increase of more than 9 mmol/L per day, with a goal of increasing only 4 to 6 mmol/L per day, in order to avoid the risk of osmotic demyelination syndrome.\cite{51}

- **Approach to Treatment of Hyponatremia**: Relative fluid restriction (1000 to 1500 mL free water per day) and discontinuation of diuretics should be the first line of treatment; true fluid restriction (total fluid intake less than urine volume) is difficult to achieve. Treatment of hypokalemia may also raise serum sodium concentration. Vasopressin receptor antagonists (vaptans) cause selective water diuresis and raise serum sodium concentrations, but are not routinely used in patients with cirrhosis. Conivaptan is a V1a receptor blocker that requires intravenous administration and is not recommended in patients with cirrhosis because of the concern that it can increase the risk of hypotension and renal compromise. Tolvaptan, an oral V2 receptor blocker, should also be avoided in patients with cirrhosis due to concerns for liver injury; this side effect was observed in a clinical study of tolvaptan in patients with polycystic kidney disease. The utility of demeclocycline, a tetracycline derivative, in patients with cirrhosis is limited due to the risk of nephrotoxicity.\cite{52} Hypertonic saline is generally avoided in patients with cirrhosis except to partially correct severe hyponatremia immediately prior to liver transplantation. Over-rapid correction before, during, and after liver transplantation should be avoided.

Hepatorenal Syndrome

Approximately 20% of hospitalized patients with cirrhosis and ascites will develop some type of renal dysfunction. In one study, over a mean follow-up of 41 months, 7.6% of hospitalized patients with ascites and cirrhosis developed HRS.\cite{53}

- **Diagnostic Criteria for Hepatorenal Syndrome**: The diagnostic criteria for hepatorenal syndrome requires all of the following: (1) cirrhosis with ascites, (2) serum creatinine greater than 1.5 mg/dL, (3) no improvement in serum creatinine (decrease to or below a level of 1.5

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mg/dL) after at least 2 days with diuretic withdrawal and volume expansion with albumin (recommended dose is 1 g/kg body weight per day up to a maximum of 100 g per day), (4) absence of shock, (5) no current or recent treatment with nephrotoxic drugs, and (6) absence of parenchymal kidney disease, as indicated by proteinuria greater than 500 mg per day, microhematuria (greater than 50 red blood cells per high power field), and/or abnormal renal ultrasonography. (Figure 11).[37]

**Classification of Hepatorenal Syndrome:** There are two types of hepatorenal syndrome: type 1 and type 2.[54] Type 1 hepatorenal syndrome is characterized by rapidly progressive renal failure with a doubling in the initial serum creatinine to a level greater than 2.5 mg/dL (or 50% reduction in the initial 24-hour creatinine clearance to a level lower than 20 mL/min) in less than two weeks; it is frequently triggered by a precipitating event, such as SBP, urinary tract infection, or intravascular volume contraction, and is associated with acute rapid deterioration of circulatory function with hypotension and activation of endogenous vasoconstrictor systems, and leads to a very poor prognosis, with a median survival of around 2 weeks in untreated patients. Type 2 hepatorenal syndrome is typically associated with refractory ascites and is characterized by a slower, progressive decline in renal function, typically with a serum creatinine that ranges from 1.5 to 2.5 mg/dL, and a median survival of 4 to 6 months.

**Management of Type 1 Hepatorenal Syndrome:** Management is focused on the treatment of the precipitating event, the renal failure, and the systemic inflammatory response syndrome. Measures to prevent Type 1 HRS include the use intravenous albumin in patients with SBP at high risk for developing HRS and the use of prophylactic antibiotics in cirrhotic patients with gastrointestinal bleeding.[55] Once Type 1 HRS is established, diuretics should be discontinued and vasoconstrictors used to decrease systemic vasodilatation and improve renal perfusion. The combination of terlipressin and albumin has been shown to be superior to albumin alone and placebo for the treatment of Type 1 hepatorenal syndrome and may be effective in more than 30% of cases.[56,57] Terlipressin is not available in the United States, so midodrine, an alpha-agonist, is used instead (starting at a dose of 5 to 7.5 mg orally three times daily, titrated up to 15 mg three times daily), in combination with octreotide, starting with 100 mcg subcutaneously three times daily, titrated up to 200 mcg three times daily and albumin (up to 40 g daily in divided doses), with a goal of increasing mean arterial pressure by 15 mmHg. This combination achieves a response rate of around 30% as shown in case series.[58] For patients in the intensive care unit, albumin infusion with norepinephrine can be considered as well for Type 1 hepatorenal syndrome.[59]

