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Ascites: Causes, Diagnosis, and Treatment

Mohamed Omar Amer and Hussien Elsiesy

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Abstract

Ascites is a pathological accumulation of fluid in the peritoneal cavity. Cirrhosis is the most common cause of ascites, representing for 85% of cases. More than one cause may be responsible for the development of ascites (multifactorial). Development of ascites is a poor prognostic event in the natural history of cirrhosis, with approximately 15 and 44% of patients with ascites succumbing in 1 and 5 years, respectively. Patients with cirrhosis need referral for liver transplantation after development of ascites. Proper history and physical examination are important in diagnosing the cause of ascites. Diagnostic paracentesis and abdominal sonogram should be performed during initial evaluation. Low salt diet and diuretic are the initial treatment option, and large volume paracentesis is an option for non-responder to diuretics. Transjugular intrahepatic portosystemic stent-shunt (TIPS) is highly valuable in properly selected patients.

Keywords: ascites, pathogenesis, diagnosis, diuretics, paracentesis, TIPS

1. Introduction

Ascites is defined as the pathological accumulation of excess fluid in the peritoneal cavity. Normally, the peritoneal cavity contains 25–50 mL of ascitic fluid, which allows for the movement of bowel loops past one other and helps hydrate serosal surfaces. With ascites, this fluid is not static within the peritoneal cavity, but is rather in a continuous exchange with the circulation through a large capillary bed under the visceral peritoneum, with about half the volume entering and leaving the peritoneal cavity every hour. Furthermore, the constituents of the fluid are in dynamic equilibrium with those of the plasma. However, the daily absorption of fluid from the peritoneal cavity back to the circulation is limited, and the maximum absorption of fluid out of the peritoneum is approximately 850 mL/d. Thus, the development of clinically significant ascites occurs when the rate of ascites formation exceeds the rate of

ascites reabsorption. For easily-controllable ascites, on the other hand, the volume of fluid that spills into the peritoneal cavity can be reduced below this absorption threshold. This is the case at the early stages of hepatic decompensating when ascites is responsive to a reduced intake of dietary sodium and to moderate doses of diuretics.

Cirrhosis is the most common cause of ascites, representing 85% of all cases of ascites [1]. In patients with cirrhosis, ascites due to portal hypertension (PHT) is primarily related to an inability to excrete adequate amounts of sodium into urine, leading to a positive sodium balance. Other causes of ascites include malignancy, heart failure, tuberculosis, alcoholic hepatitis, Budd-Chiari syndrome, and nephrogenic ascites [2]. More than one cause may be responsible for the development of ascites (multifactorial), such as the development of tuberculosis, heart failure, or peritoneal carcinomatosis in patients with cirrhosis and ascites [1]. Ascites is the most common complication of cirrhosis, as approximately 50% of patients with "compensated" cirrhosis develop ascites during 10 years of follow up [3]. The development of ascites is a poor prognostic event in the natural history of cirrhosis, with approximately 15% of patients succumbing in 1 year and 44% succumbing in 5 years [4]. Thus, these patients need to be referred for liver transplantation. Patients with cirrhosis and ascites are at high risk for other complications, including refractory ascites, spontaneous bacterial peritonitis (SBP), hyponatremia, or hepatorenal syndrome (HRS). The absence of these ascites-related complications qualifies ascites as uncomplicated [5]. Poor prognostic factors in patients with cirrhosis include hyponatremia, low arterial pressure, increased serum creatinine, and low urine sodium [6]. Among these factors, only serum creatinine is included in the Model for End-stage Liver Disease (MELD score) used for patient allocation for liver transplantation. Furthermore, serum creatinine has limitations in estimating glomerular filtration rate in cirrhosis [7], which usually underestimates the mortality risk in patients with ascites [8].

2. Pathogenesis of ascites in patients with liver cirrhosis

2.1. Pathogenesis and perpetuation of the ascites syndrome

Major factors involved in the complex pathogenesis of ascites are portal and sinusoidal hypertension, arterial vasodilatation, and neurohumoral activation, all leading to sodium and water retention [10, 11].

The pathogenesis of ascites is complex and not fully understood. The triad of portal hypertension, arterial vasodilatation, and neurohumoral activation, leading to sodium and water retention, explains, to large extent, the formation of ascites [9]. In fact, the direct cause of ascites formation in patients with cirrhosis is sodium retention, caused by decreased renal sodium excretion. The impairment in the renal ability to excrete sodium is considered the earliest manifestation of renal dysfunction in cirrhosis as shown by reduced natriuretic response to acute administration of sodium chloride [10]. Sodium retention in cirrhosis is mainly due to an increased tubular sodium reabsorption rather than decreased filtration of sodium. However, in the late stage of the disease, when hepatorenal syndrome develops,

sodium retention is caused by both increased reabsorption and decreased filtration. Sodium retention progresses with the advancement of liver disease; in the late stages of the disease, sodium retention becomes very high and the urinary sodium excretion may approach to zero. Sodium retention precedes the onset of ascites by few days, indicating that it is a cause and not a consequence of the accumulation of fluid within the abdominal cavity [10].

