Ascites: Diagnosis and Management

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KEYWORDS

- Cirrhosis • Ascites • Portal hypertension • Refractory ascites
- Transjugular intrahepatic portosystemic shunts
- Spironolactone • Furosemide
- Spontaneous bacterial peritonitis

Ascites is a common complication of cirrhosis. The development of ascites marks the onset of worsened prognosis and increased mortality in patients with cirrhosis. Ascites also causes considerable morbidity in the affected individual by producing abdominal distension, respiratory distress, formation of hernias especially around the umbilicus, worsening nutritional status, and increased susceptibility to infections. All of these contribute to repeated hospitalizations in such patients and markedly impair their quality of life. Appropriate management of ascites is thus an important pillar in the care of a patient with cirrhosis. The current concepts about the pathophysiology, diagnosis, and management of ascites are reviewed in the following sections.

PATHOPHYSIOLOGY

The main factor contributing to the development of ascites in a patient with cirrhosis is the portal hypertension which results from increased intrahepatic resistance to blood flow and is compounded by splanchnic vasodilatation as a result of local production of vasodilators (**Fig. 1**).[1–8] Cirrhosis occurs as a consequence of chronic liver injury–induced distortion of hepatic architecture and fibrosis. Increased resistance to portal blood flow as a result of cirrhosis and vascular tone because of increased production of vasoconstrictors, such as angiotensin, endothelin, cysteinyl-leukotrienes, and thromboxane leads to gradual formation of portal hypertension, collateral vein circulation, and shunting of blood to the systemic circulation. Splanchnic vasodilatation develops as persistent portal hypertension results in local overproduction of vasodilators such as nitric oxide (NO), calcitonin gene–related peptide, substance P, carbon monoxide, and endogenous cannabinoids. Among these vasodilators, NO is a potent

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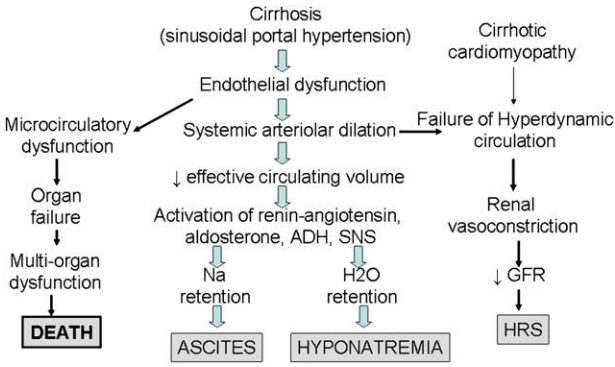

Fig. 1. The pathophysiology of cirrhosis and ascites is shown. Cirrhosis is associated with splanchnic arterial vasodilation. This leads to a decrease in effective circulating volume and a hyperdynamic circulation. The decrease in effective circulating volume causes activation of renal sodium and water retentive pathways (eg, RAAS, renal SNS, and ADH). The resulting sodium and water retention leads to ascites as a result of spillage of excess sodium and water from hepatic lymph into the peritoneal cavity. As the disease progresses, a progressive decrease in effective circulating volume develops, causing severe renal vasoconstriction and a decrease in glomerular filtration rate. The onset of cirrhotic cardiomyopathy accentuates this problem and tips the patient into hepatorenal syndrome. The accompanying circulatory disturbance leads to organ failure and death. Sepsis is frequently associated with this process.

and predominant vasodilator. Endothelial stretching and bacterial translocation are responsible for the local overproduction of vasodilators and other cytokines.[9,10] Recent data suggest that bacteria translocate to mesenteric lymph nodes in cirrhosis, and consequently stimulation of cytokine production plays an important role in the process of arterial vasodilatation.[11–13]

Splanchnic arteriolar vasodilation and consequent pooling of blood in the splanchnic circulation causes a decrease in effective arterial blood volume and arterial pressure. In response to this change in effective arterial blood volume and arterial pressure, baroreceptor-mediated activation of the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and antidiuretic hormone (ADH) cause avid renal water and sodium retention in order to restore homeostasis. Cirrhosis is also associated with increased sinusoidal pressure and decreased plasma oncotic pressure. These combine to increase hepatic lymph formation. When the capacity of the hepatic lymphatics to return hepatic lymph to the circulation is exceeded, the excess lymph (composed of an ultrafiltrate of plasma containing the retained sodium and water) spills into the peritoneal cavity, producing ascites.