In addition, TIPS can be used to improve renal function, but should be avoided in patients with advanced liver dysfunction. Ultimately, liver transplantation is the definitive treatment for this condition, and some even require renal replacement therapy as a bridge to transplantation.[60]

**Management of Type 2 Hepatorenal Syndrome:** Treatment of type 2 hepatorenal syndrome is typically centered on management of the refractory ascites, with measures such as TIPS. If eligible, these patients should be referred for consideration of liver transplantation.

**Umbilical Hernia**

Up to 20% of patients with cirrhosis and ascites can develop umbilical hernias. Complications related to these hernias include omental or bowel strangulation, typically after paracentesis or shunt procedure, and hernia perforation.[61] Patients should wear an abdominal binder to minimize strain and enlargement of the hernia and should be educated on the warning symptoms of an incarcerated hernia. Pre-emptive TIPS should be considered to prevent rupture of thin-walled umbilical hernias.[62,63] The risks and benefits of elective surgical repair need to be assessed individually. In patients who are medical candidates for surgery (e.g. Child-Turcotte-Pugh class A cirrhosis), the ascites needs to be controlled first with optimal medical management or TIPS; otherwise, the hernia will recur in over 70% of patients.[64] Emergent surgical repair due to incarceration or rupture should be performed by surgeons experienced with patients with cirrhosis. If feasible, TIPS should be considered before or after the surgery, along with dietary sodium and fluid restriction.
Hepatic Hydrothorax

Approximately 5 to 10% of patients with cirrhosis and ascites develop hepatic hydrothorax, which is typically a right-sided pleural effusion.\(^{[65]}\) It is a result of fluid being drawn up from the peritoneal cavity into the pleural space through small defects in the diaphragm. Sometimes, minimal to almost no fluid remains in the abdomen. Injection of technetium-radiolabeled sulfur colloid into the abdomen followed by transdiaphragmatic flow of the isotope into the thoracic space can confirm ascites as the origin of the pleural effusion, if needed.\(^{[66]}\) Thoracentesis does not require platelet or fresh frozen plasma transfusions, and, there is no limit to the amount of fluid that can be removed.\(^{[67]}\) Due to differences in hydrostatic pressure, the protein concentration is higher in pleural fluid than ascites. Spontaneous bacterial empyema can occur in the absence of spontaneous bacterial peritonitis and can be treated with appropriate antibiotic therapy without placement of a chest tube.\(^{[68]}\) Chest tube placement in patients with hepatic hydrothorax is associated with massive fluid losses, high morbidity (greater than 90%) and high mortality (greater than 30% in the absence of TIPS), so it should be avoided.\(^{[69,70]}\) Treatment should start with dietary sodium restriction and diuretics. Therapeutic thoracentesis can be done for dyspnea. TIPS can be performed as treatment for refractory hepatic hydrothorax. Most patients with hepatic hydrothorax will not be candidates for pleurodesis due to the rapid rate of fluid reaccumulation.
**Summary Points**

- The development of ascites indicates decompensation of cirrhosis, and patients should be referred for liver transplantation evaluation.
- Prophylactic blood products do not need to be administered prior to paracentesis, even in the setting of coagulopathy or thrombocytopenia, but paracentesis should be avoided in patients with disseminated intravascular coagulation or untreated hyperfibrinolysis.
- A SAAG of greater than or equal to 1.1 g/dL indicates portal hypertension as the cause of ascites, with cirrhosis or heart failure common causes of the portal hypertension. Additional diagnostic tests can be ordered based on clinical suspicion.
- Treatment of ascites in patients with cirrhosis should be focused on dietary sodium restriction of less than 2000 mg daily and the use of diuretics, specifically, spironolactone and furosemide, titrated using a respective ratio of 100 mg:40 mg. Fluid restriction is reserved only for those with a serum sodium concentration of less than 120 mmol/L or symptomatic hyponatremia.
- Treatment options for the management of refractory ascites include optimization of medical therapy, serial large volume therapeutic paracenteses with the use of intravenous albumin, TIPS in selected candidates, and liver transplantation. Peritoneovenous shunt is a palliative measure reserved only for patients who are not candidates for the other therapies.
- An ascitic fluid absolute polymorphonuclear count greater than or equal to 250 cells/mm³ should prompt empiric antibiotic treatment for spontaneous bacterial peritonitis with intravenous cefotaxime (2 g every 8 hours) for five days.
- Patients with untreated Type 1 hepatorenal syndrome have very poor short-term survival and should be referred for urgent liver transplantation evaluation.
- In most circumstances, placement of a chest tube is contraindicated in patients with hepatic hydrothorax due to risk of massive fluid loss and high morbidity and mortality.
Citations


