Chapter 6

Pharmacological Therapy of Ascites

Aziza Ajlan, Waleed K. Al-hamoudi and Hussein Elsiesy

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Abstract

Ascites refer to accumulation of fluids in the peritoneal cavity. Ascites is caused by multiple causes, among which liver cirrhosis is the commonest. Confirming the etiology is the first and most important step toward proper management. Assuming that ascites is always caused by cirrhosis can lead to unnecessarily sending patients with different etiologies for liver transplantation, particularly patients with non-cirrhotic portal hypertension. Calculating serum albumin ascitic gradient is important in differentiating ascites due to portal hypertension from other etiologies. The first-line therapy for ascites in cirrhosis is low salt diet and diuretics. It is important to avoid nonsteroidal anti-inflammatory drugs (NSAIDs) and nephrotoxic medications in these patients.

Keywords: ascites, treatment, pharmacological therapy, liver cirrhosis

1. Introduction

Even though liver disease remains the main cause of ascites, there are several other causes including renal diseases, infections (tuberculosis), malignancies, and heart disease (**Table 1**).

It is important to diagnose the etiology of ascites in order to properly treat it.

Detailed history, physical examination, laboratory blood test, abdominal ultrasound, and serum albumin ascitic gradient are important in narrowing the differential diagnosis of ascites.

Cirrhosis is the eighth leading cause of death in the United States [1]. Ascites is one of the most common complications of cirrhosis that leads to hospital admissions [2]. It occurs due

High SAAG ascites (>1.1)	Low SAAG ascites (<1.1)
Liver cirrhosis	Tuberculosis
Budd-Chiari syndrome	Malignancy
Sinusoidal obstructive syndrome	Pancreatic
Heart failure (high protein)	Renal
Alcoholic hepatitis	Serositis
Acute liver failure	

Table 1. Causes of ascites.

to portal hypertension and is primarily related to an inability to excrete an adequate amount of sodium into urine, leading to positive sodium balance leading to fluid retention [3]. Many patients are referred for liver transplantation after development of ascites. Evidence suggests that arterial splanchnic vasodilation leads to renal sodium and water retention in patients with cirrhosis. This permits dropping in effective arterial blood capacity with stimulation of arterial as well as cardiopulmonary volume receptors, in addition to homeostatic stimulation of vasoconstrictor and sodium-retaining systems (i.e., the RAAS (renin-angiotensin-aldosterone system) as well as the sympathetic nervous system). Renal sodium preservation causes extension of the extracellular fluid volume and accumulation of ascites and edema [4, 5]. The occurrence of ascites is directly linked to worse prognosis and compromised life quality; therefore, patients should be turned over to liver transplant center for evaluation [6]. Nearly 75% of the patients with ascites in Western Europe or the United States have cirrhosis as the primary cause. The remaining 25% of the ascites is caused by malignancy, heart failure, tuberculosis, pancreatic disease, or other miscellaneous causes [7].

Determining the cause of ascites is very important for appropriate management. The serum-ascites albumin gradient (SAAG) can be helpful for both diagnostic and therapeutic purposes. Patients with a high SAAG (≥1.1 g/dL) have portal hypertension and usually are responsive to diuretic therapy measures [8].

1.1. First-line treatment

One of the most important steps in treating ascites in this setting is to treat the underlying liver disease. In patients with alcoholic liver disease, abstinence from alcohol intake can result in dramatic improvement in the reversible component of alcoholic liver disease. This measure alone can lead to an around 75% 3-year survival. If the patient does not succeed in refraining from alcohol intake, they may die within 3 years [9]. Abstinence from alcohol intake alone may lead to either complete resolution of ascites or at least a better response to medical therapy.

Ascites in decompensated hepatitis B virus infection-related cirrhosis and autoimmune hepatitis can also have a great response to specific drug therapy, although liver disease is unlikely to be revisable by the time ascites is manifested (**Table 2**) [10].

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Treatment of ascites due to liver cirrhosis
1. Treatment of the underlying cause: stop alcohol, treat AIH, and HBV
2. Low-salt diet and diuretics
3. Water restriction if sodium <120 mmol
4. Vaptans (not effective)
5. Albumin and colloid replacement
6. Avoid nephrotoxic medications

Table 2. Treatment of ascites due to liver cirrhosis.

