REVIEW

Sarah Khan, MD
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

Maureen Linganna, MD
Department of Gastroenterology, Hepatology, and Nutrition, Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Diagnosis and management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome

ABSTRACT

Ascites is the most common decompensation-associated complication of cirrhosis leading to reduced survival. Following significant development of antimicrobial resistance and studies comparing therapeutic options, the American Association for the Study of Liver Diseases released a new guidance providing an in-depth review of those studies and updated guidelines based on expert opinions and emerging data. We review salient 2021 guidance recommendations to provide brief pearls for diagnosis and management of ascites and relevant conditions associated with decompensated cirrhosis, such as hyponatremia, hepatic hydrothorax, spontaneous bacterial peritonitis, and hepatorenal syndrome, and use of transjugular intrahepatic shunt.

KEY POINTS

All patients with new-onset ascites, worsening distention, symptoms concerning for spontaneous bacterial peritonitis, or admitted to hospital, should undergo diagnostic paracentesis.

Sodium restriction and diuresis are the mainstay of initial ascites management. Initial diuresis should begin with spironolactone, with addition of loop diuresis if needed.

Refractory ascites may require regular large-volume paracentesis followed by albumin infusion.

doi:10.3949/ccjm.90a.22028

In response to significant advances of antimicrobial resistance and studies comparing therapeutic options for ascites and hepatorenal syndrome, the American Association for the Study of Liver Disease published a new 2021 guidance[1] as a comprehensive guide for both outpatient and inpatient diagnostic evaluation and management of ascites, updated information regarding use of albumin, and specified definitions and management recommendations for hyponatremia.

ASCITES

Development of ascites is associated with a reduction of 5-year survival from 80% to 30%,[1,2] largely associated with complications that include infection and hepatorenal syndrome. A thorough evaluation is required for diagnosis of new ascites to exclude other etiologies, including heart failure, renal failure, infections, or malignancy.[1] Complete initial analysis should consist of laboratory evaluation, abdominal Doppler ultrasonography, and a diagnostic paracentesis,[1] although no data currently support this recommendation. A serum ascites albumin gradient 1.1 g/dL or greater suggests portal hypertension, massive liver metastases, or right heart failure.[1,3] In addition to patients with symptoms suggestive of infection (eg, fevers, abdominal pain), ascitic fluid cultures should be obtained for any decompensating patient, including for the development of encephalopathy, acute kidney injury, or jaundice.[1]

ASCITES MANAGEMENT

In general, angiotensin II receptor-antagonists, angiotensin-converting enzyme inhibitors, and non-steroidal anti-inflammatory drugs should be avoided in patients with ascites owing to impact on effective circulating volume and renal perfusion.[1] Though not directly nephrotoxic, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor-antagonists was noted to correlate with increased risk of end-stage renal disease in cirrhotic patients with ascites.[4]

Based on treatment response, ascites can be classified as responsive, recurrent, or refractory.[5] Initial management of ascites includes 2 g sodium restriction. Diuresis initially with spironolactone 100 to 200 mg daily is suggested for first-time ascites, and dose adjustments should be made at intervals of at least 72 hours, up to a maximum daily dose of 400 mg.[1] For recurrent ascites, combination therapy with furosemide and spironolactone is recommended with a starting dose of 40-mg furosemide to a maximum 160-mg dose daily.[5] Once ascites has been mobilized, diuretics should be tapered to the lowest effective dose to minimize adverse effects.[1] In some cases (approximately 5% to 10% of all patients with cirrhosis), ascites cannot be managed medically and becomes refractory, with 50% survival at 6 months.[1,6]

Refractory ascites occurs when one of three criteria are met: recurrence as grade 2 or 3 within 4 weeks of mobilization with diuretic therapy (early recurrence),[1,7] persistence despite maximum diuretic dosage (diuretic resistant), or recurrence or persistence of side effects from attempting to increase diuretics (diuretic intolerant).[1]

