Up to date treatment of ascites in liver cirrhosis

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Introduction

Ascites is defined as an abnormal accumulation of fluid in the abdominal cavity. Ascites is the mostcommon complication of cirrhosis, with approximately 50% of patients with compensated cirrhosisdeveloping ascites over the course of 10 years. After developing ascites that necessitateshospitalization, the risk of mortality increases to 15% at 1 year and nearly 50% at 5 years **[1,2].** The occurrence of ascites impairs patient working and social life, often leads to hospitalization, requires chronic treatment and is a direct cause of further complications, such as spontaneous bacterial peritonitis, restrictive ventilatory dysfunction, or abdominal hernias. The development of refractory ascites carries a poor prognosis, with a 1-year survival rate of less than 50**% [3].**

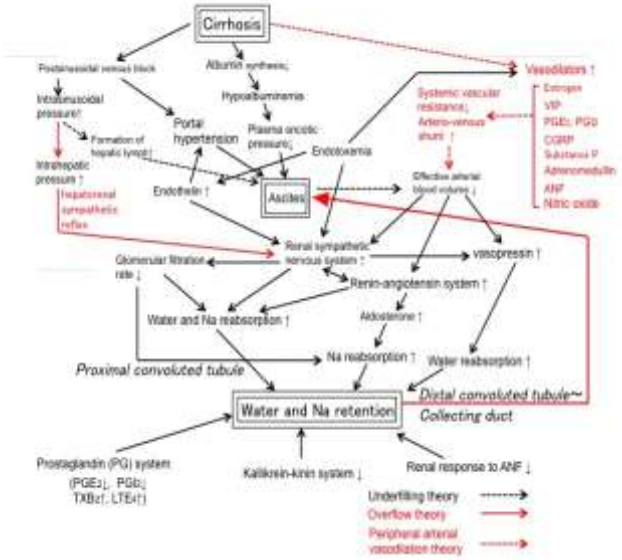
Pathogenesis of ascites in patients with liver cirrhosis

The pathogenesis of ascites is complex and not fully understood. 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**[4].**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 **[5].** The triad of portal hypertension, arterial vasodilatation, and neurohumoral activation, leading to sodium and water retention, explains, to large extent, the formation of ascites **[6]**.

Complications of ascites

-Spontaneous bacterial peritonitis
-Hepatorenal Syndrome
-Hepatic hydrothorax
-Hyponatremia

Pathophysiologic backgrounds and main theories of ascites formation in liver cirrhosis*[7]*



Assessment of the severity of ascites

The International Ascites Club classifies ascites according to the grade **[8]**Mild: Detectable only on ultrasonography, Moderate: Moderate distention of abdomen, Large: Marked distension of abdomen ("tense"), presence or absence of complications (Uncomplicated: Ascites with no infection and hepatorenal syndrome or Complicated: Ascites with infection or hepatorenal syndrome), and response to diuretic treatment (Diuretic resistant**:** No response to a sodium-restricted diet and high-dose diuretic treatment, Diuretic intractable**:** Side effects induced by diuretics preclude optimal dosing).

Definition and diagnostic criteria for refractory ascites in cirrhosis

The International Ascites Club defines refractory ascites as ascites that cannot be managed by medical therapy either because of a lack of response to maximum doses of diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) or because patients develop complications related to diuretic therapy that preclude the use of an effective dose of diuretics [9]**.**

Diuretic-resistant ascites: ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to sodium restriction and diuretic treatment. Diuretic-intractable ascites: ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic induced complications that preclude the use of an effective diuretic dosage.

Treatment of cirrhotic ascites

The approach for the treatment of ascites depends on the grade of ascites. In grade 1 or mild ascites.There are no recommendations for the treatment of grade 1 ascites**[10]**.Patients who develop grade 2 ascites do not require hospitalisation, unless other complications are present. Grade 3 ascites can be treated with initial large volume paracentesis followed by dietary sodium restriction and diuretics (with the exception of refractory ascites) **[11].**

Dietary sodium restriction and diuretics

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. Less than 10% of patients with cirrhosis and ascites are refractory to standard medical therapy **{12}.**

Single large volume paracentesis

Therapeutic large volume paracentesis (LVP) should be performed to alleviate abdominal discomfort or respiratory distress in hemodynamically stable patients with tense ascites or ascites that are refractory to diuretics. There are few absolute contraindications for LVP. Coagulopathy and thrombocytopenia (both very common in cirrhotic patients) are themselves not absolute contraindications. LVP is a safe procedure, and the risk of local complications, such as hemorrhage or bowel perforation, is extremely low **[13].**The most effective method to preventing circulatory dysfunction after LVP is the administration of albumin.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.

Serial therapeutic paracentesis

Serial paracenteses is a safe option for patients with refractory ascites. LVP up to total paracentesis 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. Up to 5 L of ascites can be taped safely without the need for albumin infusion. A concern with the administration of albumin is the added cost as well as the small infectious risk. A small study demonstrated no difference in PICD, hyponatremia, renal impairment, rate of ascites recurrence, and 6-month survival in patients receiving standard versus half albumin doses**[14]**; if confirmed in a larger study, this albumin infusion adjustment could help decrease costs in treating with albumin.

