Evaluation and Management of Cirrhotic Ascites


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Ascites is the pathologic accumulation of fluid in the peritoneal cavity. The development of ascites is a major event in the natural history of cirrhosis and is associated with a significant deterioration in prognosis. It occurs in approximately 60% of cirrhotics within 10 years.[1] Although cirrhosis accounts for approximately 75 % of patients with ascites, other causes should be kept in mind especially malignancy (10%), cardiac failure (3%), tuberculosis (2%), pancreatitis (1%) and other rare causes.[1]

INTRODUCTION

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PATHOPHYSIOLOGY

The most important mechanism contributing to development of ascites in cirrhosis is renal sodium retention, which is a consequence of arterial splanchnic vasodilation. The main mechanism for arterial splanchnic vasodilation is via the actions of nitric oxide, a vasodilator released due to the development of portal hypertension. Eventually, activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) may occur, accentuating retention of sodium and further expansion of extracellular fluid volume with subsequent formation of ascites. Decreased colloid osmotic pressure and increased permeability of peritoneal capillaries also contribute to the development of ascites that may result from nephrotic syndrome, malnutrition, protein-losing enteropathy and diminished protein synthesis due to liver disease.

EVALUATION OF ASCITES

Single or multi-factorial insults to the liver ultimately lead to cirrhosis, the most common being alcohol abuse, chronic hepatitis C and obesity with concomitant nonalcoholic fatty liver (Table 1.). The main goals in

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the assessment of a patient with suspected ascites are to confirm its presence, establish a likely etiology and to determine whether it is infected or malignant. An appropriate medical history, physical examination and subsequent evaluation with imaging studies are integral in this process. A focused history should be directed towards[1] establishing the presence of ascites (i.e. recent weight gain, change in abdominal girth and other signs of fluid retention such as peripheral edema) and[2] inquiring about known history or risk factors for hepatic or non-hepatic diseases that may cause ascites (Table 2.).

Some common symptoms of ascites include increased abdominal girth, early satiety and shortness of breath, depending on the amount of fluid accumulation in the abdomen. The physical examination should focus on stigmata of cirrhosis and clinical signs suggesting the presence of ascites. Physical examination findings such as shifting dullness usually require the accumulation of at least 1500ml of fluid, however no single physical sign for ascites has been found to be both sensitive and specific. The most useful findings for helping diagnose ascites is a positive fluid wave or shifting dullness while the most useful findings for ruling out ascites is the absence of bulging flanks, flank dullness or shifting dullness.[2] When the diagnosis is in doubt, abdominal ultrasonography is the imaging modality of choice. Additionally, ultrasonography provides information regarding hepatic echogenicity and vasculature.

Multiple grading systems for ascites are available. Recently, a revised grading system for ascites has been proposed by the International Ascites Club.[3,4]

- Grade 1: Mild ascites detectable only by ultrasound
- Grade 2: Moderate ascites with moderate symmetrical distention of abdomen
- Grade 3: Large or gross ascites with marked abdominal distention

Table 1. Etiologies of Hepatic Cirrhosis

Alcoholic liver disease
Chronic hepatitis B
Chronic hepatitis C
Non-alcoholic fatty liver disease
Hemochromatosis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Autoimmune hepatitis
Biliary obstruction
Biliary atresia/neonatal hepatitis
Congenital biliary cysts
Cystic fibrosis
Genetic metabolic disease
Wilson's disease
Alpha-1 antitrypsin deficiency
Vascular abnormalities
Chronic, passive hepatic congestion caused by right-sided heart failure

Table 2. Etiology of Ascites

Cirrhosis	81 %
Cancer	10 %
Heart Failure	3 %
Tuberculosis	2 %
Pancreatic disease	1 %
Dialysis	1 %
Other	2 %