The cardiac output and plasma volume increase in the early stages of liver cirrhosis, which maintains circulatory function compensated. However, decrease in cardiac output as a result of cirrhotic cardiomyopathy occurs in the advanced stage of liver cirrhosis and contributes to a further fall in effective arterial blood volume and arterial pressure. This causes marked activation of systemic vasoconstrictive mechanisms that particularly affect the kidneys and decrease glomerular filtration and renal plasma flow. In its most severe form, this leads to progressive renal failure, that is, hepatorenal syndrome.

DIAGNOSIS

The goals of the diagnostic assessment of a patient with ascites are to establish the presence of ascites, determine its severity, determine its cause, and detect the

presence of complications of ascites, which include spontaneous bacterial peritonitis and renal failure. A good clinical assessment provides invaluable information about these goals.

A correct diagnosis of the cause of ascites is the essential first step to its successful treatment. Cirrhosis accounts for approximately 85% of ascites in the United States, whereas nonhepatic diseases cause most of the remaining cases (**Box 1**).[14] A history of risk factors for liver diseases such as viral hepatitis, alcohol abuse, metabolic syndrome, familial liver diseases, autoimmune disease, and so on should be obtained. Cancer is the second most common cause of ascites. A history of cancer should lead to exploring the possibility that ascites could be caused by peritoneal carcinomatosis. Heart failure is the third common cause of ascites and a history of heart failure could hint at a cardiogenic etiology as a potential cause of ascites. A history of tuberculosis, kidney disease on dialysis, pancreatic disease, and so on are also relevant, and questions about these less common diseases should also be asked.

The physical examination should focus on stigmata of cirrhosis and signs suggesting the presence of ascites. Stigmata of cirrhosis such as spider angioma and palmar erythema may coexist with ascites. A full and bulging abdomen should lead to the evaluation of ascites. Flank dullness on percussion is usually characteristic of ascites. A positive shifting dullness usually suggests the presence of more than 1500 mL of

Box 1
Causes of ascites

1. Portal hypertension
   - Presinusoidal causes, eg, portal vein thrombosis (usually ascites is mild if present at all)
   - Sinusoidal causes, eg, cirrhosis, vitamin A toxicity
   - Postsinusoidal causes, eg, venoocclusive disease, Budd-Chiari syndrome, constrictive pericarditis, congestive heart failure
2. Neoplastic causes
   - Peritoneal carcinomatosis
   - Lymphoma
   - Hepatocellular cancer
   - Ovarian cancer
   - Mesothelioma
3. Inflammatory causes
   - Infectious causes, eg, tuberculosis, Whipple disease
   - Chemical causes, eg, talc peritonitis
   - Immunologic disorders, eg, systemic lupus erythematosus, vasculitis
   - Allergic causes, eg, eosinophilic gastroenteritis
4. Miscellaneous causes
   - Nephrotic syndrome
   - Dialysis-associated ascites
   - Ovarian hyperstimulation syndrome
   - Thoracic duct obstruction

fluid.[15] An obese abdomen can masquerade as ascites, and an abdominal ultrasonogram may be required to establish the presence of ascites in an obese patient. An abdominal ultrasonogram is usually performed in patients with ascites not only to assess the presence of ascites and a mass, but also to investigate the hepatic echogenicity and vasculature.

