Management of Patients with Ascites

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Ascites is the accumulation of free fluid in the peritoneal cavity. In over 80% of cases, it is a result of cirrhosis. Ascites develops in 60% of patients with cirrhosis within 10 years of the diagnosis of cirrhosis, and its development marks a turning point in the natural history of the disease. The mainstays of treatment are twofold: sodium restriction and diuretics. The development of spontaneous bacterial peritonitis is another ominous sign that requires indefinite antibiotic prophylaxis to prevent future infections. A referral to a transplant centre is essential once ascites or spontaneous bacterial peritonitis develop.

Key words: *ascites, portal hypertension, cirrhosis, spontaneous bacterial peritonitis, paracentesis, albumin infusion*

Introduction

Ascites is the pathological accumulation of free fluid in the peritoneal cavity. This entity was described even by the ancient Egyptians and Greeks. In 300 BC, Erasistratus of Cappadocia first described the "hardness of the liver" as a risk factor for ascites formation. He was correct, as cirrhosis accounts for over 80% of ascites cases.

Ascites is the most common complication of cirrhosis and can result in significant impairment in an individual's quality of life. Nearly 60% of people with compensated cirrhosis develop ascites within 10 years of the diagnosis of cirrhosis.[1] The development of ascites in cirrhosis is associated with a probability of survival of 85% at 1 year and 56% at 5 years.[2] Individuals with ascites are at risk for dilutional hyponatremia, spontaneous bacterial peritonitis (SBP), hepatic hydrothorax, and hepatorenal syndrome. For that reason, patients with advanced cirrhosis (see below) who are candidates for liver transplantation and who develop ascites should be referred to a transplant centre for a liver transplant evaluation. The classic cutoff of advanced age as a contraindication for liver transplantation is not applied in all centres as it is considered that physiological rather than chronological age is more important in the evaluation of candidates. However, very old individuals (age >75) with comorbid conditions (age is a contraindication as well) are turned down for liver transplantation in most centres.

This article focuses on the practical aspects of the evaluation and treatment of patients with ascites.

Causes of Ascites

The most common cause of ascites is portal hypertension secondary to cirrhosis, which accounts for over 80% of ascites cases. In approximately 20% of cases, there is a nonhepatic cause for the ascites. These include malignancy, heart failure, tuberculosis, hemodialysis, pancreatitis, and other rare causes (Figure 1).

The presentation of new-onset ascites requires a diagnostic evaluation. The successful treatment of ascites is dependent on an accurate diagnosis of the etiology of the fluid retention; patients with ascites without portal hypertension usually do not respond to the treatments used in patients with cirrhosis.

History and Physical Examination

A general evaluation should include a complete history and physical examination. Risk factors for underlying liver disease should be addressed. On physical examination, one should look for stigmas of chronic liver disease and portal hypertension such as spider angiomas, palmar erythema, jaundice, icterus, splenomegaly, gynecomastia, muscle wasting, and atrophy. Patients without signs of portal hypertension or cirrhosis should be examined for other noncirrhotic causes of ascites. Jugular venous distension can be seen in patients with heart failure. Kussmaul's sign is seen in patients with constrictive pericarditis. Anasarca can be associated with nephrotic syndrome and congestive heart failure. Firm lymphadenopathy is found in patients with an underlying malignancy.

Patients need at least 1,500 mL of peritoneal fluid to be detected reliably by physical examination.[3] Ultrasonography can detect as little as 100 mL of abdominal fluid and should be used for obese individuals and for patients in whom the physical examination is unreliable.[4] There are several techniques available for diagnosing ascites on physical examination, with the most accurate being flank dullness; without this, the patient has a <10% likelihood of having ascites. Shifting dullness also is a useful diagnostic manoeuvre; if ascites is present, percussion of the lateral aspect of the right flank demonstrates a shift in the location of the dullness when the patient is percussed in the supine, followed by the right lateral decubitus position.

Patients may present with a rapid onset of ascites, as in alcoholic hepatitis or peritoneal carcinomatosis, but in general ascites develops insidiously over a course of weeks to months. Dyspnea may be present as a consequence of increasing abdominal distension or pleural effu-

sions. Typically, in cirrhosis the pleural effusion is unilateral and right-sided; a bilateral pleural effusion should prompt further evaluation for an underlying cardiac cause of the ascites. Any patient with fever, chills, encephalopathy, and rebound tenderness should be evaluated for SBP.[5] However, only a minority of patients with SBP present with these symptoms. The diagnosis always requires an examination of the peritoneal fluid.