Runyon, BA, Montano, AA, Akriviadis, EA, et al. Ann Intern Med 1992; 117:215

Table 3. Classification of Ascites

HIGH ALBUMIN GRADIENT (SAAG > 1.1g/dL)
Cirrhosis
Alcoholic hepatitis
Congestive heart failure
Budd-Chiari syndrome
LOW ALBUMIN GRADIENT (SAAG < 1.1g/dL)
Peritoneal carcinomatosis
Peritoneal tuberculosis
Pancreatitis
Serositis
Nephrotic syndrome

Table 4. Ascitic Fluid Analysis

ROUTINE
Cell count and differential
Bacterial culture with bedside inoculation into blood culture bottle
Albumin
Total Protein
SOMETIMES USEFUL
Lactate dehydrogenase
Glucose
Amylase
Gram stain
Triglyceride (ascites appear milky)
RARELY HELPFUL
pH
Lactate
AFB smear and culture (might be helpful in certain circumstances)
Cytology
Bilirubin

PARACENTESIS

Abdominal paracentesis with appropriate ascitic fluid analysis is the most efficient way to determine etiology and establish the presence or absence of infection.[5] Paracentesis is a safe procedure with a low incidence of complications (<1%) despite comorbid coagulopathy often present in patients with cirrhosis. Serious complications such as hemoperitoneum and bowel perforation occur in less than 0.1% of patients.[6-8] Coagulopathy should only preclude paracentesis when there is clinical evidence of disseminated intravascular coagulopathy (DIC).

In order to select the appropriate site for paracentesis, ultrasound guidance is frequently used. Indications for abdominal paracentesis in patients with cirrhosis include fever, abdominal pain, hepatic encephalopathy, gastrointestinal bleeding and worsening liver or renal function. Additionally, patients with cirrhosis admitted with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).

APPEARANCE

The gross appearance of ascitic fluid is of limited value in evaluation of ascites, but may help in the differential diagnosis and provide valuable clinical information regarding the etiology of ascites. For example, turbid or cloudy fluid suggests infectious etiology, bloody fluid suggest traumatic ascites or malignancy where as milky fluid suggests chylous ascites with increased triglycerides contents.

ASCITIC FLUID ANALYSIS

Measurement of the serum-ascites albumin gradient (SAAG) is useful when the diagnosis of cirrhosis is not established. To calculate SAAG, ascitic fluid albumin concentration is subtracted from the serum albumin concentration. A SAAG > 1.1 g/dL indicates portal hypertension though it does not determine the specific cause.[9] A SAAG < 1.1g/dL indicates that the patient does not have portal hypertension-related ascites and suggests pancreatitis, serositis, peritoneal carcinomatosis, peritoneal tuberculosis or nephritic syndrome as the cause.[10, 11] (Table 3.). To evaluate for spontaneous bacterial peritonitis, ascitic fluid should

(continued on page 50)

(continued from page 48)

be sent for a differential cell count and fluid should be inoculated into blood culture bottles at bedside and sent for culture (Table 5.).

SBP can be diagnosed if the ascitic fluid has an absolute polymorphonuclear (PMN) count ≥ 250 cells/mm^3 and patients should receive antibiotics soon after cultures have been drawn.[5, 12, 13] A total ascitic protein level of < 1.5g/dL confers an increased risk of SBP, and these patients may benefit from antibiotic prophylaxis.[14]

MANAGEMENT OF ASCITES

The initial management of ascites should begin with dietary sodium restriction to < 2 grams/day (88 mmol/day), which requires a "no added salt" diet and avoidance of pre-prepared foods. Dietary sodium restriction is only successful in 10-20% of patients.[15] Minimizing the use of nephrotoxic medications including non-steroidal anti-inflammatory drugs (NSAID), angiotensin converting enzyme-inhibitors, angiotensin II antagonists, alpha1-adrenergic blockers and aminoglycoside antibiotics may reduce risk of developing acute renal failure, hyponatremia and diuretic resistance.[16-19]