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Figures

Figure 1 Natural History and Survival of Patients with Ascites

This figure shows the 1- and 5-year survival of patients with ascites. Patients who do not develop complications have markedly better survival than those who develop dilutional hyponatremia, refractory ascites, or hepatorenal syndrome.

**Figure 2 Differential Diagnosis of Ascites**

Abbreviations: SAAG = serum-ascites albumin gradient; SBP = spontaneous bacterial peritonitis; CHF = congestive heart failure; LDH = lactate dehydrogenase; CEA = carcinoembryonic antigen.


<table>
<thead>
<tr>
<th>Disorder</th>
<th>SAAG</th>
<th>Additional Diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 1.1 g/dL</td>
<td>&lt; 1.1 g/dL</td>
</tr>
<tr>
<td>Liver related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>X</td>
<td>Ascitic fluid cell count and differential for SBP, total protein</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>X</td>
<td>Imaging</td>
</tr>
<tr>
<td>Sinusoidal Obstruction Syndrome</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis, hepatic granulomas</td>
<td>X</td>
<td>Liver biopsy</td>
</tr>
<tr>
<td>Polycystic liver disease</td>
<td>X</td>
<td>Imaging</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
<td>X</td>
<td>Liver biopsy</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF, constrictive pericarditis, pulmonary hypertension</td>
<td>X</td>
<td>Echocardiogram, right heart catheterization</td>
</tr>
<tr>
<td>Neoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>X</td>
<td>Imaging</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>X</td>
<td>Imaging</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis</td>
<td>X</td>
<td>Imaging, cytology</td>
</tr>
<tr>
<td>Malignant chylous ascites</td>
<td>X</td>
<td>Ascitic fluid triglyceride, imaging</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculous peritonitis</td>
<td>X</td>
<td>Mycobacterial culture on directed peritoneal biopsy and ascitic fluid</td>
</tr>
<tr>
<td>Secondary bacterial peritonitis</td>
<td>X</td>
<td>Ascitic fluid glucose, LDH, Gram’s stain, CEA, alkaline phosphatase</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>X</td>
<td>24-hour urine protein</td>
</tr>
<tr>
<td>Pancreatic ascites</td>
<td>X</td>
<td>Ascitic fluid amylase</td>
</tr>
<tr>
<td>Thyroid myxedema</td>
<td>X</td>
<td>Serum thyroid tests</td>
</tr>
<tr>
<td>Postoperative lymphatic leak</td>
<td>X</td>
<td>Ascitic fluid triglyceride</td>
</tr>
</tbody>
</table>
Figure 3 Bulging Flanks

This illustration shows a patient with bulging flanks.
Figure 4 Shifting Dullness

To perform the shifting dullness test, place the patient in the supine position, percuss the entire abdominal region, and mark the dullness-tympany transition point (left figure). Then place the patient in the right lateral decubitus position, wait 30 to 60 seconds, repeat the percussion, and again mark the dullness-tympany transition point (right figure). A positive shifting dullness test is indicated by a shifting of the transition point.
In most situations, the preferred site for performing a diagnostic paracentesis is the left lower quadrant. The midline region is not considered as safe due to the epigastric arteries in this region.
To identify the preferred region for paracentesis in the left lower quadrant, first locate the anterior superior iliac spine. Then, mark a spot 2 finger breadths (3 cm) cephalad and 2 finger-breadths (3 cm) medial to the anterior superior iliac spine.
Figure 6 Inferior Epigastric Arteries

The region of the inferior epigastric arteries should be avoided during paracentesis due to risk of arterial rupture if punctured during the procedure.
Figure 7 Paracentesis Z Technique