In a patient with known cirrhosis who presents with worsening ascites, precipitating events such as excessive salt intake, alcohol consumption, infections, medications such as nonsteroidal anti-inflammatory drugs, and nonadherence with diuretic therapy should be assessed. Progression of the underlying liver disease, portal vein thrombosis, parenchymal renal disease, and development of hepatocellular carcinoma may precipitate the development of ascites even in the most adherent patient.

Diagnostic Tests

As part of the evaluation for new-onset ascites, standard electrolyte, hematological, liver, and coagulation tests should be ordered. A 24-hour urine collection for urine sodium (UNA) is of key importance in directing therapy as patients with severe sodium retention—UNA <10 mEq/L—have a poor response to diuretics. Abdominal ultrasonography with Doppler can be used to evaluate the liver parenchyma, rule out hepatocellular carcinoma, and evaluate the patency of the portal venous system; ultrasonography of the kidneys can be performed simultaneously. If cardiac disease is suspected, echocardiography should be ordered. It should be noted that in the presence of ascites, a percutaneous liver biopsy is contraindicated as its presence increases the risk of complications; however, a transjugular approach can be used to obtain a biopsy if one is warranted.

A diagnostic paracentesis of at least 30 mL of fluid is essential to fully elucidate the etiology of the ascites. It also should be performed in all patients requiring hospitalization and in those with any evidence of clinical deterioration such as fever, abdominal pain, hypotension, or encephalopathy.[6] Baseline parameters to be determined in ascitic fluid are cell count, culture in blood culture bottles, albumin, and total protein. Glucose, lactate dehydrogenase, amylase, bilirubin, triglyceride, tuberculosis smear, and cytological analyses of the fluid are optional and provide important information in the differential diagnosis of ascites in selected cases (Table 1). The cell count is the most useful test in determining bacterial infection. The diagnosis of SBP is made when the fluid sample has a polymorphonuclear count >250/mm^3.[6,7]

The difference between serum albumin concentration and ascites albumin concentration (serum-ascites albumin gradient) in patients with cirrhosis and ascites is usually ≥1.1 g/dL. Values <1.1 g/dL suggest a cause of ascites other than cirrhosis (Table 2).[8] Most patients with cirrhosis have a total ascitic fluid protein concentration <1.5 g/dL, and these individuals have a greater risk of developing SBP.[9–12] An elevated fluid protein is found in patients with cardiac ascites.

Table 1: Analysis of Ascitic Fluid Characteristics

Fluid Characteristic	Implication
Appearance	
Clear	Uncomplicated ascites is usually a transparent yellow
Turbid or cloudy	Spontaneously infected fluid is often turbid or cloudy
Milky	Chylous ascites; usually there is an elevated triglyceride level
Pink or bloody	Traumatic tap vs. intraperitoneal hemorrhage; repeat paracentesis on opposite side and if remains bloody, then concern for hemorrhage
Brown	Ascitic bilirubin concentration of approximately 40% of the serum bilirubin concentration is normal; any greater value warrants further evaluation for a gallbladder or duodenal perforation
Cell count and differential	A polymorphonuclear cell count of ≥250/mm^3 is diagnostic of SBP
Culture	Assess for bacteria in ascites; a multimicrobial ascitic fluid culture should raise suspicion of secondary peritonitis
Albumin	Used to determine the SAAG (see Table 2)
Total protein	<15 g/L is a risk factor for developing SBP; elevated in cardiac ascites
Amylase	Typically <40 IU/L; but in the setting of pancreatitis or gut perforation, it can be as high as 2,000 IU/L
Triglycerides	Chylous ascites has a triglyceride concentration >200 mg/dL
Bilirubin	>40% the serum bilirubin suggests either bile leak, gallbladder or duodenal perforation
Cytology	Assesses for the presence of malignant cells

SAAG = serum-ascites albumin gradient; SBP = spontaneous bacterial peritonitis.