Patients who do not respond to conservative measures may benefit from oral diuretics. First line therapy is a combination of spironolactone and furosemide.[20] Typical starting doses are 100 mg/d of spironolactone and 40 mg/d of furosemide. Maximum accepted doses are 400mg/d of spironolactone and 160 mg/d of furosemide.[21] Furosemide in particular should be administered on a once daily schedule. Response should be monitored on the basis of changes in daily body weight, clinical examination and laboratory tests such as electrolytes level. The recommended maximum weight loss to prevent renal failure and/or hyponatremia is 0.5 kg/d in patients without peripheral edema and 1 kg/day in those with peripheral edema.[22] Diuretics should be discontinued if there is progressive renal failure, severe hyponatremia (sodium < 120 mmol/L), worsening hepatic encephalopathy or incapacitating muscle cramps.[20, 23, 24]

For patients with large volume ascites, therapeutic or large volume paracentesis (LVP) is well tolerated. LVP does not often produce adverse hemodynamic changes, although it may result in further activation of RAAS. This has been termed paracentesis-induced circulatory dysfunction (PICD) and administration of albumin after LVP may blunt development of PICD. Current practice guidelines from the American Association for the Study of Liver Diseases (AASLD) state that it is reasonable (but not mandatory) to give 5 to 10g of albumin (25%) per liter of ascites removed in patients (Table 8.) with greater than 5L of fluid removed to prevent circulatory dysfunction.[25]

Table 5. Definition and Diagnosis of Bacterial Peritonitis in Cirrhotics

TYPE	ASCITIC CELL COUNT	ASCITES CULTURE	TREATMENT
Sterile	< 250 PMNs	Negative	None
Spontaneous bacterial peritonitis	≥ 250 PMNs	Monobacterial infection	3rd generation Cephalosporin
Culture negative neutrocytic ascites	≥ 250 PMNs	Negative	3rd generation Cephalosporin
Non neutrocytic bacterascites	< 250 PMNs	Monobacterial infection	Only if symptomatic or persistently positive culture
Secondary	≥ 250 PMNs	Polymicrobial infection	(1) Base on culture and sensitivities (2) Identify the source of infection

Rimola A, Gracia-Tsao G, Navasa M, et al. J Hepatol 2000;32:142–153

Table 6. Treatment of Ascites and Spontaneous Bacterial Peritonitis (SBP)

COMPLICATION	TREATMENT	DOSAGE
Ascites	Sodium restriction	Maximum 2,000 mg per day
	Spirinolactone (Aldactone)	Start 100 mg orally per day; maximum 400 mg per day
	Furosemide (Lasix)	Start 40 mg orally per day; maximum 160 mg per day
	Albumin	8 to 10 g IV per liter of fluid (if > 5L) removed for paracentesis
	Fluid restriction	Recommend if serum sodium is < 120 to 125 mEq per L
SBP	Ceftriaxzone	1 gram IV per day
	Norfloxacin	400 mg orally twice daily for treatment 400 mg orally twice daily for 7 days with GI bleed 400 mg orally per day for prophylaxis
	Trimethoprim/Sulfamethoxazole (Bactrim, Septra)	1 single-strength tablet orally per day for prophylaxis 1 single-strength tablet orally twice daily for 7 days with GI bleed
	Albumin	1.5 g per kg IV within six hours of detection and 1g per kg IV on day 3

REFRACTORY ASCITES

Refractory ascites (RA) signifies a poor prognosis. The definition of refractory ascites is the (1) lack of response to maximum dose diuretics while remaining complaint with low-sodium diet, (2) frequent re-accumulation of ascites shortly after therapeutic paracentesis and (3) inability to tolerate diuretics due to recurrent side effects (i.e. hyponatremia, hypokalemia, hyperkalemia, renal insufficiency, or encephalopathy). Measurement of urinary sodium may be beneficial in identifying patients who are non-compliant with their sodium restriction diet. Either a 24-hour urine collection or spot urine sodium concentration can be performed. In clinical settings, if the random urine sodium concentration is greater

Table 7. Diagnostic Criteria of Hepatorenal Syndrome

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL
- No improvement of serum creatinine (decrease to a level of 1.5) after at least 2 days with diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