2. Diet and diuretics

The first-line treatment of patients with cirrhosis and ascites includes (1) dietary sodium restriction (2000 mg/day [88 mmol/day]) and (2) oral diuretics [11]. Evidence suggests that renal sodium retention in these patients is mainly caused by increased proximal as well as distal tubular sodium reabsorption instead of reduction of filtered sodium load [12, 13]. Although the mechanism by which enhanced proximal tubular reabsorption of sodium occurs has not been fully established, the increased reabsorption of sodium along the distal tubule is mainly due to hyperaldosteronism [14]. Therefore, aldosterone antagonists are considered the treatment of choice and are more effective than loop diuretics. Amiloride (with doses of 10–40 mg/day), a diuretic acting in the collecting duct, is less effective than the active metabolite spironolactone and much more expensive and should be used as an alternative only in those patients who develop side effects with aldosterone antagonists (e.g., tender gynecomastia) [15]. There has been a long argument, whether aldosterone should be administered alone or coupled with loop diuretics. Two studies have assessed both approaches. The first used aldosterone antagonists in a stepwise increase every 7 days (up to 400 mg/day) in combination with furosemide (40–160 mg/day, in 40 mg/day steps) considered only in patients not exhibiting proper response to maximum doses of aldosterone antagonists versus joint treatment of aldosterone antagonists and furosemide from the commencement of treatment (100 in addition to 40 mg/day with the option to build the dose in a stepwise manner every 7 days in view of lack of response up to 400 and 160 mg/day) [16, 17]. The results of the two studies were inconsistent with each other probably due to differences in patient populations, in particular, with regard to the percentage of patients with the first episode of ascites [17]. Initiation of both drugs appears to be the favored approach in attaining quick natriuresis and preserving normokalemia. Single morning dosing enhances adherence. Dosing more than once daily decreases adherence and may lead to nocturia.

The maximum doses are 400 mg/day of spironolactone and 160 mg/day of furosemide [8, 11]. Furosemide can be suspended for a short period of time in patients with hypokalemia, which is very common in the setting of alcoholic hepatitis.

Other diuretics including triamterene, metolazone, and hydrochlorothiazide have also been used to treat ascites [11].

Eplerenone is a newer aldosterone antagonist that has been used in heart failure [18]. There is only one study evaluating the use of eplerenone in ascites with comparable results to aldactone [19]. It could also serve as substitute of spironolactone in patients who develop tender gynecomastia [20].

Other loop diuretics, such as torasemide and bumetanide, are currently not being used as they did not seem to demonstrate superiority to the current agents, let alone their cost.

It's important to mention though, in all patients, diuretic therapy should aim to achieve weight loss of no more than 0.5 kg/day if peripheral edema is absent and 1 kg/day in those with peripheral edema to avoid diuretic-related renal failure and/or hyponatremia which is mainly due to intravascular volume depletion [7]. Other complications of diuretic therapy include hepatic encephalopathy, electrolyte disorders, gynaecomastia, and muscle cramps [13, 21–37]. If cramps are severe, diuretic dose should be decreased or stopped, and albumin infusion [37], baclofen, and L-carnitine may relieve symptoms [23–27, 37].

3. Fluid restriction

Fluid restriction is not necessary in treating most patients with cirrhosis and ascites unless sodium is less than 120. The chronic hyponatremia commonly observed in cirrhotic ascites patients is occasionally fatal if not corrected. One study with 997 cirrhotic patients with ascites showed that the serum sodium is ≤120 mmol/L in 1.2% of the patients and ≤ 125 mmol/L in only 5.7%. Rapidly correcting serum sodium with hypertonic saline in this setting makes the patients prone to more complications rather than the hyponatremia itself.

4. Vaptans

Vaptans are "vasopressin receptor antagonists" and have been studied, mainly in heart failure and in the setting of cirrhosis [38, 39]. Their value in treating hyponatremia and in reducing fluid overload has been investigated. They appear to be useful in treating mild hyponatremia. However, correction of hyponatremia solely may not associate with more important clinical outcomes. The intravenous agent conivaptan has been approved for use for treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients [38]. The manufacturer advises clinician to exercise extra precaution as rapid correction of hyponatremia can have serious/irreversible clinical outcomes, i.e., central pontine myelinolysis. An oral formulation—tolvaptan—increases serum sodium in patients who have baseline values of <130 mmol/L [40]. Of note, correction of sodium is not permanent, and hyponatremia may return when medication is stopped [41].