Therapeutic large volume paracentesis (> 5 L) can be used for refractory ascites with fewer side effects than diuresis.[1,8,9] Removal of large amounts of fluid, particularly > 8 L, can lead to circulatory shifts and postparacentesis circulatory dysfunction, which manifests as hepatorenal syndrome, hepatic encephalopathy, or dilutional hyponatremia.[1,10,11] Albumin infusion with 6 to 8 g/L of ascitic fluid removed is recommended to mitigate this risk.[1,10,12]

Nonselective beta blockers, used in managing portal hypertension, are associated with higher incidence of postparacentesis circulatory dysfunction,[13,14] although there is insufficient evidence to recommend against their use in cirrhosis. Instead, caution is advised in the setting of renal insufficiency, hyponatremia, or hypotension.[15]

Transjugular intrahepatic portosystemic shunt placement is a useful treatment for refractory ascites in certain patients, particularly for those with low Model for End-stage Liver Disease scores[16] and confers a 93% chance of 1-year transplant-free survival compared with 53% for patients managed with paracenteses, diuretics, and albumin.[17] Following placement, it may take up to 6 months for ascites resolution, and so salt restriction should be continued following transjugular intrahepatic portosystemic shunt placement. It is recommended to discontinue diuretic therapy to allow return of splanchnic volume to systemic circulation. Despite good results in patients with low Model for End-stage Liver Disease scores, scores ≥ 18 are generally considered high risk for transjugular intrahepatic portosystemic shunt.[18] Patients who are not candidates for transjugular intrahepatic portosystemic shunt should be considered for referral for liver transplantation.[1,18]

Hyponatremia and hepatic hydrothorax are also frequently encountered with cirrhosis, defined as a serum sodium less than 135 mEq/L.[1,19] Seen in 49% of patients with cirrhosis, low serum sodium is associated with severe ascites and frequent ascitic complications.[19] The most common subtype is hypervolemic hyponatremia, owing to third spacing and vasopressin activation, while hypovolemic hyponatremia may occur with diuretic use.[19,20] Rate of sodium correction is based on acuity with goal rate of increase in serum sodium for chronic cases of 4 to 6 mEq/L over 24 hours.[21,22] In acute cases, correction should be faster, though the exact rate is not specified in the guidance.[1] Specific management of hyponatremia is based on severity, as follows[1,3,17,23]:

- Mild hyponatremia (126–135 mEq/L) may be monitored.[1]
- Moderate hyponatremia (120–125 mEq/L) with hypervolemia is managed with fluid restriction and diuretics. Vaptans (vasopressin receptor antagonists) are limited in use due to high cost and should be used only up to 30 days. For hypovolemic patients, normal saline and decreased diuretics may be used.[1]
- Severe hyponatremia (< 120 mEq/L) may be managed with concentrated albumin infusion. Hypertonic saline is considered in limited subsets of patients, in the critical care setting or peri-transplant.[1]

Hepatic hydrothorax, a difficult-to-manage complication of cirrhosis, is a transudative pleural effusion due to translocation of peritoneal fluid through diaphragmatic defects and reported to occur in 4% to 12% of patients with cirrhosis.[24] Though typically right-sided, it may occur on the left, bilaterally, and

in the absence of ascites.[24] It is associated with high mortality risk, exceeding that predicted by the Model for End-stage Liver Disease score.[1,3,24] Management is similar to that of ascites, with fluid restriction and diuresis.[1] Abdominal hernias, particularly umbilical hernias, are common in the setting of ascites due to increased intra-abdominal pressure. Surgical repair may be considered when ascites management and nutritional status have been optimized.[24]