Portal hypertension (PHT) plays a major role in the development of ascites in patients with liver cirrhosis. The increased sinusoidal hydrostatic pressure and splanchnic capillary pressure are essential, and ascites usually develops in patients with a hepatic venous pressure gradient greater than 12 mmHg [11]. Patients with liver cirrhosis without portal hypertension do not develop ascites. In addition, lowering portal pressure in patients with cirrhosis and portal hypertension after surgical or radiological portosystemic shunts usually leads to better control of ascites. Sinusoidal or post sinusoidal portal hypertension is required for the development of ascites. On the other hand, presinusoidal hypertension alone, such as portal vein thrombosis (PVT), usually does not cause ascites unless associated with another contributing factor.

Additionally, portal hypertension results in increased level of vasodilator substances, e.g., nitric oxide (NO). This causes splanchnic and peripheral vasodilation and decreased effective blood volume leading to decreased renal blood flow and, subsequently, activation of the renin-angiotensin-aldosterone system (RAAS), sympathetic overactivity, and non-osmotic release of vasopressin [6, 12]. Renin is secreted from the renal juxtaglomerular apparatus secondary to changes in blood volume, changes in serum sodium, and increased activity of the sympathetic nervous system. In turn, renin will convert angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting enzymes (ACE) in the lungs. Angiotensin II stimulates the release of aldosterone from the zona glomerulosa of the adrenal cortex [12]. Aldosterone stimulates sodium reabsorption in the distal tubule. Similarly, the renal sympathetic nervous activity stimulates sodium reabsorption in the proximal tubule, loop of Henle, and distal and collecting tubules. In patients with cirrhosis and portal hypertension, both the secondary hyperaldosteronism and the increased activity of the renal sympathetic nervous system play an important role in the pathogenesis of sodium retention. This excess sodium retention and the associated hypervolemia causing increased hydrostatic pressure will lead to excess transudation from both the hepatic sinusoids and the splanchnic capillaries, exceeding the re-absorptive capacity of the peritoneal surface and lymphatic system, which results in the development of ascites. Indeed, the formation of ascites depends on the balance between the hepatic sinusoidal and splanchnic filtration on the one hand and the lymph drainage on the other hand. Contrary to earlier theories, decreased plasma oncotic pressure has no role in the formation of ascites, and low plasma albumin level has little effect on the rate of ascites formation [13].

Furthermore, three theories of ascites formation have been proposed: underfilling, overflow, and peripheral arterial vasodilation (**Table 1**). The underfilling theory suggests that portal hypertension leads to increased filtration of fluid from the hepatic sinusoids and the splanchnic capillaries, leading to decreased effective circulating blood volume. This activates the plasma renin, angiotensin, aldosterone, and sympathetic nervous system, resulting in renal

1	Under filling theory: increased filtration of fluid from the hepatic sinusoids and the splanchnic capillaries, leading to decreased effective circulating blood volume
2	Overflow theory: increased renal reabsorption of sodium unrelated to decreased blood volume
3	Peripheral arterial vasodilation: portal hypertension leads to vasodilation, which causes decreased effective arterial blood volume and hyperdynamic circulation
4	Renal resistance to atrial natriuretic peptide

Table 1. Pathogenesis of ascites.

sodium and water retention. The overflow theory suggests that the primary abnormality is increased renal reabsorption of sodium unrelated to decreased blood volume. Several hypotheses that aim to explain this abnormality have been suggested including decreased hepatic synthesis of a natriuretic agent, decreased hepatic clearance of sodium retaining agent, or a primary hepatorenal reflex of unknown etiology. This overflow theory was supported by the observation that patients with cirrhosis have intravascular hypervolemia rather than hypovolemia, and sodium retention precedes ascites formation [14]. Nevertheless, both the underfill and overflow theories do not fully explain the formation of ascites and lack strong, supporting evidence. Finally, the arterial vasodilation hypothesis includes components of both the underfill and overflow theories. It suggests that portal hypertension leads to vasodilation, which causes decreased effective arterial blood volume and hyperdynamic circulation. This in turn activates neurohumoral systems leading to sodium retention and expansion of plasma volume, causing overflow of fluid into the peritoneal cavity. The theory also states that ascites formation is caused initially by underfilling of the intravascular compartment and is maintained by expansion of the intravascular compartment [12]. Moreover, the forward theory of ascites formation is a new modification of the vasodilation theory combining arterial underfilling with a forward increase in splanchnic capillary pressure and filtration with increased lymph formation [15].