Table 2: Classification of Ascites by Serum-Ascites Albumin Gradient*

High Gradient (≥1.1 g/dL)	Low Gradient (<1.1 g/dL)
Cirrhosis	Peritoneal carcinomatosis
Congestive heart failure	Tuberculosis (without cirrhosis)
Fulminant hepatic failure	Pancreatitis (without cirrhosis)
Portal vein thrombosis	Biliary (without cirrhosis)
Liver metastases	Nephrotic syndrome
Alcoholic hepatitis	Connective tissue diseases
Budd-Chiari syndrome	Chlamydial/gonococcal infection
Veno-occlusive disease	Bowel obstruction
Myxedema	

*Serum albumin concentration minus ascitic albumin concentration.

Management of Ascites

One of the important aspects in managing ascites is consideration of referral of suitable candidates to a transplant centre. Patients that benefit from an evaluation and referral are those that have developed a previous episode of SBP, refractory ascites, increased serum creatinine and have high Child-Pugh scores > 9 or high Model for end-stage liver disease (MELD) score >15. Treatment of ascites is aimed at two facets: nutrition and diuretic therapy. A low-sodium diet of 70–90 mEq/d (or <2,000 mg/d) is a mainstay of management. This restriction causes a negative sodium balance and helps minimize ascites. Diuretics increase sodium excretion by reducing the tubular reabsorption of sodium. The response to diuretics should be evaluated regularly by measuring body weight, urine volume, and sodium excretion.

Spironolactone, the most commonly used diuretic, inhibits sodium reabsorption by binding to the mineralocorticoid receptor in the renal collecting tubules, thus blocking the effects of aldosterone. It has a half-life of 24 hours and requires only once daily dosing of 50–400 mg. Common side effects include hyperkalemia (usually in the setting of renal insufficiency), painful gynecomastia, hyponatremia, muscle cramps, renal insufficiency, and hepatic encephalopathy. Furosemide is a loop diuretic used in combination with spironolactone at a dosage of 20–160 mg/d. Furosemide is usually added to sprinolactone in order to increase natriuresis and achive better control of ascites; however it should not be used as single therapy in patients with cirrhosis, because it may place patients with mild sodium retention at risk for volume depletion and pre-renal failure. Furosemide is started at a dose 20–40mg/day and may be increased to 80mg and up to 160mg/day. Common side effects include hypokalemia, hypomagnesemia, tinnitus, muscle cramps, renal insufficiency, and hepatic encephalopathy.

Treatment of ascites with diuretics is dependent on the grade of ascites (Table 3 and Figures 2–4).[13] For grade 1 ascites, no specific therapy is required. Those with grade 2 ascites can be managed as outpatients with sodium restriction and spironolactone (50–200 mg/d in a single dose). Furosemide can be added (20–40 mg/d) to increase the natriuretic effect in individuals with peripheral edema. The goal of treatment should be to achieve a weight loss of 300–500 g/d in people without peripheral edema and 800–1,000 g/d in people with peripheral edema.[13] If there is no response, the dosage of diuretics should be increased stepwise every 7 days up to 400 mg/d of spironolactone and 160 mg/d of furosemide. Once the patient is at the goal, the dosage of diuretics may be decreased in select cases.

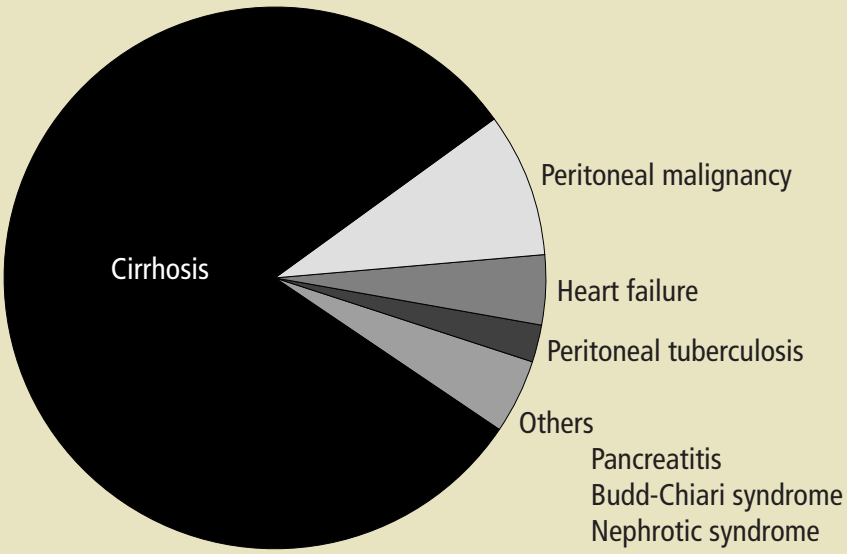
Individuals with grade 3 ascites require a large-volume paracentesis plus intravenous 20% albumin (6–8 grams per litre tapped) initially. A large volume paracentesis is defined as a tap greater than 6 litres. There is no limit as to how much can be tapped, but in the majority of cases patients will have between 6–10 litres removed at one session. Patients with massive peripheral edema may require a second paracentesis shortly thereafter because of a rapid shift of fluid from interstitial tissue to the abdominal cavity. Next, they should be started on relatively high dosages of diuretics (spironolactone 200 mg/d with furosemide 40 mg/d)