Salerno F, Gerbes A, Gine`s P, et al. Gut 2007;56:1310–1318

than urine potassium, this suggests non-compliance to a sodium-restricted diet. Treatment options for RA include therapeutic paracentesis with albumin infusion, transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation. Repeated LVP with albumin infusion is the most widely used therapy for refractory ascites and is generally performed every 2 to 4 weeks in an outpatient setting. TIPS reduces the portal pressure, the cardinal pathophysiologic event that causes inappropriately increased renal sodium reabsorption.[26] TIPS is costly and portends an increased risk of encephalopathy related morbidity but it does reduce the need for diuretics and LVP.[27, 28] The ideal candidate for TIPS has relatively preserved liver function (i.e. bilirubin < 5mg/dl, INR < 2 or Child-Pugh score < 11), preserved renal function, no concomitant active infection and is free of encephalopathy.[28, 29] A meta-analysis of individual patient data from four randomized trials of TIPS compared to LVP showed a survival advantage of TIPS. Moreover, survival superiority of TIPS is apparent at higher as well as lower MELD scores.[30] Given the fact that patients with refractory ascites have a particularly poor prognosis, referral to a liver transplantation center should be considered.

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) has been found in approximately 15% of hospitalized patients with cirrhosis and ascites; as such diagnostic paracentesis should be performed routinely at time of admission.[14] Suspicion for SBP is raised if there is a change in the clinical status of the patient that may include one or more of the following: fever, abdominal pain, altered mental status, gastrointestinal bleed and/or worsening liver or renal function. Occasionally, a patient with cirrhosis and ascites may develop peritonitis from an independent event, such as diverticulitis, abscess or complications from surgery. Such cases of secondary bacterial peritonitis are often characterized by polymicrobial bacteria or fungal species in ascites.

Diagnosis of SBP is established with an ascitic fluid neutrophil count $\geq$ 250 cells/mm.[3, 31] Culture negative SBP can be seen in as many as 60% of patients with infection and increased ascitic fluid neutrophil count; management and treatment is similar to culture positive SBP.[32] When the ascites culture is positive, the most common pathogens include gram-negative bacteria (i.e. *Escherichia coli*) and gram-positive cocci (i.e. *streptococci* and *enterococci*).[33, 34] Therefore, ascitic fluid culture is not necessary for the diagnosis of SBP, but it is important in guiding antibiotic therapy. Positive ascitic fluid culture and an ascitic neutrophil count less than 250 cells/mm^3 is termed bacterascites (Table 4.). Only those patients who exhibit signs of infection or in whom a second paracentesis reveals a neutrophil count $\geq$ 250 cells/mm^3 should be treated with antibiotics, otherwise they should be followed clinically for worsening symptoms.[14]

(continued on page 54)

(continued from page 52)

Management of Spontaneous Bacterial Peritonitis

Empiric antibiotic therapy, third generation cephalosporins, should be started immediately after diagnostic paracentesis.[35] Alternative options include amoxicillin/clavulanic acid and quinolones such as ciprofloxacin. For uncomplicated SBP, a 5-day course of antibiotics has been shown to be as effective as 10 days.[36] Treatment may be switched to oral quinolone therapy after 2 days of intravenous antibiotics.[37] SBP resolves in approximately 90% of patients with antibiotic therapy. A routine second paracentesis within 48 hours after treatment may help gauge the effectiveness of therapy though it is not supported by evidence. However, if symptoms such as fever or abdominal pain persist, repeat paracentesis can be performed to assess the response of the PMN count to antibiotics. At 48 hours, the ascitic PMN count will be below the pretreatment value and frequently a 25% decrease in pretreatment PMN is observed if treatment has been appropriate.[38] The use of albumin as an adjunct to antibiotics in cases of SBP is discussed later.

Prophylaxis of Spontaneous Bacterial Peritonitis

Given the cost and risk of developing resistant organisms, the use of prophylactic antibiotics should be restricted to patient at high risk of SBP. The high-risk population includes patients with (1) acute gastrointestinal bleed, (2) low total ascitic protein (< 1.5g/dl) and (3) previous history of SBP (secondary prophylaxis).