Nitric oxide (NO) is the main vasodilator implicated in the systemic vasodilatation, and is primarily synthesized in the systemic vascular endothelium by NO synthase [16, 17]. Patients with portal hypertension have evidence of increased NO synthesis [18]. Calcitonin gene-related peptide (CGRP) and adrenomedullin are also potent vasodilatating factors, which have been found in increased levels especially in patients with ascites and hepatorenal syndrome (HRS) [18]. There is also evidence of increased resistance to vasoconstrictive substances, such as noradrenaline, angiotensin II, and vasopressin, which are most likely related to changes in receptor affinity, down-regulation of receptors, and to post-receptor defects related to increased NO expression [19]. Furthermore, alterations in vascular compliance is considered [20, 21], evidence show that it precedes neurohumoral activation and renal sodium and water retention [18].

Another mechanism that may contribute to ascites formation is renal resistance to atrial natriuretic peptide (ANP). ANP is a potent natriuretic peptide released from the cardiac atria in response to expansion of the intravascular volume. In compensated cirrhosis, ANP helps to maintain sodium balance by antagonizing the effect of antinatriuretic factors (aldosterone

and sympathetic overactivity). In later stages, renal resistance to ANP develops and leads to sodium retention [22].

The severity of renal sodium retention parallels the progression of cirrhosis due to the accentuation of the underlying vascular hemodynamic abnormalities and the associated activation of neurohumoral vasoactive mechanisms leading to avid renal reabsorption of sodium and water in the advanced stage of cirrhosis [15]. Furthermore, with progression of cirrhosis, renal perfusion and glomerular filtration rate progressively decline, leading to increased sodium reabsorption at the proximal convoluted tubule and decrease in its delivery to distal segments of the nephron [15]. Thus, in late stages of cirrhosis, renal sodium reabsorption mainly occurs proximal to the site of action of both the spironolactone and the loop diuretics rendering them ineffective. In addition, the increased resistance to vasoconstrictive substances, such as noradrenaline, angiotensin II, and vasopressin, accentuate the relative underfilling of the effective arterial blood volume, which aggravates the hypovolemic effects of diuretics, precluding the continuation of effective dosages of diuretics [23]. Accordingly, refractoriness to diuretic treatment is the end result of the accentuation of the hemodynamic abnormalities characterizing advanced cirrhosis. With further progression of liver disease and increased accentuation of these renal and vascular changes, these same mechanisms lead to hyponatremia and hepatorenal syndrome.

3. Evaluation of patients with ascites

The diagnosis of ascites is suspected based on the patient history and physical examination, and usually confirmed by abdominal ultrasound. The cause of ascites is identified based on the history, physical examination, laboratory tests, abdominal imaging, and ascitic fluid analysis. Patients with ascites usually present with abdominal distention, which may also be associated with abdominal discomfort, early satiety, weight gain, and shortness of breath. In addition, patients usually have symptoms and signs of the underlying cause of ascites. Since cirrhosis is the most common cause of ascites [1], history and physical examination should be directed for symptoms and signs of cirrhosis as well as risk factors for development of cirrhosis. Patients with cirrhosis may have other symptoms associated with hepatic decompensation, such as hepatic encephalopathy jaundice or gastrointestinal bleeding. Physical examination of patients with ascites due to liver cirrhosis usually reveals spider angioma, palmar erythema, jaundice, muscle wasting, gynecomastia, leukonychia, parotid enlargement, and abdominal wall collaterals. The liver and spleen may be palpable. Patients also need to be investigated for risk factors for cirrhosis including alcohol, viral hepatitis B and C, autoimmune liver disease, and other causes of cirrhosis. Those who lack an apparent cause for cirrhosis should also be questioned about lifetime body weight and diabetes as nonalcoholic steatohepatitis has been identified to be the cause of cirrhosis in many of these patients [24].

In addition to the clinical evaluation for cirrhosis, patients with ascites need to be evaluated for other causes including alcoholic hepatitis, heart failure, malignancy (peritoneal carcinomatosis, massive liver metastases, etc.), pancreatitis, nephrotic syndrome, tuberculous peritonitis,