Recently, satavaptan was particularly investigated to define its effectiveness in managing ascites rather than hyponatremia, was found to be "not clinically beneficial" in the controlling of ascites in cirrhosis, and was linked with higher mortality compared to placebo [42]. It is also more expensive than first-line therapy.

5. Intravenous albumin

An open-label, randomized controlled trial in patients with new onset ascites demonstrates that weekly 25 g infusions of albumin for 1 year followed by infusions every 2 weeks improved survival and decreased the risk of ascite recurrence compared to diuretics alone [43].

In patients who undergo large-volume paracentesis (LVP) > 5 L secondary to refractory ascites, the administration of albumin prevents post-paracentesis circulatory dysfunction (PPCD) [44]. Circulatory homeostasis has detrimental effects in cirrhotic patients as it leads to rapid rebuildup of ascites [45]. Around 20% of these patients develop dilutional hyponatremia secondary to hepatorenal syndrome and/or water retention. The portal pressure usually rises in patients developing circulatory dysfunction after LVP, probably due to a raised intrahepatic resistance due to the action of vasoconstrictor systems on the hepatic vascular bed [46–54]. Finally and most importantly, circulatory dysfunction is usually linked to decreased survival [44, 53].

LVP coupled with albumin infusion is more effective than diuretics and significantly cuts the length of hospital stay. It also has lower frequency of hyponatremia, renal impairment, and hepatic encephalopathy when compared with diuretics. However, there were no differences between the two approaches with respect to hospital readmission or survival [45, 55].

Albumin has shown to be more effective than dextran-70 and polygeline (other plasma expanders) for the stoppage of PPCD [44]. If <5 L of ascites are eliminated, dextran-70 (8 g/L of ascites removed) and polygeline (150 mL/L of ascites removed) show effectiveness comparable to that of albumin. Nevertheless, albumin has higher efficacy than these other plasma expanders if in the case of removal of more than 5 L of ascetic fluid [44]. In spite of that, randomized trials did not show survival advantage in patients treated with albumin versus those treated with other plasma expanders [44, 53, 56]. To demonstrate survival benefit of albumin, larger trials are warranted. Of note, a published meta-analysis included 17 trials involving 1225 patients, demonstrating a lessening in mortality with an odds ratio of death of 0.64 (95% CI, 0.41–0.98) in the albumin group [57, 58]. Albumin was superior to other plasma expanders in which a mean volume of ascetic fluid removed was 5.5–15.9 L [58]. Studies have administered between 5 and 10 g of albumin per liter of fluid removed; 6–8 g/L have been the most frequently used doses [58]. Another study compared albumin doses in 70 patients; the 4 g/L group had comparable PPCD and renal impairment to the 8 g/L group [46, 59].

Albumin is usually infused throughout and/or shortly after the paracentesis. In Europe, only a 20% intravenous solution is available. While in the United States, 5% and 25% intravenous solutions are available, all are isotonic. Using the 5% solution increases the sodium load five times.

6. Drugs to be avoided or used with caution

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be avoided in patients with cirrhosis and ascites even in low doses as they can induce arterial hypotension and renal failure [60, 61]. If used, blood pressure and renal function must be monitored carefully [7].

The administration of nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, ibuprofen, and aspirin, in patients with cirrhosis and ascites is associated with a high risk of development of acute renal failure and hyponatremia and lowers the effect of diuretics [7]. This occurs primarily due to inhibition of renal prostaglandin synthesis leading to deficiency in glomerular filtration rate, which is due to a reduced renal perfusion [62]. Cyclooxygenase-2 (COX-2) inhibitors may provide an alternative for short term as preliminary data show that short-term administration of celecoxib does not impair renal function and does not alter response to diuretics [62].

Beta-blockers have been shown to reduce survival in patients with refractory ascites [63, 64]. This has been linked to their undesirable effect on blood pressure and the increase in the rate of paracentesis-induced circulatory dysfunction [63, 64].