Table 3: Classification of Ascites in Cirrhotic Patients According to International Ascites Club

Ascites Grade	Description
Grade 1	Fluid is detected by ultrasonography only
Grade 2	Moderate amount of fluid in the peritoneal cavity with symmetrical distension of the abdomen
Grade 3	Large or tense abdomen with marked abdominal distension

Source: Data from Moore KP et al., 2003.[13]

Figure 1: Causes of Ascites



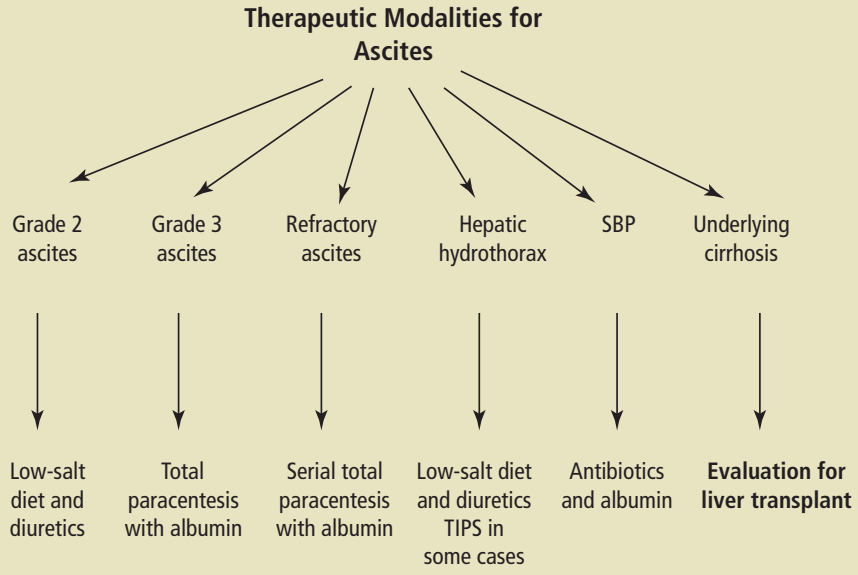
and a low-sodium diet. Diuretics then should be adjusted based on individual response.

In patients taking diuretics who do not achieve the desired weight loss, a urine sodium should be determined; patients with urine sodium >90 mEq/d (i.e., urine sodium greater than theoretical—and prescribed—sodium intake) are not adhering to sodium restriction. A low-sodium diet is extremely challenging to maintain, and the patient may require a consultation with a nutritionist to be successful.

Refractory Ascites

Refractory ascites is defined as ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the lack of response to sodium restriction and diuretic treatment or because of the development of diuretic-induced complications that preclude the use of an effective diuretic dose. This condition occurs in only 10% of individuals with ascites.[14] Treatment strategies include repeated therapeutic paracentesis plus intravenous albumin or the use of a transjugular intrahepatic portosystemic shunt (TIPS), a nonsurgical method of portal decompression whereby an intrahepatic stent is inserted between one hepatic vein and the portal vein using a transjugular approach. The reduction in portal pressure is accompanied by a resolution of ascites in most patients. This method may be associated with several side effects and complications including hepatic encephalopathy, cardiac failure, and obstruction of the stent. For this reason a TIPS is usually contraindicated for adults > 70–75 years of age [15] These side effects include hepatic encephalopathy, obstruction of the shunt, congestive heart failure, hemolytic anemia, and impairment in liver function.[16]

Figure 2: Treatment Algorithm for Ascites



SBP = spontaneous bacterial peritonitis; TIPS = transjugular intrahepatic portosystemic shunt.