acute liver failure, Budd-Chiari syndrome, and sinusoidal obstruction syndrome. Patients with malignant ascites may have symptoms related to the underlying malignancy, such as weight loss, whereas patients with ascites due to heart failure may have dyspnea, orthopnea, congested neck veins, and lower limb edema. Approximately 5% of ascites patients have 2 or more causes of ascites formation, i.e., "multifactorial" ascites. Most commonly, this presents as cirrhosis with another etiology as peritoneal tuberculosis. Laboratory test abnormalities seen in patients with ascites are related to the underlying cause of the ascites. Laboratory test abnormalities seen in patients with ascites are related to the underlying cause of the ascites. Patients with cirrhosis or heart failure usually have abnormal liver tests, increased serum bilirubin, hypoalbuminemia, elevated international normalized ratio (INR) in addition to thrombocytopenia, anemia, and leukopenia. Patients suspected of having ascites should have abdominal ultrasound to confirm the presence of ascites and to look for possible causes such as cirrhosis or malignancy. Ultrasound is probably the most cost-effective imaging modality. In patients with cirrhosis, ultrasound may reveal evidence of liver cirrhosis and portal hypertension including dilation of the portal vein to ≥13 mm, dilation of the splenic vein to ≥11 mm, reduction in portal venous blood flow velocity, splenomegaly (diameter >12 cm), and recanalization of the umbilical vein. Furthermore, ultrasound may also reveal evidence of hepatocellular carcinoma (HCC), which can be further evaluated with CT or magnetic MRI. Cardiac evaluation and echocardiography may also be needed to differentiate between cardiac ascites and cirrhotic ascites. Ascites due to cardiomyopathy can mimic that due to alcoholic cirrhosis. Pulmonary hypertension can also lead to heart failure and ascites. Jugular venous distension is present in the patients with cardiac ascites, but not in the ascites due to cirrhosis. Measuring the blood level of brain natriuretic peptide or pro-brain natriuretic peptide can help differentiating ascites due to heart failure (level usually about 6100 pg/ml) from ascites due to cirrhosis (166 pg/ml) [25].

4. Diagnostic paracentesis

Once the presence of ascites is confirmed, diagnostic paracentesis should be done to identify the cause of ascites and to rule out infection of the ascitic fluid. Abdominal paracentesis is indicated for all patients with new onset ascites [26]. Abdominal paracentesis is a safe procedure, and minor complications are rarely reported. The most common complication is abdominal wall hematomas, occurring in less than 1% of patients despite having abnormal prothrombin time in majority of cases [27]. This indicates that giving blood products such as platelets and fresh-frozen plasma before paracenteses is not needed [27, 28]. Routine tests of coagulation do not reflect bleeding risk in patients with cirrhosis; these patients usually have normal global coagulation because of a balanced deficiency of procoagulants and anticoagulants. Although more serious complications (hemoperitoneum or bowel entry by the paracenteses needle) may occur [28], they are rare (<1/1000 paracenteses) and should not deter the performance of this procedure. Bleeding complications occur mainly in patients with cirrhosis who have impaired renal function tests due to the associated platelet dysfunction in these patients [29]. Coagulopathy should preclude paracentesis only when there is clinically evident hyperfibrinolysis or clinically evident disseminated intravascular coagulation. A shortened euglobulin clot lysis time (<120 minutes) documents hyperfibrinolysis [30]. Epsilon aminocaproic acid

can be used to treat hyperfibrinolysis, and paracentesis can be performed after the lysis time has normalized on treatment [31].

5. Evaluation of ascitic fluid

The basic tests ordered on ascitic fluid samples include an analysis of the appearance, serum-to-ascites albumin gradient (SAAG), cell count and differential, culture, and total protein [26]. Fluid appearance can range from water-clear to frankly purulent, bloody, or chylous. The ascitic fluid cell count with the differential is the most important test performed on ascitic fluid to rule out infection since ascitic fluid infection is a treatable cause of deterioration as well as a preventable cause of death in patients with cirrhosis and ascites. Early diagnosis and proper treatment of ascitic fluid infection are crucial in patients with cirrhosis and ascites. Antibiotic treatment should be initiated in patients with a neutrophil count of ≥250/mm [32].

Culture of the ascitic fluid should be done in patients with new onset ascites, patients admitted to the hospital for ascites, in patients who develop fever or abdominal pain, and also in patients with cirrhosis who develop unexplained deterioration: increasing jaundice, azotemia, acidosis, or encephalopathy [32]. To increase the sensitivity of detecting bacterial growth in ascitic fluid, the ascitic fluid should be inoculated into blood culture bottles at the bedside; ascitic fluid culture is positive in only 50% of patients with spontaneous bacterial peritonitis (SBP) by older methods, compared to approximately 80%, if the fluid is inoculated into blood culture bottles at the bedside and prior to administration of antibiotics [33, 34]. A single dose of an effective antibiotic usually leads to a negative bacterial culture [35].

Initially, ascitic fluid was classified as an exudate or transudate based on total protein concentration. Recently, this exudate/transudate classification has been replaced by the SAAG, which is a more useful measure for determining the presence or absence of portal hypertension [1, 36]. However, the ascitic fluid total protein concentration remains of some value as patients with an ascitic fluid protein of <1 g/dL have a high risk of SBP requiring prophylactic antibiotics [37]. The SAAG is easily calculated by subtracting the ascitic fluid albumin value from the serum albumin value, which should be obtained the same day. The SAAG accurately identifies the presence of portal hypertension; SAAG ≥1.1 g/dL (≥11 g/L) predicts that the patient has portal hypertension with 97% accuracy, while SAAG <1.1 g/dL (<11 g/L) indicates that the patient does not have portal hypertension [1].