Both blood pressure and renal function should be monitored closely in patients who have refractory ascites with consideration not to initiate or discontinue beta-blockers in such setting.

7. Colloid replacement

Colloid replacement therapy remains as a contentious issue in therapeutic paracentesis. One study compared the use of albumin (10 g/L of fluid removed) versus no albumin in 105 patients with tense ascites, following therapeutic paracentesis [65]. The no-albumin group had statistically significantly more changes in electrolytes, plasma renin, and serum creatinine, but no more clinical morbidity or mortality compared to the albumin group [65]. There are no studies that demonstrate decreased survival in patients without plasma expander compared to patients given with albumin after paracentesis [44].

Polygeline (plasma expander) is no longer used in many countries because of the possible risk of transmission of prions. Some evidence suggest that the use of saline is not linked to a high risk to develop PPCD after small-volume paracentesis [53]; there are no randomized controlled studies comparing saline versus albumin in patients who require paracentesis of less than 5 L. The use of starch as a plasma expander has been addressed in few studies in patients with cirrhosis and grade 3 ascites treated with LVP, revealing some concerning issues regarding the likelihood for starch to induce renal failure and hepatic accumulation of starch [66, 67].

On the other hand, a health economic analysis model suggested that it is more cost-effective to use albumin after LVP compared with alternative cheaper plasma volume expanders. This finding was mainly attributed to the fact that the administration of albumin post-paracentesis is associated with a smaller number of liver-related complications within the first 30 days which leads to increased total health cost [56].

8. Other treatment options

Activation of neurohumoral systems with sodium and water retention plays a major role in the pathogenesis of refractory ascites; thus, drugs that may improve circulatory and renal function,

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principally vasoconstrictors, have been investigated. Vasoconstrictors such as the α1-adrenergic agonist midodrine or terlipressin improve circulatory and renal function in patients with and without refractory ascites. Terlipressin is given in intravenous boluses (1 mg at onset of paracentesis, 1 mg at 8 h and 1 mg at 16 h) in addition to oral midodrine (for 72 h post-paracentesis), which appear to be as good as albumin in suppressing plasma renin elevation in randomized trials; terlipressin is not commercially offered in the United States [51, 68, 69].

9. Spontaneous bacterial peritonitis (SBP)

Ascitic fluid infection is common (12% in older series) and is associated with mortality rate that surpassed 90% [70–72]. This mortality rate can be reduced to 20% with early diagnosis and treatment [6, 73]. The diagnosis of spontaneous bacterial peritonitis (SBP) is made in the presence of raised ascitic fluid absolute polymorphonuclear leukocyte (PMN) count (i.e., ≥250 cells/mm^3 [0.25 × 10^9/L]). Treatment of SBP is a separate topic; we will discuss the importance of albumin and other therapies in addition to antibiotic use.

10. Empiric treatment

Empiric antibiotic therapy should be initiated in patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm^3 (0.25 × 10^9/L). About 60% of the patients present with culture-negative ascites. If cultures are positive, however, the most common pathogens include Gram-negative bacteria (GNB), usually *Escherichia coli* and Gram-positive cocci (mainly streptococcus species and enterococci) [71, 74]. The epidemiology of bacterial infections differs between community-acquired (in which GNB infections predominate) and nosocomial infections (in which Gram-positive infections predominate).

Moderately broad-spectrum therapy is necessary in patients with suspected ascitic fluid infection unless otherwise indicated by culture and sensitivity when available. In a controlled trial, cefotaxime, a cephalosporin from the third generation, is shown to be superior to ampicillin plus tobramycin [75]. Cefotaxime or a similar third-generation cephalosporin seems to be the best therapeutic option for anticipated SBP; it is used to cover 95% of the flora including the three most common isolates: *E. coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae* [75]; usually, a 5-day treatment is as effective as 10 days in the treatment [76]. To achieve ascetic fluid levels that are 20-fold above the killing power after 1 dose of cefotaxime, 2 g intravenously every 8 h is required [77]. In neutrocytic ascites, a 5-day course of ceftriaxone 1 g intravenously twice per day was sufficient in treating culture-negative ascites [78].

Amoxicillin/clavulanic acid, intravenously and then orally, has comparable outcomes with respect to SBP resolution and mortality, compared with cefotaxime [79] and at reduced cost.