Assessment of the Severity of Ascites

The International Ascites Club classifies ascites according to severity, complication, and response to diuretic treatment. Ascites can be classified into grade 1 (mild), grade 2 (moderate), and grade 3 (large) according to severity; into uncomplicated according to absence of complication; and into diuretic-resistant and diuretic-intractable according to the response to diuretic treatment (**Table 1**).[5,16,17]

Laboratory Studies Including Ascites Fluid Analysis

History and physical examination are important first steps in establishing the diagnosis of new-onset ascites, which should be further confirmed by an abdominal paracentesis and ultrasonography (**Box 2**). The presence of cirrhosis can be further assessed by measuring tests of liver function such as the serum bilirubin, albumin, and international normalized ratio (INR). These are often abnormal in patients with cirrhosis, although it is possible to have ascites as a result of cirrhosis in the presence of near normal values of these parameters. It is important to check renal function (serum creatinine) to establish a baseline and to determine if functional renal insufficiency is present. It is also worth remembering that a serum creatinine of 1.5 mg/dL, which is often considered to be near normal, represents considerable decrease in glomerular filtration in patients with cirrhosis who have decreased muscle mass. The presence of an underlying hepatocellular cancer should be sought with imaging studies and an alpha fetoprotein test. Endoscopy is sometimes performed to look for varices as further corroborative evidence for the presence of portal hypertension in cases where the diagnosis is not clear-cut. Similarly, a liver biopsy is performed in selected patients with ascites and liver disease of unknown etiology. Abdominal ultrasonography, CT, or MRI is used to image the liver to screen for hepatocellular carcinoma, portal vein thrombosis, and hepatic vein thrombosis.

Appropriate ascitic fluid analysis is probably the most efficient and effective method of diagnosing the cause of ascites.[15,18] The left lower quadrant of the abdomen, 2 finger breadths cephalad and 2 finger breadths medial to the anterior superior iliac crest, is the best location for paracentesis because it has thinner abdominal wall and larger pool of fluid accumulation.[19] The prothrombin time is often prolonged (approximately 71%) in patients with cirrhosis; however, the risk for bleeding is less than 1% after paracentesis in these patients even without any interventions to correct the coagulopathy.[20] The possibility for more serious complications such as hemoperitoneum and bowel perforation is remote, and they occur in less than 0.1% of patients.[21] Coagulopathy should preclude paracentesis only when there is clinical evidence of fibrinolysis or disseminated intravascular coagulation.[20]

In light of the presence of spontaneous bacterial peritonitis (SBP) in approximately 15% of hospitalized patients with cirrhosis and ascites, all such patients should be screened for SBP at the time of admission to the hospital.[22–25] Ascitic fluid should be analyzed in patients with new-onset ascites.[2] Ascitic fluid analysis to detect SBP is required in all patients with any evidence of clinical deterioration such as fever, abdominal pain, gastrointestinal bleeding, hepatic encephalopathy, hypotension, or renal failure.[26] The SAAG has been proven superior to the total-protein-based

Table 1
Classification of ascites according to severity, complication, and response to diuretic treatment

Severity				Refractory	
Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Large)**	**Uncomplicated**	**Diuretic-Resistant**	**Diuretic-Intractable**
Ascites is only diagnosed on ultrasonography	Clinically sensiblemoderate distension of abdomen	Clinically marked or tense distension of abdomen	Ascites that is not complicated with infection and hepatorenal syndrome	Ascites is unresponsive to sodium restricted diet and high-dose diuretic treatment	Diuretic-induced adverse effects preclude the use of an effective diuretic dosage

Box 2
Evaluation of a patient with cirrhosis and ascites

General evaluation

- Complete blood count, platelets

Evaluation of liver disease

- Serum bilirubin, AST, ALT, alkaline phosphatase, serum albumin
- Prothrombin time, INR
- Tests to determine cause of liver disease, eg, hepatitis C antibody
- Upper abdominal imaging by ultrasonogram/CT scan[a]
- Esophagogastroduodenoscopy
- MELD score

Evaluation of renal functions

- Serum creatinine and electrolytes
- Urinalysis including microscopic examination
- 24-h urinary sodium and/or protein[b]

Ascitic fluid analysis

- Cell count
- Bacterial culture with bedside inoculation into blood culture bottle
- Total protein and albumin
- Glucose, lactate dehydrogenase, amylase, triglycerides, and cytology, if indicated according to clinical situation[c]

[a] To look for hepatocellular cancer or portal vein thrombosis.
[b] Usually done if urinalysis indicates proteinurea or if noncompliance with sodium restriction is suspected.
[c] Usually glucose, albumin, and protein are the only routinely performed tests initially. The other tests are done if a diagnostic dilemma is present.