While SAAG in patients with ascites due to heart failure can be affected with diuretics, the SAAG in the setting of cirrhosis remains stable unless portal pressure decreases significantly [38]. If the results of these tests are abnormal, further testing can be performed on another ascitic fluid sample. These additional ascitic fluid tests are requested based on the clinical scenario. The following is a list of tests that can be conducted to test for ascites.

- Glucose concentration: White blood cells, bacteria, and malignant cells consume glucose; thus, the concentration of glucose may be low in peritoneal carcinomatosis and bowel perforation [35, 39].

- Lactate dehydrogenase (LDH) concentration: The ascitic fluid/serum (AF/S) ratio of LDH is about 0.4 in cirrhotic ascites without infection. In SBP, the ascitic fluid LDH level rises such that the ascitic fluid/serum (AF/S) ratio of LDH approaches 1.0. In the case of bowel perforation, or peritoneal carcinomatosis, the ascitic fluid/serum (AF/S) ratio of LDH is greater than 1.0 [40].

- Gram stain: The sensitivity of ascitic fluid gram stain is only 10%. The main benefit of gram stain of ascitic fluid is to differentiate between SBP and bowel perforation where there is polymicrobial growth in bowel perforation and monomicrobial growth in SBP [41].

- Amylase concentration: The ascitic fluid amylase concentration is increased in pancreatitis or bowel perforation reaching approximately 2000 unit/L [42].

- Tests for tuberculous peritonitis: A variety of tests have been used for the detection of tuberculous peritonitis including direct smear, culture, cell count with predominance of mononuclear cells, and adenosine deaminase. Only patients at high risk for tuberculous peritonitis should have testing for mycobacteria on the first ascitic fluid specimen. The sensitivity of smear of ascitic fluid for mycobacteria is almost zero [43], while the sensitivity of fluid culture for mycobacteria reaches 50% [44]. Polymerase chain reaction testing for mycobacteria, laparoscopy with biopsy, and mycobacterial culture of tubercles are the most rapid and accurate methods of diagnosing tuberculous peritonitis [45].

- Cytology: It should be requested only if malignant ascites is suspected. The sensitivity of ascitic fluid cytology in peritoneal carcinomatosis is approximately 100% [46]. However, because not all cases of malignant ascites are associated with peritoneal carcinomatosis, the overall sensitivity of cytology smears for the detection of malignant ascites is 58–75% [47]. Hepatocellular carcinoma (HCC) rarely metastasizes to the peritoneum.

- Triglyceride concentration: Chylous ascites has a triglyceride content greater than 200 mg/dL (2.26 mmol/L) and usually greater than 1000 mg/dL (11.3 mmol/L) [48].

- Bilirubin concentration: Ascitic fluid bilirubin value greater than the serum suggests bowel perforation or biliary leak [49].

6. Treatment of ascites

Proper management depends on the cause of ascites. Patients with high SAAG (portal hypertensive) ascites usually respond to dietary salt restriction and diuretics. Conversely, patients with low SAAG ascites (with the exception of nephrotic ascites) do not respond to dietary salt restriction and diuretics; treatment of ascites in these patients depends on successful treatment of the underlying disorder. Improvement of cirrhosis alone can lead to control of ascites and better response to diuretics. This is particularly true for patients with alcoholic liver disease [50], Hepatitis B virus (HBV)-related liver disease [51], and autoimmune hepatitis, where specific treatment of cause of cirrhosis by ceasing alcohol consumption, HBV antiviral therapy, or immunosuppression can lead to regression of cirrhosis and better control of ascites.

The approach for the treatment of ascites depends on the grade of ascites. According to the International Ascites Club, ascites is classified into three grades according to the severity of ascites [5].

Grade 1—Mild ascites detectable only by ultrasound examination.

Grade 2—Moderate ascites with moderate abdominal distension.

Grade 3—Marked ascites with marked abdominal distension.

Currently, there are no recommendations for the treatment of grade 1 ascites. Grade 2 ascites can be treated with dietary sodium restriction and diuretics. Grade 3 ascites can be treated with initial large volume paracentesis followed by dietary sodium restriction and diuretics [52].

7. First-line therapy for ascites

7.1. Dietary sodium restriction

The first-line treatment of patients with cirrhosis and ascites is dietary sodium restriction (2000 mg per day [88 mmol per day]) [53]. This is generally equivalent to a no added salt diet, and avoiding pre-prepared meals. More strict sodium restriction may improve mobilization of ascites, although it is not recommended because it is less palatable and may worsen the already existing malnutrition in patients with cirrhosis. Total non-urinary sodium excretion is less than 10 mmol per day in afebrile patients with cirrhosis without diarrhea [54]. Based on that, ascites can be controlled if urinary excretion of sodium exceeds 78 mmol per day (88 mmol intake per day − 10 mmol nonurinary excretion per day) in patients on restricted sodium diet. However, only 10–15% of patients have urinary excretion of sodium greater than 78 mmol per day and only those patients can be considered for dietary sodium restriction alone. Measurement of urinary sodium excretion is a helpful parameter to assess compliance with dietary sodium restriction. Patients with urinary excretion of sodium greater than 78 mmol per day without improvement of ascites are not compliant with salt restriction. Urinary sodium excretion can be measured by random urinary sodium concentrations, 24-hour urinary sodium or urine sodium/potassium ratio.