Another antibiotic that produces a similar SBP resolution rate and hospital survival compared with cefotaxime is ciprofloxacin. Ciprofloxacin is administered as either for 7 days intravenously or for 2 days intravenously followed by 5 days orally. Nevertheless, the cost is higher compared

with cephalosporin-based options [80]. However, the use of intravenous antibiotic at the start, followed by oral step-down administration with ciprofloxacin, is more cost-effective than intravenous cefotaxime [81]. Ofloxacin also has produced similar results to intravenous cefotaxime when given orally in uncomplicated SBP, without renal failure, hepatic encephalopathy, gastrointestinal bleeding, ileus, or shock [82].

It is important to mention that, if ascitic fluid neutrophil count does not decrease to less than 25% of the pretreatment value after 48 h of antibiotic treatment, there is a high likelihood of failure to respond to therapy [83, 84]. In such scenarios antibiotic therapy should be broaden to cover more resistant pathogens.

11. Secondary prophylaxis of spontaneous bacterial peritonitis

The ideal prophylactic agent should be safe, affordable, and effective at decreasing the episodes of SBP while preserving the protective anaerobic flora (selective intestinal decontamination) [73]. Given the high cost and the risk of developing resistant organisms, the use of prophylactic antibiotics must be strictly restricted to patients with the following risk factors: (1) patients with acute gastrointestinal hemorrhage, (2) patients with low total protein content in ascitic fluid and no prior history of SBP (primary prophylaxis), and (3) patients with a previous history of SBP (secondary prophylaxis).

The cumulative recurrence rate at 1 year is approximately 70% in patients who survive an episode of SBP with survival rate of up to 30–50% and falls to 25–30% at 2 years [73]. Several antimicrobial regimens have been proposed as secondary prophylaxis. Norfloxacin was studied in a randomized, double-blind, placebo-controlled trial of (400 mg/day orally) in patients who had a previous episode of SBP [85, 86]. Norfloxacin was found to reduce the likelihood of SBP recurrence from 68 to 20% and the likelihood of SBP due to Gram-negative bacteria from 60 to 3%. Other studies evaluated the impact of ciprofloxacin, trimethoprim-sulfamethoxazole, and norfloxacin on SBP recurrence, but they included patients with and without previous episodes of SBP. All studies showed a reduced incidence of SBP with antibiotic prophylaxis [87–89].

The emergence of resistant, extended-spectrum B-lactamase-producing *Enterobacteriaceae* has occurred as a result of the extensive use of quinolones to prevent SBP [90–92].

Alternatively, ofloxacin, dosed at 400 mg bid for about 8 days, was found to be as good as parenteral cefotaxime in the treatment of SBP in patients without vomiting, shock, grade II (or higher) hepatic encephalopathy, or serum creatinine greater than 3 mg/dL [82]. A more cost-effective choice when compared to intravenous ceftazidime in a randomized trial would be the administration of intravenous ciprofloxacin followed by oral administration in patients who had not received quinolone prophylaxis [93]. Patients' flora may become resistant to quinolone prophylaxis, and hence treatment with alternative agents is warranted.

Reduction in mortality was reported in one trial when patients with SBP were randomized to receive cefotaxime alone versus cefotaxime plus 1.5 g albumin per kg body weight within 6 h of enrollment and 1.0 g/kg on day 3. A reduction in mortality from 29 to 10% was described [93]. Another study has revealed that albumin must be administered when the

serum creatinine is >1 mg/dL, total bilirubin >4 mg/dL, or blood urea nitrogen >30 mg/dL. If the patient does not meet these prerequisite criteria, then albumin is not indicated [94–97]. Albumin is superior to hydroxyethyl starch in spontaneous bacterial peritonitis [98].

Author details

Aziza Ajlan[1], Waleed K. Al-hamoudi[2,3] and Hussein Elsiesy[2,4]*

*Address all correspondence to: helsiesy@gmail.com

1 Department of Pharmacy, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

2 Department of Liver Transplantation, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

3 Division of Gastroenterology, King Saud University, Riyadh, Saudi Arabia

4 Department of Medicine, Alfaisal University, Riyadh, Saudi Arabia

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