The paracentesis Z technique is performed to minimize the risk of a peritoneal fluid leak. The Z technique consists of pulling the skin down by approximately 2 centimeters before inserting and advancing the needle. After the needle has been inserted, the skin is released. The concept is that the punctured hole in the skin, muscle, and facia do not entirely overlap if the z technique is used.
**Figure 8 Management of Ascites Due to Cirrhosis**


<table>
<thead>
<tr>
<th>Management of Ascites Due to Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treatment of underlying disorder (e.g. alcoholic liver disease, hepatitis B, autoimmune hepatitis)</td>
</tr>
<tr>
<td>2. Dietary sodium restriction (less than 2000 mg per day)</td>
</tr>
<tr>
<td>3. Diuretic therapy (maintain ratio spironolactone 100 mg: furosemide 40 mg)</td>
</tr>
<tr>
<td>4. Therapeutic paracentesis</td>
</tr>
<tr>
<td>5. Fluid restriction only if serum sodium &lt;120 mEq/L or symptomatic hyponatremia</td>
</tr>
</tbody>
</table>
**Figure 9 Absolute Contraindications to Performing Transjugular Intrahepatic Portosystemic Shunt (TIPS) Pro**


<table>
<thead>
<tr>
<th>Absolute Contraindications for TIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (especially right-sided)</td>
</tr>
<tr>
<td>Severe tricuspid regurgitation</td>
</tr>
<tr>
<td>Severe pulmonary hypertension (mean PA pressure greater than 45 mmHg)</td>
</tr>
<tr>
<td>Extensive polycystic liver disease</td>
</tr>
<tr>
<td>Uncontrolled infection</td>
</tr>
<tr>
<td>Unrelieved biliary obstruction</td>
</tr>
</tbody>
</table>

Abbreviations: TIPS = Transjugular Intrahepatic Portosystemic Shunt; PA = Pulmonary Artery
**Figure 10 Relative Contraindications to Performing Transjugular Intrahepatic Portosystemic Shunt (TIPS) Procedure**


<table>
<thead>
<tr>
<th>Relative Contraindications for TIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete hepatic vein obstruction</td>
</tr>
<tr>
<td>Complete portal vein thrombosis</td>
</tr>
<tr>
<td>Hepatocellular carcinoma (especially if centrally located)</td>
</tr>
<tr>
<td>Severe coagulopathy (INR greater than 5)</td>
</tr>
<tr>
<td>Severe thrombocytopenia (platelet count less than 20,000/cm³)</td>
</tr>
<tr>
<td>Recurrent or severe spontaneous hepatic encephalopathy</td>
</tr>
<tr>
<td>Advanced liver dysfunction (bilirubin greater than 5 mg/dL or MELD greater than 17)</td>
</tr>
<tr>
<td>Moderate pulmonary hypertension</td>
</tr>
<tr>
<td>Cardiac systolic dysfunction (EF less than 60%)</td>
</tr>
<tr>
<td>Cardiac diastolic dysfunction</td>
</tr>
<tr>
<td>Advanced age (greater than 69 years)</td>
</tr>
</tbody>
</table>

Abbreviations: TIPS = Transjugular Intrahepatic Portosystemic Shunt; INR = International Normalized Ratio; MELD = Model for End-Stage Liver Disease; EF = Ejection Fraction
Figure 11 Diagnostic Criteria for Hepatorenal Syndrome


<table>
<thead>
<tr>
<th>Diagnostic Criteria for Hepatorenal Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Cirrhosis with ascites</td>
</tr>
<tr>
<td>2) Serum creatinine greater than 1.5 mg/dL</td>
</tr>
<tr>
<td>3) No improvement in serum creatinine (decrease to or below a level of 1.5 mg/dL) after at least 2 days with diuretic withdrawal and volume expansion with albumin (recommended dose is 1 g/kg body weight per day up to a maximum of 100 g per day)</td>
</tr>
<tr>
<td>4) Absence of shock</td>
</tr>
<tr>
<td>5) No current or recent treatment with nephrotoxic drugs</td>
</tr>
<tr>
<td>6) Absence of parenchymal kidney disease, as indicated by proteinuria greater than 500 mg per day, microhematuria (greater than 50 red blood cells per high power field), and/or abnormal renal ultrasonography</td>
</tr>
</tbody>
</table>