exudate/transudate analysis in categorizing ascites in prospective studies and has replaced the total-protein-based exudate/transudate concept in clinical practice.[14,27]

Calculation of SAAG is performed by measuring same-day albumin concentrations of serum and ascitic fluid and then subtracting the ascitic fluid albumin value from the serum albumin value. A SAAG value greater than or equal to 1.1 g/dL (11 g/L) predicts ascites as a result of portal hypertension with approximately 97% accuracy.[14] A SAAG greater than or equal to 1.1 g/dL may also be present in medical conditions such as congestive heart failure, Budd-Chiari syndrome, and portal hypertension—a second cause for ascites formation.[14,17] A SAAG less than 1.1 g/dL occurs commonly in peritoneal carcinomatosis, peritoneal tuberculosis, pancreatitis, serositis, and nephrotic syndrome.[14,17]

When there is no evidence of perforation of an intra-abdominal viscus or inflammation of intra-abdominal organs, an ascitic fluid neutrophil count greater than or equal to 250 cells/ mm^3 confirms the diagnosis of SBP.[15,16,28] The cell count is the most helpful parameter in diagnosing SBP. A urine dipstick is a quick test to detect neutrophil in ascites and may provide an early suspicion of SBP at bedside.[29,30] Gram stain of ascitic fluid is not necessary because it is rarely helpful.[31] When culture of ascitic fluid

is performed, the fluid should be inoculated in blood culture bottles as opposed to sterile culture vials. In sterile vials, growth of an organism is noted in about 50% of cases whereas culture of ascitic fluid in blood culture bottles increases the probability of identification of an organism to about 80%.[32,33]

Cell count and differential, albumin, total protein concentration, and SAAG are tested in the initial screening of ascitic fluid if the ascites is believed to be likely uncomplicated on clinical grounds. Further testing is needed if the results of these tests are abnormal. Cell count and differential are usually adequate in patients receiving serial outpatient therapeutic paracentesis.[15] Lactate dehydrogenase, total protein, and glucose may help differentiate spontaneous from secondary bacterial peritonitis.[34] Ascitic fluid carcinoembryonic antigen (CEA) and alkaline phosphatase levels are useful for the differentiation of primary from secondary bacterial peritonitis with intestinal perforation. An ascitic fluid CEA greater than 5 ng/mL or ascitic fluid alkaline phosphatase values greater than 240 IU/L suggest gut perforation into ascitic fluid.[35] A high amylase level in ascitic fluid is diagnostic of pancreatic ascites. Ascitic fluid amylase should be determined whenever there is an increased clinical suspicion for pancreatic disease.[36–38] It is usually accompanied by increased total protein levels and decreased SAAG.

Bloody ascites with red blood cell count greater than 50,000 cells/mm^3 occurs in approximate 2% of patients with liver cirrhosis.[39] Hepatocellular carcinoma is the cause of bloody ascites in about 30% of patients with cirrhosis. However, the cause of bloody ascites cannot be found in about 50% of the cases. In patients with decompensated cirrhosis, cancer antigen 125 (CA 125) is usually elevated in both blood and ascites in proportion to the degree of ascites and does not necessarily indicate carcinoma as the underlying cause of ascites.[40–42]

Ascitic fluid cytology is an expensive test and has a low yield if it is not used in selective patients. One study showed that only 7% ascitic fluid cytologies are positive.[43] In peritoneal carcinomatosis, if adequate concentrated ascitic samples are sent and processed promptly, it is highly positive. The sensitivity of cytology in detecting peritoneal carcinomatosis is 96.7% if 3 samples are sent.[43] Breast, colon, gastric, or pancreatic carcinoma is usually the underlying cause of peritoneal carcinomatosis. Mycobacteria in ascitic fluid are difficult to detect. Smears for mycobacteria usually do not work, with sensitivity approaching 0%; however, the sensitivity of ascitic fluid culture for mycobacteria is approximately 50%.[44] Patients with high pretest probability for tuberculous peritonitis should be tested for mycobacteria on the first ascitic fluid sample.[45] Laparoscopy with peritoneal biopsy and mycobacterial culture of tubercles are the most rapid and accurate methods of diagnosing tuberculous peritonitis.