7.2. Diuretics

Renal sodium retention in the setting of liver cirrhosis and ascites is due to increased proximal and distal tubular reabsorption of sodium [55, 56]. The mechanism of increased proximal tubular reabsorption of sodium is not completely understood, while the increased sodium reabsorption in the distal tubule is due to hyperaldosteronism [55]. In patients with liver cirrhosis, secondary hyperaldosteronism is a major factor promoting renal sodium retention in the distal tubules and collecting ducts of the nephron. Clinical trials have shown that spironolactone is the drug of choice for the initial treatment of ascites. Spironolactone achieves a better natriuresis than "loop" diuretics in cirrhotic patients with ascites [56]. Although spironolactone

is effective for mobilization of ascites, most patients will eventually require both diuretics. Furthermore, starting with both drugs is more effective in achieving rapid mobilization of ascites and maintaining normokalemia [57, 58].

The initial doses of both diuretics are 100 mg/d for spironolactone and 40 mg/d for furosemide. If inadequate, the dose can be increased every 3–5 days to a maximum dose of 400 mg aldactone and 160 mg of furosemide [53]. The target of diuretic therapy is to achieve 0.5 kg/day weight loss in patients without peripheral edema and up to 1 kg/day in patients with peripheral edema while monitoring renal function and sodium [59]. Furosemide can be temporarily withheld in patients presenting with hypokalemia; this is very common in the setting of alcoholic hepatitis. Patients with parenchymal renal disease or post liver transplantation may tolerate less spironolactone than usual because of hyperkalemia. Single morning dosing maximizes compliance. Dosing more than once daily reduces compliance and can cause nocturia. The use of diuretics may be associated with several complications such as renal failure, electrolyte disorders, muscle cramps, and hepatic encephalopathy [30, 31, 55–57, 59–63].

Gynecomastia is the main side effect of spironolactone, but metabolic acidosis with or without hyperkalemia may also occur in patients with renal impairment. Other side effects of furosemide include potassium depletion, metabolic hypochloremic alkalosis, and hyponatremia, as well as hypovolemia, leading to renal dysfunction. The use of intravenous furosemide is not recommended, as it may cause an acute reduction in renal perfusion and subsequent azotemia in patients with cirrhosis and ascites. Amiloride (10–40 mg per day) is another aldosterone antagonist and can replace spironolactone in patients with tender gynecomastia. However, amiloride is more expensive and has been shown to be less effective than spironolactone [61]. Triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites [64].

Hydrochlorothiazide can also cause rapid development of hyponatremia when added to the combination of spironolactone and furosemide; it should be used with extreme caution or avoided entirely.

While patients are on diuretics, monitoring of body weight, blood pressure, orthostatic symptoms, and serum electrolytes, urea, and creatinine levels needs to be checked regularly. If weight loss is inadequate, assessment of urinary sodium excretion needs to be done by urine sodium/potassium ratio or by 24-hour urine sodium. Patients who are excreting urine sodium/potassium greater than 1- or 24-hour urine sodium greater than 78 mmol per day and not losing weight are not compliant with dietary sodium restriction. These patients should not be labeled as diuretic-resistant that require second-line therapy. On the other hand, in patients who are not losing weight and their urinary sodium excretion is less than 1- or 24-hour urine sodium less than 78 mmol per day, the dose of diuretic needs to be increased gradually [26]. Following mobilization of ascites, diuretics should be reduced to maintain patients with minimal or no ascites to avoid diuretic-induced complications.

In patients with ascites and lower limb edema, there is no limit for daily weight loss due to the use of diuretics because there is no limit for mobilization of fluid from the interstitial fluid to the vascular compartment [65]. However, in patients with ascites and no lower limb edema, daily weight loss of 0.5 kg is a reasonable daily maximum as this is likely the maximum daily

mobilized fluid from ascites to the vascular compartment. Diuretics should be stopped if the patient has hepatic encephalopathy, rising serum creatinine (>2.0 mg/dl) while on diuretics or if there is hyponatremia (<120 mmol/L) not corrected with fluid restriction [26].

Dietary sodium restriction and a dual diuretic regimen with spironolactone and furosemide have been shown to be effective in more than 90% of patients in achieving a reduction in the volume of ascites to acceptable levels [58]. Less than 10% of patients with cirrhosis and ascites are refractory to standard medical therapy [30, 56–58, 66, 67].