SPONTANEOUS BACTERIAL PERITONITIS

The most common source of bacterial infection in patients with cirrhosis is spontaneous bacterial peritonitis (SBP), accounting for 27% to 36% of infections.[1,4,25,26] Clinical deterioration (ie, jaundice, altered mentation, or acute kidney injury) should prompt exclusion of SBP with a diagnostic paracentesis. In hospitalized patients, diagnostic paracentesis should be performed even in the absence of symptoms suggestive of SBP.[27] Diagnosis of SBP is established when the fluid absolute neutrophil count is greater than 250 cells/mm^3 and is further confirmed with positive cultures.[1,28] Empiric intravenous antibiotics after cultures are obtained are the mainstay of management of SBP and spontaneous bacterial empyema, as each hour's delay in treatment increases mortality by 10%.[1,4,5,29]

Effective empiric antibiotic choice plays a key role in timely management of SBP.[1] Third generation cephalosporins are effective if local prevalence of multidrug resistant organisms is low, while broad coverage therapy (ie, piperacillin-tazobactam with vancomycin) is recommended for high prevalence of multidrug resistant organisms, history of prior multidrug resistant organisms infection, nosocomial and hospital-acquired infections, or in critical illness. Daptomycin should be added if there is history of vancomycin-resistant *Enterococcus*. Some confusion arises with positive cultures and fewer than 250 cells/mm^3 of neutrophils; such cases do not require antibiotics and likely are contaminants.[1]

In addition to antibiotics, albumin dosed at 1.5 g/kg on day 1 and 1 g/kg on day 3 should be administered and is especially helpful if concomitant acute kidney injury or jaundice are present.[5,30,31] Repeat paracentesis/thoracentesis after 2 days of therapy may be done to assess treatment response.[1] Treatment, secondary prophylaxis with norfloxacin, or ciprofloxacin in the absence of norfloxacin, should be used. For cases of gastrointestinal hemorrhage, prophylaxis with intravenous ceftriaxone 1 g every 24 hours for 7 days should be used.[1] Primary SBP prophylaxis should also be considered in the following cases of cirrhosis without bleeding[1]:

- Ascitic protein < 1.5 g/L
- Renal dysfunction (serum creatinine ≥ 1.2 mg/dL, blood urea nitrogen > 25 mmol/L, or serum sodium < 130 mEq/L)
- Liver failure, with a Child-Turcotte-Pugh mortality predicting score greater than 9 (severity determined by a higher score ranging from good hepatic function with 5 points to advanced hepatic dysfunction with 15 points) or a bilirubin greater than 3 mg/dL.[1,7,12,30]

ACUTE KIDNEY INJURY

Patients with cirrhosis and ascites are at risk of acute kidney injury (ie, increase in creatinine ≥ 0.3 mg/dL within 48 hours or ≥ 50% increase in creatinine over 7 days), with an estimated prevalence in hospitalized patients between 27% and 53%.[1,32,33] The two most common causes of acute kidney injury are prerenal azotemia and acute tubular necrosis. Prerenal azotemia may be secondary to hypovolemia or hepatorenal syndrome. The diagnosis of hepatorenal syndrome is made once hypovolemia/shock, nephrotoxic exposure, and structural kidney damage have been excluded in a patient with ascites who presents with prerenal acute kidney injury.[1,32,33]

The principle management of hepatorenal syndrome is vasoconstrictor and albumin therapy for up to 14 days. In the United States, midodrine and octreotide in combination are used for hepatorenal syndrome therapy, though their efficacy is low.[33] The preferred treatment is terlipressin, a vasoconstrictor that may be used outside of the intensive care unit, which has been shown to improve the likelihood of reversal of hepatorenal syndrome without dialysis and 10-day survival relative to placebo (29.1% vs 15.8%; P = .012).[3,34,35] It was very recently approved in the United States in limited settings, and centers are in the process of developing protocols to incorporate its use for hepatorenal syndrome treatment.[36] An alternative with comparable efficacy is norepinephrine, though use is limited to the intensive care unit.[1] Some studies have looked into using vasopressin in place of octreotide, which has been associated with improved survival and recovery, though use in the United States has thus far been limited.[1,37]

Response to therapy may be defined as creatinine decrease to less than 1.5 mEq/L or within 0.3 mEq/L of baseline.[1] If a response is not seen on maximum doses of therapy for 4 consecutive days, vasoconstrictors may be discontinued.[1] In treatment failure, renal replacement therapy is reserved for those referred for transplant, or

based on reversibility of other organ dysfunction. In patients with limited expectation for renal recovery, dual liver-kidney transplant may be considered.