TREATMENT

General Management

The fundamental goal of ascites management is to induce a negative sodium balance (**Box 3**). Activation of sympathetic nervous system, RAAS, and ADH play an important role in the pathophysiology of ascites formation. Physiologically, an upright position activates these systems that theoretically worsen sodium and fluid retention and decrease response to diuretics in patients with cirrhosis and ascites.[46,47] Moderate physical activity may induce more profound effects on these systems.[48,49] These findings support the traditional practice to recommend bed rest as part of the treatment for ascites. However, bed rest is impractical, especially in patients with mild and moderate ascites. Another concern is that bed rest may further decondition the patient, weaken physical strength, and induce muscle atrophy in patients with

Box 3
Treatment of ascites

1. General measures:
   a. Sodium restriction
   b. Maintain caloric intake at goal
   c. Protein intake (1 g/kg/d unless patient is severely encephalopathic or catabolic)
   d. Immunization: pneumococcal vaccine, influenza vaccine
2. Treatment of underlying liver disease:
   a. Alcohol abstinence
   b. Hepatitis B: antiviral therapy for E antigen positive subjects
   c. Hemochromatosis: phlebotomy
   d. Wilson disease: chelation therapy
3. Standard medical treatment (diuretics + paracentesis):
   a. Distal tubule acting diuretics, eg, spironolactone
   b. Loop-acting diuretics, eg, furosemide
   c. Large volume paracentesis (>5 L)
4. Transjugular intrahepatic portasystemic shunts (TIPS)
5. Peritoneovenous shunts
6. Liver transplantation

cirrhosis and ascites. There are no controlled trials to support the theory of bed rest. Therefore, bed rest is not generally recommended for the management of patients with uncomplicated ascites.[17]

Dietary sodium restriction and oral diuretics are mainstays of treatment for patients with cirrhosis and ascites. Stringent dietary sodium restriction mobilizes ascites in patients with portal hypertension. Negative sodium balance leads to fluid and weight loss in patients with cirrhosis and ascites. It is usually sodium restriction, not water restriction, that induces weight loss, because water follows sodium passively.[50] Dietary sodium should be restricted to 2000 mg/d (88 mmol/d). Nonurinary excretion of sodium is about 10 mmol/d. One of the goals of treatment is to achieve negative sodium balance. In order to achieve negative sodium balance, urinary sodium excretion should be greater than 78 mmol/d. If weight loss is not as expected, measurement of urinary sodium excretion may be helpful.[18] Collection of 24-hour urine for sodium measurement is cumbersome. Random urine "spot" sodium concentration is a more quick and convenient method to determine urinary excretion with 97% accuracy.[51] Sodium restriction is effective in reducing the dose of diuretics, providing faster solution for ascites, and a shorter hospital stay.[52,53] However, dietary sodium restriction is successful in achieving a negative sodium balance in only about 10% to 15% of patients with cirrhosis and ascites.[54] Compliance with sodium restriction is a practical issue in daily management of patients with cirrhosis and ascites because most patients are reluctant to go along with sodium restriction alone. There are no controlled trials regarding fluid restriction. Most experts believe fluid restriction has no role in the management of patients with uncomplicated ascites.[15,17] Water restriction is recommended only when the serum sodium decreases to values below 130 mEq/L.

Consideration should be given to treatment of the underlying cause of cirrhosis, particularly for alcohol-related and hepatitis B–related cirrhosis. Abstinence can result in dramatic improvement in liver function and even resolve ascites in the course of a few months in patients with alcoholic hepatitis and cirrhosis. The benefits of abstinence are seen in patients with alcoholic liver disease and cirrhosis of varying severity.[55,56]