Patients with liver cirrhosis are in a state of systemic and splanchnic vasodilatation caused by nitric oxide and other vasodilators. Blood pressure is maintained in these patients due to the compensatory increased levels of vasopressin, angiotensin, and aldosterone and sympathetic overactivity [68]. The use of drugs, which decrease the level or antagonize the effect of these hormones, is expected to lower blood pressure and affect survival of those patients. These include angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers [69]; these drugs should be avoided in patients with ascites and in the rare situation where the benefit of using these drugs overweighs their risks, and blood pressure and renal function must be monitored carefully to avoid rapid development of renal failure.

Other drugs that should be avoided in patients with ascites are Prostaglandin inhibitors such as nonsteroidal anti-inflammatory drugs. These drugs antagonize the vasodilator effect of prostaglandins on renal artery causing reduction of urinary sodium excretion and can also cause azotemia [70]. Only unusual patients whose risk of an ischemic cardiac or neurologic event exceeds the risk of worsening azotemia or gut bleeding should take low dose aspirin.

7.3. Single large volume paracentesis (LVP)

Large volume paracentesis is associated with circulatory dysfunction called post paracentesis circulatory dysfunction (PPCD). It leads to complication in patients with liver cirrhosis including rapid accumulation of ascites [71–74], development of HRS and/or water retention leading to dilutional hyponatremia [72], further increase of portal pressure [75], and shortened survival [73]. The most effective method to preventing circulatory dysfunction after LVP is the administration of albumin [73]. Large volumes of fluid have been safely removed with the concomitant administration of intravenous albumin (6–8 g/L of fluid removed) [76]. However, single 5-L paracentesis can be performed safely without albumin infusion [77]. LVP with albumin is the best treatment option in patients with grade 3 ascites; it is more effective and safer than diuretics as it is associated with less hyponatremia, renal impairment, and hepatic encephalopathy. There were no differences between the two approaches with respect to hospital readmission or survival [71–73, 78–81]. LVP is a safe procedure, and the risk of local complications, such as hemorrhage or bowel perforation, is extremely low [29].

Additionally, although paracentesis removes the fluid more rapidly than does careful diuresis, paracentesis does nothing to correct the underlying problem that led to the initial ascites formation, i.e., sodium retention, and it should not be viewed as first-line therapy for all patients with ascites. Dietary sodium restriction and diuretics should follow paracentesis to prevent or decrease fluid re-accumulation.

8. Refractory ascites

Refractory ascites is defined as ascites that is unresponsive to a sodium-restricted diet and high doses of diuretics or recurs rapidly after therapeutic paracentesis [82]. Refractory ascites is classified as diuretic-resistant ascites when there is poor control of ascites as well as low urinary sodium excretion (<78 mmol/d), despite maximal diuretics or diuretic intractable ascites, where the use of high-dose diuretics is not applicable due to development of clinically significant complications of diuretics [5]. Once the patient is considered diuretic-resistant, diuretics should be discontinued and these patients will need second-line therapy. The European guideline recommends discontinuing diuretics if the urine sodium is <30 mmol/day during diuretic therapy. Oral midodrine 7.5 mg three times daily has been shown to increase urine volume, urine sodium, mean arterial pressure, and survival in patients with refractory ascites. Midodrine can be added to diuretics to increase blood pressure and theoretically convert diuretic-resistant patients back to diuretic-sensitive [83]. Once ascites becomes refractory to medical treatment, the median survival of patients is approximately 6 months [82, 84–86].

Hence, patients with refractory ascites should be considered for liver transplantation. The MELD score system which predicts survival in patients with cirrhosis [87, 88] does not include low arterial pressure, low serum sodium, low urine sodium, or Child-Turcotte-Pugh (CTP) score, all of which are important prognostic factors [84–88]. Consequently, patients with refractory ascites may have a poor prognosis despite a relatively low MELD score (e.g., <18). For these reasons, inclusion of additional parameters in the MELD score, such as serum sodium, is suggested [88–90].

9. Second-line therapy for ascites

Patients with refractory ascites who do not respond to first-line therapy of dietary sodium restriction and diuretics may benefit from second-line therapy. Second-line therapy for ascites includes serial therapeutic paracenteses, transjugular intrahepatic portosystemic stent-shunt (TIPS), peritoneovenous shunt (PVS), and liver transplantation.