REFERENCES

1. **Biggins SW, Angeli P, Garcia-Tsao G, et al.** Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 74(2):1014–1048. doi:10.1002/hep.31884
2. **Pant C, Jani BS, Desai M, et al.** Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012. J Investig Med 2016; 64:33–38. doi:10.1136/jim-d-15-00181
3. **Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG.** The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med 1992; 117(3):215–220. doi:10.7326/0003-4819-117-3-215
4. **Hsu WF, Yu SH, Lin JT, et al.** Renal effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with liver cirrhosis: a nationwide cohort study. Gastroenterol Res Pract 2019; 2019:1743290. doi:10.1155/2019/1743290
5. **Moore KP, Wong F, Gines P, et al.** The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003; 38(1):258–266. doi:10.1053/jhep.2003.50315
6. **Moreau R, Delegue P, Pessione F, et al.** Clinical characteristics and outcome of patients with cirrhosis and refractory ascites. Liver Int 2004; 24(5):457–464. doi:10.1111/j.1478-3231.2004.0991.x
7. **Salerno F, Guevara M, Bernardi M, et al.** Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis [published correction appears in Liver Int 2010; 30(8):1244]. Liver Int 2010; 30(7):937–947. doi:10.1111/j.1478-3231.2010.02272.x
8. **Gines P, Arroyo V, Quintero E, et al.** Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. Gastroenterology 1987; 93:234–241. doi:10.1016/0016-5085(87)91007-9
9. **Bernardi M, Carceni P, Navickis RJ, Wilkes MM.** Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. Hepatology 2012; 55(4):1172–1181. doi:10.1002/hep.24786
10. **Ruiz-del-Arbol L, Monescillo A, Jimenéz W, Garcia-Plaza A, Arroyo V, Rodés J.** Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. Gastroenterology 1997; 113(2):579–586. doi:10.1053/gast.1997.v113.pm9247479
11. **Tan HK, James PD, Wong F.** Albumin may prevent the morbidity of paracentesis-induced circulatory dysfunction in cirrhosis and refractory ascites: a pilot study. Dig Dis Sci 2016; 61(10):3084–3092. doi:10.1007/s10620-016-4140-3
12. **Runyon BA; AASLD.** Introduction to the revised American Association for the Study of Liver Diseases Practice guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013; 57(4):1651–1653. doi:10.1002/hep.26359
13. **Sersté T, Melot C, Francoz C, et al.** Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology 2010; 52(3):1017–1022. doi:10.1002/hep.23775
14. **Sersté T, Francoz C, Durand F, et al.** Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. J Hepatol 2011; 55(4):794–799. doi:10.1016/j.jhep.2011.01.034
15. **Reiberger T, Mandorfer M.** Beta adrenergic blockade and decompensated cirrhosis. J Hepatol 2017; 66(4):849–859. doi:10.1016/j.jhep.2016.11.001
16. **Tan HK, James PD, Sniderman KW, Wong F.** Long-term clinical outcome of patients with cirrhosis and refractory ascites treated with transjugular intrahepatic portosystemic shunt insertion. J Gastroenterol Hepatol 2015; 30(2):389–395. doi:10.1111/jgh.12725
17. **Bureau C, Thabut D, Oberti F, et al.** Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites [published correction appears in Gastroenterology 2017; 153(3):870]. Gastroenterology 2017; 152(1):157–163. doi:10.1053/j.gastro.2016.09.016
18. **Angermayr B, Cejna M, Karnel F, et al.** Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. Gut 2003; 52(6):879–885. doi:10.1136/gut.52.6.879
19. **Angeli P, Wong F, Watson H, Ginès P; CAPPS Investigators.** Hyponatremia in cirrhosis: results of a patient population survey. Hepatology 2006; 44(6):1535–1542. doi:10.1002/hep.21412