Spontaneous Bacterial Peritonitis

Gram-negative bacteria, particularly *Escherichia coli,* are responsible for 80% of cases of SBP, with *Streptococcus viridians, Staphylococcus aureus,* and *Enterococcus faecalis* isolated in the remaining 20% of cases.[17] The diagnosis of SBP is made when the ascitic fluid has >250/mm^3 neutrophils. A positive culture is not needed for the diagnosis of SBP.

Antibiotics with an intravenous third-generation cephalosporin (cefotaxime or ceftriaxone) are the treatment of choice for SBP.[7] Treatment is required for 5–7 days. Renal insufficiency may occur in up to one-third of patients with SBP and is related to an impairment of circulatory function with an activation of the vasoconstrictor systems.[18] Albumin should be administered to prevent this complication at a dose of 1.5 g/kg at the diagnosis of the infection and 1 g/kg 48 hours later.[19]

Individuals with SBP have a very poor 1-year survival of only 30–50%.[20] Therefore, all patients with SBP should be evaluated for liver transplantation once they have recovered from their first episode of SBP. Patients should be treated indefinitely for SBP prophylaxis, with norfloxacin 400 mg daily, ciprofloxacin 750 mg weekly, or double-strength trimethoprim-sulfamethoxazole (once daily dose) five times a week.[21]

There are two conditions associated with an increased risk of SBP; for these, primary prophylaxis of SBP is recommended. The first condition is gastrointestinal hemorrhage. Multiple studies have shown that short-term (7 days) administration of oral norfloxacin 400 mg twice a day or intravenous ceftriaxone 1 g/d reduces the incidence of SBP, bacteremia, and rebleeding.[22–25] The second condition is a serum creatinine level of >1.2 mg/dL, ascitic fluid protein levels <15 g/L, a Child-Pugh score >9, or dilutional hyponatremia (serum sodium <130 mEq/L). In a recent randomized controlled trial of norfloxacin versus placebo, primary prophylaxis with norfloxacin (400 mg/d) reduced the 1-year probability of developing SBP (7% vs. 61%) and hepatorenal syndrome (28% vs. 41%) and improved the 3-month (94% vs. 62%) and the 1-year (60% vs. 48%) survivals compared with placebo.[26]

Conclusion

Ascites is the most common complication of cirrhosis and results in significant morbidity and mortality, with 50% mortality at 2–3 years. The development of ascites or SBP warrants a referral to a transplant centre. The mainstays of treatment involve sodium restriction and diuretic therapy. With adequate treatment and patient adherence to treatment, only 10% of patients have refractory ascites that require a TIPS.