Primary prophylaxis (no prior history of SBP) with oral quinolones for SBP should be considered in cirrhotics with ascitic fluid total protein less than 1.5 g/dL who fulfill at least one of the following criteria: serum creatinine ≥ 1.2 mg/dL, blood urea nitrogen ≥ 25 mg/dL, serum sodium ≤ 130 mEq/L or Childs Pugh > 9 points and bilirubin > 3 mg/dL.[39, 40] In patients who had one or more episodes of SBP, secondary prophylaxis with norfloxacin (400 mg/day) or trimethoprim-sulfamethoxazole therapy is recommended (Table 6.). In settings where norfloxacin is unavailable, ciprofloxacin (500 mg PO once daily) is an acceptable alternative. Due to theoretical risk of developing bacterial resistance, it is generally not recommended to use intermittent dosing of antibiotics for prophylaxis.

HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) can be defined as renal failure in a patient with advanced liver disease in the absence of an identifiable alternative cause (Table 7.). HRS occurs in approximately 30% of patients with SBP and is associated with a high mortality.[14] All patients with HRS should have an expedited referral for liver transplantation and receive prompt treatment prior to liver transplantation, as treatment may improve post-transplant outcomes.[41] HRS can be classified into two types, each having different clinical and prognostic characteristics. Type 1 HRS is characterized by doubling of serum creatinine above 2.5 mg/dL in less than 2 weeks and Type 2 HRS is a slowly progressive or stable renal dysfunction not meeting criteria for Type 1 HRS.[42] Type 1 HRS may be precipitated by SBP, gastrointestinal bleeding or any systemic infection leading to multi-organ dysfunction; whereas Type 2 HRS is characterized by a stable progressive course in patients with refractory ascites.[43] The risk of developing HRS can be markedly reduced by administrating intravenous albumin 1.5 g/kg at diagnosis of SBP and 1.0 g/kg on day 3.[44] Although

Table 8. Albumin Infusion After Paracentesis

Amount of ascitic fluid removed	Albumin (25%) infusion after LVP*
Less than 5.0 L	No Albumin infusion
5.0-6.0 L	~ 50 g of 25 % albumin infusion
6.1-8.0 L	~ 75 g of 25 % albumin infusion
8.1-10.0 L	~ 100 g of 25% albumin infusion

*LVP = large volume paracentesis

the evidence is not conclusive, vasoactive drugs, such as octreotide and midodrine in combination with albumin infusion may be considered for the treatment of Type 1 HRS.[45] Other treatment options, including TIPS may improve renal function in selected patients however there is insufficient data to support the routine use of TIPS in patients with HRS.[46] Renal replacement therapy, including intermittent hemodialysis, continuous renal replacement therapy and hybrid therapies such as sustained low efficiency dialysis, may be useful in patients who do not respond to pharmacological therapy and fulfill the criteria for renal support and are deemed eligible for liver transplantation.[47]

CONCLUSION

Patients with cirrhosis and ascites have a poor long-term survival without liver transplantation. Most respond well to general lifestyle modifications and diuretic treatment. For patients with refractory ascites, large volume paracentesis plus albumin administration is the most widely accepted therapy. TIPS placement is an alternative treatment option for patients without severe liver failure or encephalopathy and for those who are unwilling to undergo repeated paracentesis. Patients with ascites are at risk of developing several complications, including spontaneous bacterial peritonitis and hepatorenal syndrome that can lead to severe morbidity and mortality. It is important to examine ascitic fluid and rule out infection. Those patients at risk of developing SBP should receive prophylactic antibiotic treatment. The most severe complication of SBP is HRS. Type 1 HRS develops rapidly and has a very poor prognosis. Type 2 HRS develops gradually in patients with refractory ascites. Combination treatment with albumin and vasoactive drugs in HRS type 1 yields the best survival data. For those patients whose liver disease is not responsive to medical therapy liver transplantation is the only treatment option. ■

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