20. **Gines P, Guevara M, Arroyo V, Rodes J.** Hepatorenal syndrome. Lancet 2003; 362(9398):1819–1827. doi:10.1016/S0140-6736(03)14903-3
21. **Sterns RH.** Disorders of plasma sodium--causes, consequences, and correction. N Engl J Med 2015; 372(1):55–65. doi:10.1056/NEJMra1404489
22. **Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH.** Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. Clin J Am Soc Nephrol 2007; 2(6):1110–1117. doi:10.2215/CJN.00910207
23. **D'Amico G, Garcia-Tsao G, Pagliaro L.** Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006; 44(1):217–231. doi:10.1016/j.jhep.2005.10.013
24. **Badillo R, Rockey DC.** Hepatic hydrothorax: clinical features, management, and outcomes in 77 patients and review of the literature. Medicine (Baltimore) 2014; 93(3):135–142. doi:10.1097/MD.0000000000000025
25. **Fernández J, Acevedo J, Castro M, et al.** Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012; 55(5):1551–1561. doi:10.1002/hep.25532
26. **Piano S, Singh V, Caraceni P, et al.** Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology 2019; 156(5):1368–1380.e10. doi:10.1053/j.gastro.2018.12.005
27. **Runyon BA; AASLD Practice Guidelines Committee.** Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009; 49(6):2087–2107. doi:10.1002/hep.22853
28. **Wong CL, Holroyd-Leduc J, Thorpe KE, Straus SE.** Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? JAMA 2008; 299(10):1166–1178. doi:10.1001/jama.299.10.1166
29. **Arabi YM, Dara SI, Memish Z, et al.** Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology 2012; 56(6):2305–2315. doi:10.1002/hep.25931
30. **Gatta A, Angeli P, Caregaro L, Menon F, Sacerdoti D, Merkel C.** A pathophysiological interpretation of unresponsiveness to spironolactone in a stepped-care approach to the diuretic treatment of ascites in nonazotemic cirrhotic patients. Hepatology 1991; 14(2):231–236. pmid:1860680
31. **Sort P, Navasa M, Arroyo V, et al.** Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341(6):403–409. doi:10.1056/NEJM199908053410603
32. **Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS.** Hepatorenal syndrome [published correction appears in Nat Rev Dis Primers 2018; 4(1):33]. Nat Rev Dis Primers 2018; 4(1):23. doi:10.1038/s41572-018-0022-7
33. **Angeli P, Ginès P, Wong F, et al.** Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites [published

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

correction appears in J Hepatol 2015; 63(1):290]. J Hepatol 2015; 62(4):968–974. doi:10.1016/j.jhep.2014.12.029
34. **Wong F, Pappas SC, Curry MP, et al.** Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. N Engl J Med 2021; 384(9):818–828. doi:10.1056/NEJMoa2008290
35. **Wong F, Curry M, Reddy K, et al.** The CONFIRM study: a North American randomized controlled trial (RCT) of terupressin plus albumin for the treatment of hepatorenal syndrome type 1 (HRS-1) [Abstract]. Hepatology 2019; 70:1480A.
36. **US Food and Drug Administration.** FDA approves treatment to improve kidney function in adults. September 14, 2022. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-improve-kidney-function-adults-hepatorenal-syndrome. Accessed March 13, 2023.
37. **Kiser TH, Fish DN, Obritsch MD, Jung R, MacLaren R, Parikh CR.** Vasopressin, not octreotide, may be beneficial in the treatment of hepatorenal syndrome: a retrospective study. Nephrol Dial Transplant 2005; 20(9):1813–1820. doi:10.1093/ndt/gfh930

Address: *Maureen Linganna, MD, Department of Gastroenterology, Hepatology, and Nutrition, A51, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; linganm@ccf.org*