9.1. Serial therapeutic paracenteses

Serial paracenteses is a safe option for patients with refractory ascites. Large volume paracenteses up to total paracenteses can be done on regular basis or in demand. Diuretics can be stopped in these patients, especially if urine sodium is still <30 mmol/day, but dietary sodium restriction should be maintained to decrease the rate of fluid accumulation. The frequency of paracenteses depends on the patient's compliance with the low-sodium diet. Patients who need more frequent taping than 10 L every 2 weeks are not compliant with diet. Paracentesis of large volume of ascitic fluid is associated with changes in electrolytes, plasma renin, aldosterone, and angiotensin levels and may also develop acute rise of serum creatinine [72–74]. An albumin infusion of 6–8 g/L of fluid removed given during paracenteses, or shortly after, abolishes these hormonal changes and appears to improve survival [73]. Up to 5 L of ascites can be taped safely without the need for albumin infusion [77]. An alternative approach with

similar efficacy to albumin infusion is intravenous terlipressin (1 mg at onset of paracentesis, 1 mg at 8 hours, and 1 mg at 16 hours) as well as midodrine orally (for 72 hours after paracentesis) [83, 91].

9.2. Transjugular intrahepatic portosystemic stent-shunt (TIPS)

TIPS is a side-to-side portosystemic shunt created between the portal vein and the hepatic vein via intrahepatic self expandable stent [92–96]. TIPS can achieve portal decompression, and therefore prevention of complications of portal hypertension such as variceal bleeding, ascites, and hydrothorax. Additionally, TIPS increases glomerular filtration and urine output, promotes natriuresis, and reduces the plasma renin activity, aldosterone, and noradrenaline levels causing improvement of renal dysfunction related to the circulatory and hormonal changes in cirrhotic patients [97–99]. The main indication for TIPS is refractory ascites, uncontrolled acute variceal bleeding, and secondary prevention of gastric variceal bleed. It may have a role in hydrothorax, hepatorenal, and hepatopulmonary syndrome [100].

Early studies comparing TIPS with large volume paracentesis were disappointing. Despite better control of ascites in patients undergoing TIPS, there was no survival advantage in TIPS in addition to increased morbidity due to hepatic encephalopathy and deterioration of liver function [94]. This can be explained by poor patient selection in early experience with TIPS. However, in the meantime, better selection of patients for TIPS together with the use of polytetrafluorethylene (PFTE)-covered stents resulted in high response rate comparable with surgical shunts. The good results of TIPS obviate the need for surgical shunt [101, 102]. Recent studies had shown that TIPS is not only more effective in control of ascites than repeated large volume paracentesis but also improves survival [92, 93, 95, 96].

The main complication of TIPS is the development of hepatic encephalopathy which is more reported with TIPS than with repeated large volume paracentesis [103–107]. Other complications include shunt thrombosis and stenosis. Uncovered stents are complicated by stenosis in up to approximately 80% of cases [11, 108]. TIPS usually converts diuretic-resistant patients into diuretic-sensitive patients, therefore diuretics and dietary salt restriction must be started in these patients to maintain control of ascites. Absolute and relative contraindication to TIPS insertion includes congestive heart failure, severe pulmonary hypertension, severe hepatic decompensation, recurrent portosystemic encephalopathy, polycystic liver disease, hepatic abscess, and hepatocellular carcinoma [100].

10. Third-line therapy for ascites

10.1. Peritoneovenous shunts

The peritoneovenous shunt (PVS) has been widely used as a suitable alternative to repeated large volume paracentesis in patients with refractory ascites [109]. The negative pressure in the chest allows fluid to move from the high-pressure intraperitonium to the chest through the one-way valve tube through subcutaneous tissue of the chest wall to the internal jugular vein to the superior vena cava. Among the various complications associated with PVS, the

most common one is the obstruction of the prosthesis, which occurs in 40–60% of patients during first year of follow-up [110]. This procedure has a very limited use due to high complication rate, low long-term patency rate without survival advantage [58, 111]. However, it can be used in patients with refractory ascites who are not candidate for TIPS or liver transplant or for serial paracenteses because of multiple abdominal scars or distance from a physician willing and capable of performing paracenteses (**Table 2**).
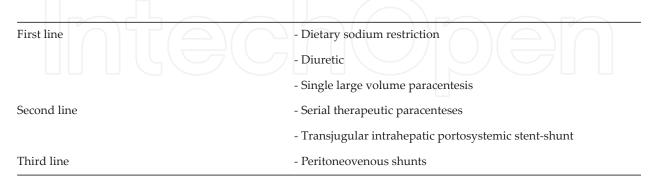
First line	- Dietary sodium restriction
	- Diuretic
	- Single large volume paracentesis
Second line	- Serial therapeutic paracenteses
	- Transjugular intrahepatic portosystemic stent-shunt
Third line	- Peritoneovenous shunts

Table 2. Treatment of ascites.

11. Conclusion

Liver cirrhosis is the main cause of ascites; ascites in the setting of liver cirrhosis is caused by portal hypertension that leads to vasodilation, with decreased effective arterial blood volume and hyperdynamic circulation. SAAG and ascitic fluid cell count are an important diagnostic tools.

The first-line therapy is low salt diet and diuretics, which is effective in nearly 90% of patients, LVP with albumin is the best treatment option in patients with intractable ascites, and TIPS can be used in selected patients with good results. Surgical shunt for ascites is almost obsolete.

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