A nutritionist can play an important role in providing education regarding salt and caloric intake. Protein-calorie malnutrition and weight loss are common among patients with cirrhosis and ascites. Such patients often complain of dyspeptic symptoms such as early satiety, nausea, and postprandial fullness. A study has reported significant reduction in median postprandial gastric volume and gastric accommodation; and paracentesis improves fasting gastric volume, tolerance to ingestion of maximum volume, and caloric intake.[57] Decreased oral intake and absorption of nutrients, increased energy expenditure, and altered fuel metabolism with a starvation pattern of metabolism are the underlying mechanisms for malnutrition in patients with cirrhosis and ascites.[58–60] Nutritional therapy with improved nutritional status may reduce the occurrence of infection and perioperative morbidity. Although there are no studies that show the value of nutritional status correction to improve ascites management and hard outcomes such as mortality, absence of evidence does not indicate the absence of an effect. One can imagine that good nutritional support may be essential to make the patient a good candidate for liver transplant. Supplemental enteral nutrition is needed in patients with severe malnutrition and may improve liver function and hepatic encephalopathy.[58–61]

Specific therapies for ascites

Diuretics have been the mainstay of treatment for patients with cirrhosis and ascites since they first became available. Patients with grade 1 ascites have mild ascites that can only be detected by ultrasound. These patients should have a sodium-restricted diet but do not require diuretics. Patients with grade 2 or higher severity require diuretics to reduce edema and ascites. Activation of RAAS plays an important role in the development of ascites. Spironolactone is the diuretic of choice because it is an aldosterone antagonist that acts on the distal tubules in the kidney to increase sodium excretion and conserve potassium. As a single agent, spironolactone has been shown to be more efficacious than furosemide in a randomized clinical trial.[62] However, it is used as a single agent mostly in patients with minimal fluid overload.[63]

Furosemide is a loop diuretic that causes marked natruresis and diuresis. It is less efficacious than spironolactone as a single agent in the treatment of patients with cirrhosis and ascites.[62] It is usually used as an adjunct to spironolactone treatment. It should be used with caution because it can cause hyponatremia, hypokalemia, and prerenal renal failure. Because of its good oral availability and intravenous administration–induced acute reduction in renal glomerular filtration rate, furosemide is usually used as an oral agent.[64,65] Simultaneous use of spironolactone and furosemide increases the natriuretic effect and prevents hypokalemia.[15] Furosemide 40 mg and spironolactone 100 mg daily are usually started as an initial dose in patients with moderate to severe ascites. It usually takes 3 to 5 days for the diuretics to show their maximal effects.[66] The doses of spironolactone and furosemide can be increased simultaneously in a stepwise manner until the maximal doses of 400 mg spironolactone and 160 mg furosemide every day are reached if desired weight loss and natriuresis are not attained.[15,18]

Dietary sodium restriction should always be implemented together with the use of diuretics. The desired rate of daily weight loss depends upon the severity of edema.

In patients with severe edema, diuretics can be given to patients with cirrhosis and ascites without limitation of daily weight loss. Once ascites has resolved, daily maximal weight loss of 0.5 kg is probably a reasonable goal.[67] This approach of dual diuretics regimen in combination with dietary sodium restriction has been used successfully in achieving improvement of ascites to an acceptable level in more than 90% of patients in a large, multicenter, randomized, controlled clinical trial.[68] Efforts should be made to avoid overdiuresis that can lead to decreased intravascular volume, prerenal kidney impairment, hepatic encephalopathy, and hyponatremia.[69] Serum creatinine greater than 2.0 mg/dL, or serum sodium less than 120 mmol/L indicate that diuretics should be discontinued and alternative treatment considered.[15] The hepatic encephalopathy associated with volume contraction is best treated with albumin infusions. In patients with cirrhosis who have ascites, side effects of spironolactone include hyperkalemia and decreased libido, impotence, and gynecomastia in men and menstrual irregularity in women, as a result of its antiandrogenic activity. Patients with organic renal disease may not tolerate spironolactone because of hyperkalemia, a serious complication that frequently limits its use in such a situation. Amiloride may be considered as an alternative in patients with tender gynecomastia, but it was shown to be more expensive and less effective than spironolactone in a randomized controlled clinical study.[65] Tamoxifen at a dose of 20 mg twice daily has been reported to be effective in managing the gynecomastia.[63]