Transjugular intrahepatic portosystemic stent-shunt (TIPS)

TIPS reduce the portosystemic pressure gradient by shunting the blood from the portal vein to the hepatic vein and is usually inserted by an interventional radiologist using local anesthesia **[15,16].**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 **[17].**Some studies have compared the efficacy of TIPS to LVP**[18].**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. The main complication of TIPS is the development of hepatic encephalopathy which is more reported with TIPS than with repeated large volume paracentesis**[19,20].**Other complications include shunt thrombosis and stenosis. Uncovered stents are

complicated by stenosis in up to approximately 80% of cases**[21].**

Peritoneo-venous shunt (PVS)

PVS was designed to palliate ascites by reinfusingascitic fluid into the systemic circulationPVS prolonged the time to the recurrence of ascites compared with diuretic treatmentand LVP with albumin infusion. However, the poor long-term patency, excessive complications and no survival advantage compared with medical therapy have restricted its indication only to patients for whom other treatment modalities are impossible **[22].**

Cell-free and concentrated ascites reinfusion therapy (CART)

This therapy aims to maintain serum albumin levels by filtrating and concentrating the removed ascitic fluid, followed by intravenous reinfusion of the collected proteins**[23].** The benefit of CART in reducing albumin use has been emphasized, although the cost of instruments for CART, higher than that of albumin solution, is considered as a drawback**[7,24].** The advantages of this therapy are that albumin transfusion can be reduced; furthermore, the risk of infection or allergic reaction is reduced. However, CART is difficult to carry out in patients with SBP, because inadvertent reinfusion of filtrated, concentrated endotoxins in ascites might result in high fever or shock.

Automated Low-Flow Ascites Pump System (alfapump [AP] system)

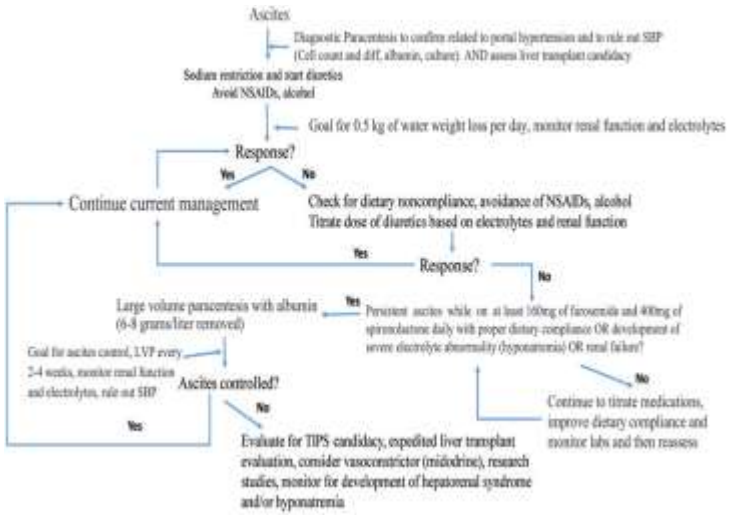
The automated low-flow ascites pump (Alfapump) system consists of a subcutaneously implanted battery-powered programmable pump. It is connected to catheters that transfer ascites from the peritoneal cavity to the bladder, from which it is eliminated with urine. The device has internal sensors that monitor pump function. In two multicenter safety and efficacy studies, **[25]**Alfapumpensured a significant reduction of the number and volume of paracentesis in patients with advanced cirrhosis and refractory ascites. However, adverse effectsdirectly related to the device occurred in about one-thirdto half **[26]**of cases. In a multicentre RCT in patients with refractory ascites, Alfapumpreduced the median number of paracentesisper month by 85% with respect to LVP, and significantly improved quality of life and nutritional parameters, as assessed by hand-grip strength and body mass index. Alfapumphad no effect on survival and was associated with a significantly higher incidence of serious adverse events (85.2 vs. 45.2%), mainly represented by AKI **[27].**

Thus, even though Alfapumpis effective inreducing the need for paracentesis in patients with refractory ascites, its frequent side effects require close monitoring of patients. Indeed, in addition to device-related adverse event, itshould be noted that the evaluation of kidney and circulatory function in 10 patients with cirrhosis and refractory ascites carrying Alfapump has shown a significant GFR decline withinsix months, which was associated with a marked increase in plasma renin activity and norepinephrine concentration**[28].**This likely represented the pathophysiological background of 18 episodes of AKI experienced by seven patients.

Extracorporeal ultrafiltration of ascitic fluid (EUA)

Extracorporeal ultrafiltration of ascitic fluid (EUA), which is a technique to reinject concentrated ascites continuously by using a dialyser and pump for haemodialysis, is another available means of treating refractory

ascites which was first reported by **[29].** Adding an insignificant influence on the circulation **[30]**from EUA, intra-abdominal albumin is reported to backflow to blood and it is possible to perform EUA without the complications that are sometimes encountered with intravenous reinfusion of ascites (IRA).



An algorithm for the management of ascites and refractory ascites[31]

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