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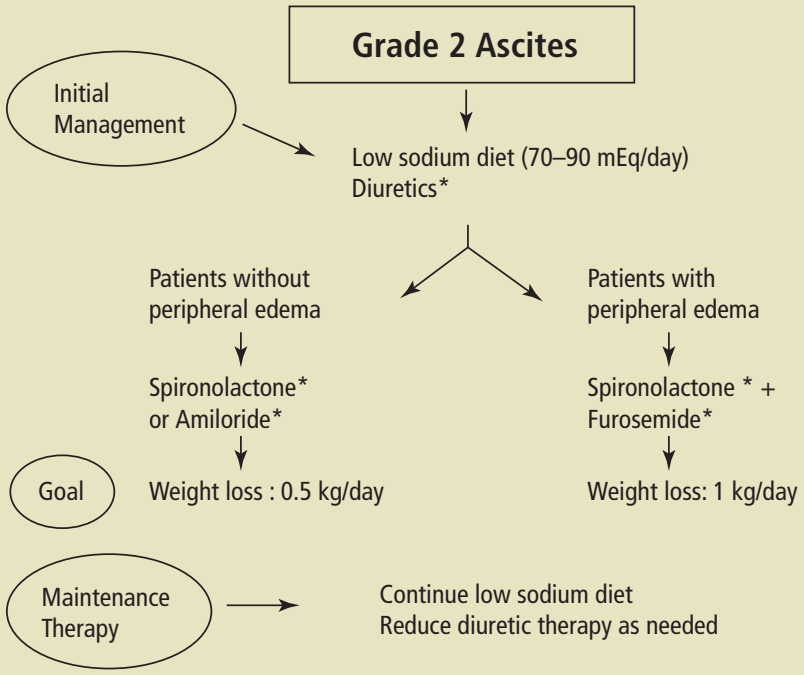
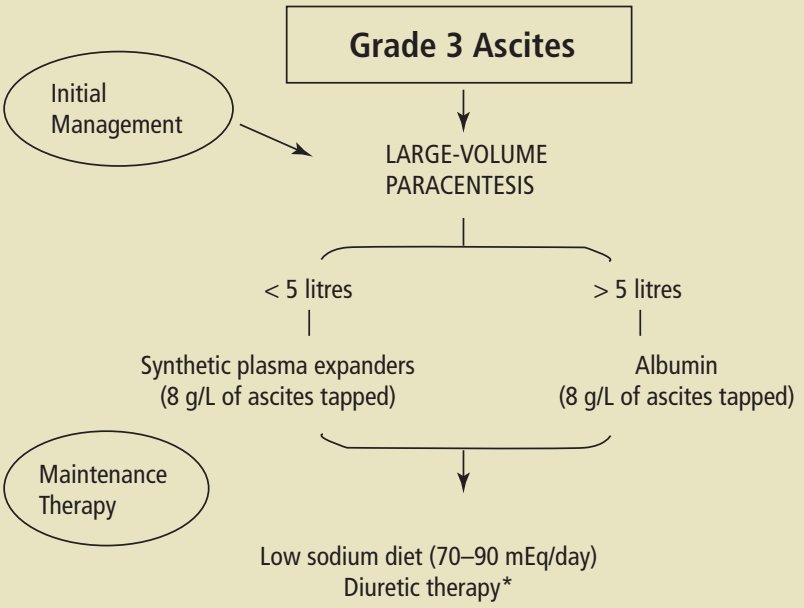
Figure 3: Treatment Strategy for Patients with Cirrhosis and Grade 2 Ascites



*Recommended diuretics include spironolactone (50–200 mg/d). Low dosages of furosemide (20–40 mg/d) may be added in patients with peripheral edema. If there is no response, check adherence to treatment and low-sodium diet. Increase the dosage of diuretics in stepwise fashion to achieve weight loss and resolution of ascites.

Figure 4: Treatment Strategy for Patients with Cirrhosis and Grade 3 Ascites



*If the patient was not taking diuretics before the development of large ascites, start with spironolactone (200 mg/d as single dose) and furosemide 40 mg/d and adjust the dosage to maintain the patient with mild or no ascites or edema. Check body weight daily and urine sodium weekly. Monitor the patient closely during the first 3–4 weeks of therapy. If the patient was taking diuretics, start with a dosage higher than that taken before paracentesis. If ascites and edema increase, check adherence to treatment and low-sodium diet. Increase the dosage of diuretics in stepwise fashion every 7 days up to 400 mg/d of spironolactone and 160 mg/d of furosemide.

Key Points

Individuals with cirrhosis diagnosed with ascites have an elevated mortality at 2–3 years; as a result, suitable candidates should be evaluated for liver transplantation.

A diagnostic paracentesis (cell count, albumin, total protein, and cultures in blood culture bottles) is required in all patients presenting with their first episode of ascites and those requiring hospitalization.

The mainstay of therapy for patients with cirrhosis and moderate ascites is a low-sodium diet accompanied by the use of diuretics (spironolactone and furosemide).

Patients diagnosed with SBP have a 1-year probability of survival of only 30–50%. Therefore, all patients should be evaluated for liver transplantation once they have recovered from their first episode of SBP, and all should receive prophylactic antibiotics indefinitely until transplantation.

Patients with a previous history of SBP who have gastrointestinal bleeding or a low total protein value <15 g/L in their ascitic fluid should receive primary antibiotic prophylaxis for SBP.

Clinical Pearls

Patients that present with ascites do not always have cirrhosis, thus a through history and exam are necessary and asctic fluid analysis must always be performed.

The first line of therapy should commence with a salt restricted diet (2 grams/day) and diuretics oral spironolactone with or without oral furosemide).

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