Clonidine is a centrally acting alpha-2 agonist that has sympatholytic activity in patients with cirrhosis.[70–72] Simultaneous administration of clonidine and spironolactone has been shown in studies to increase natriuresis and body weight loss more efficiently, to induce an earlier diuretic response, and fewer complications such as hyperkalemia and renal impairment.[73–75] Diuretic use is one of the underlying causes of muscle cramps. In patients with cirrhosis and ascites receiving diuretic therapy, muscle cramps may require a reduction in diuretic dosage. Quinidine sulfate at a dose of 400 mg daily or intravenous albumin at 25 g/wk reduces the frequency and severity of diuretic-induced muscle cramps in patients with cirrhosis and ascites.[76,77]

Therapeutic paracentesis

Diuretics alone may be inadequate in managing patients with large or refractory ascites. Therapeutic paracentesis does not correct the underlying pathophysiological process that results in ascites formation in patients with cirrhosis but usually relieves symptoms caused by abdominal tension. In prospective studies the safety of a single 5 L or less paracentesis without postprocedure colloid infusion for intravascular volume expansion has been shown.[78,79] Large volume paracentesis (LVP) can be performed safely with the administration of intravenous albumin infusion (8 g/L of ascites removed).[80] LVP with intravenous albumin infusion rapidly removed ascites, was more effective in maintaining an ascites-free state, and was associated with fewer complications and shorter hospital stay when compared with diuretic therapy.[69,81] Total paracentesis followed by postparacentesis volume expansion with albumin is as safe as serial LVP alone.[78,80]

A complication of LVP is the development of postparacentesis circulatory dysfunction.[82] This is characterized by worsening vasodilation, hyponatremia, activation of sodium-retentive hormones and sometimes azotemia. It is a marker for poorer outcomes and can be partially prevented by the use of albumin given intravenously at a dose of 6 to 8 g per liter of ascites removed.[83] Although albumin was formerly thought to be a simple volume expander, it is now thought that albumin may have

important effects on the endothelial dysfunction and circulatory disturbances associated with cirrhosis.[84]

Transjugular intrahepatic portosystemic shunts

These procedures decompress the portal vein by providing a low-resistance channel between the intrahepatic portion of the portal vein and the hepatic vein. They increase venous return to the heart and improve the effective circulating volume. This leads to improved renal perfusion and a decrease in renal tubular sodium reabsorption, thereby causing a natriuresis. Transjugular intrahepatic portosystemic shunts (TIPS) effectively removes ascites and maintains an ascites-free state. However, these benefits are offset by an increased incidence of hepatic encephalopathy.[85,86] The incidence of hospitalization and overall survival are not impacted by TIPS. The outcomes after TIPS depend on the model end-stage liver disease (MELD) score.[87] The ideal candidate for TIPS is one who has relatively preserved hepatic synthetic function and renal function and who is free of encephalopathy.

Peritoneovenous shunts

A peritoneovenous shunt has been used for the treatment of refractory ascites. It also increases the central volume and induces diuresis. Although as effective as repeated LVP, it does not improve survival. Enthusiasm for this procedure has waned because of the increased risk of complications, such as disseminated intravascular coagulation, infection, and occlusion of the subclavian vein and superior vena cava, which can preclude a liver transplant.

Management of uncomplicated ascites

This is usually managed with a combination of general measures and the use of diuretics and sodium restriction. Initially when patients present with moderate or severe ascites, a LVP is done to make the patients comfortable and then sodium restriction and diuretics are used to maintain an ascites-free state. Although this is effective in most patients, some patients progress to the refractory ascites state. Only liver transplant provides long-term survival in patients with end-stage liver disease, and in the absence of an obvious contraindication to transplantation, such patients should be referred expeditiously to a transplant center.

Management of refractory ascites

Diuretic refractory ascites (see **Table 1**), that is, ascites that does not respond to maximal diuretic doses, is associated with increasing systemic vasodilation and activation of systemic sodium and water retentive mechanisms. Increasing vasodilation decreases effective circulating volume and renal perfusion. This decreases delivery of the drugs to their site of action (the distal tubule for spironolactone and the lumen of the loop of Henle for furosemide) and causes diuretic resistance.

Repeated LVP or TIP are the most commonly used modalities for the treatment of refractory ascites. Although they relieve ascites immediately, they are associated with recurrence of ascites in most patients and do not improve survival. Repeated LVP is associated with discomfort, protein loss and malnutrition, the need for repeated hospitalization, and health care resource utilization. It is, however, a relatively inexpensive approach.

TIPS is substantially superior to LVP for long-term control of ascites (**Fig. 2**).[86] This does not translate to improved survival and the decrease in ascites-related health care resource utilization is offset by increased encephalopathy-related morbidity. Also, for the same survival outcomes, TIPS is less cost-effective than LVP. Hyperbilirubinemia, severe hypoprothrombinemia, and renal failure are risk factors associated with a poor

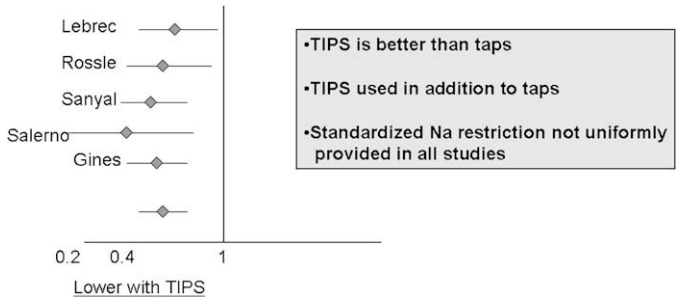

Fig. 2. A meta-analysis of TIPS versus LVP shows TIPS to be superior to LVP for control of ascites as shown by the odds ratio in individual studies. (*Data from* Albillos A, Bañares R, González M, et al. A meta-analysis of transjugular intrahepatic portosystemic shunt versus paracentesis for refractory ascites. J Hepatol 2005;43:990–6.)

outcome after TIPS.[87] Although TIPS is better than LVP for control of ascites in general,[88] the outcomes of TIPS for refractory ascites are best in those who have failed repeated LVP and who have relatively preserved liver and renal function (ie, a creatinine less than 1.5 mg/dL, INR less than 1.5, and bilirubin less than 2 mg/dL). Ideally, it should be used as a bridge to liver transplant.

Hyponatremia is another major management challenge in patients with cirrhosis and ascites. It occurs in about 50% of patients with cirrhosis and is associated with increased mortality (**Fig. 3**).[89] It is generally managed by volume restriction. There are anecdotal reports of improvement with albumin infusions as well. The role of aquaretic drugs in the management of ascites-related hyponatremia is under investigation.

Spontaneous bacterial peritonitis

SBP should always be considered in the differential diagnosis when a patient with cirrhosis and ascites develops fever, abdominal pain, altered mental status, variceal hemorrhage, or azotemia. It is diagnosed by a diagnostic paracentesis and treated with a third-generation cephalosporin.[90] A 5-day course has been found to be as effective as a 10-day course for uncomplicated SBP.[91] Typically, treatment is switched to oral quinolone therapy after 3 to 5 days of intravenous antibiotics. SBP recurs frequently and secondary prophylaxis with oral quinolones is effective in

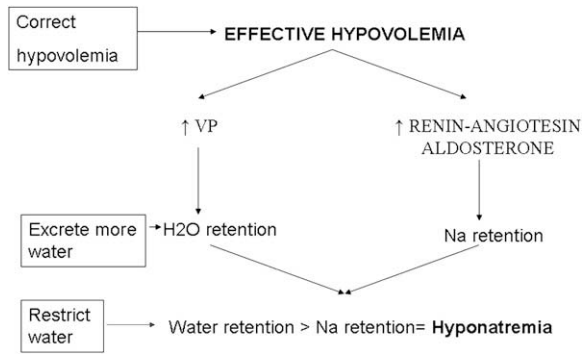

Fig. 3. A pathophysiology-based approach to the treatment of hyponatremia associated with cirrhosis.

preventing recurrence and is therefore recommended.[92] Primary prophylaxis for SBP should be considered in those with low-protein ascites and severe hepatic synthetic dysfunction.[93]

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