

# Management of cirrhotic ascites

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**Abstract:** The most common complication to chronic liver failure is ascites. The formation of ascites in the cirrhotic patient is caused by a complex chain of pathophysiological events involving portal hypertension and progressive vascular dysfunction. Since ascites formation represents a hallmark in the natural history of chronic liver failure it predicts a poor outcome with a 50% mortality rate within 3 years. Patients with ascites are at high risk of developing complications such as spontaneous bacterial peritonitis, hyponatremia and progressive renal impairment. Adequate management of cirrhotic ascites and its complications better quality of life and increases survival. This paper summarizes the pathophysiology behind cirrhotic ascites and the diagnostic approaches, as well as outlining the current treatment options. Despite improved medical treatment of ascites, liver transplantation remains the ultimate treatment and early referral of the patient to a highly specialized hepatology unit should always be considered.

**Keywords:** cirrhosis, ascites, portal hypertension, arterial vasodilation, hepatorenal syndrome, spontaneous bacterial peritonitis

## Introduction

Ascites is defined as accumulation of more than 25 ml of fluid in the peritoneal cavity. In Western countries, development of ascites is in 75% of cases due to underlying cirrhosis [European Association for the Study of the Liver, 2010], but other less common etiologies of ascites such as malignancy, congestive heart failure, Budd Chiari syndrome, tuberculosis and pancreatitis should be considered – especially if ascites is the first presenting symptom.

Ascites is one of the most frequent complications to cirrhosis occurring in approximately 60% of patients within 10 years of diagnosis [Gines *et al.* 1987a]. The development of ascites in the setting of cirrhosis represents a landmark in the natural history of cirrhosis, predicting a poor prognosis with 50% mortality within 3 years [Fernandez-Esparrach *et al.* 2001; Guevara *et al.* 2005]. Consequently, occurrence of ascites signifies the need to consider referral for liver transplantation, which remains the ultimate treatment option of cirrhosis. Ascites formation often develops in cirrhotic patients presenting with acute-on-chronic liver failure (ACLF), which is acute worsening of liver function due to a precipitating event, e.g. infection, upper gastrointestinal bleeding, electrolyte disturbances [Angeli *et al.* 2014].

Portal hypertension is a prerequisite for development of cirrhotic ascites [Ripoll *et al.* 2007]. Survival of cirrhosis depends mainly on the degree of portal hypertension, the degree of liver insufficiency and the degree of circulatory dysfunction.

The principles behind treatment of ascites include diuretics, paracentesis, insertion of a transjugular intrahepatic portosystemic shunt (TIPS), as well as managing complications to ascites such as spontaneous bacterial peritonitis (SBP). SBP occurs in approximately 25% of patients due to bacterial translocation [Wiest and Garcia-Tsao, 2005; Wiest *et al.* 2014], which is crossing of gut bacteria or bacterial products from the gut lumen to the blood (and ascitic fluid). Bacterial translocation happens as a result of altered intestinal motility, intestinal bacterial overgrowth, increased intestinal permeability and impaired immune defense mechanisms in the cirrhotic patient [Guarner and Soriano, 2005].

Since ascites signifies a deterioration of renal and circulatory function, these patients are also at high risk of developing severe hyponatremia and hepatorenal syndrome (HRS), which together with SBP represent significant clinical and treatment challenges. HRS and SBP further aggravate

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the risk of a poor outcome [Gines *et al.* 1993; Garcia-Tsao, 2001; Gines and Schrier, 2009].

There is a strong rationale for an active approach in the management of cirrhotic ascites as a successful treatment may improve symptoms and outcome.

### Pathogenesis of ascites formation in the cirrhotic patient

The pathophysiology behind formation of ascites is complex but three key factors are involved: portal hypertension; splanchnic and peripheral arterial vasodilation; and neurohumoral activation [Bernardi and Caraceni, 2001; Gentilini *et al.* 2002].

Cirrhotic ascites primarily develops due to impaired renal sodium excretion leading to a positive sodium balance and hence water retention, causing expansion of the extracellular fluid volume. The decreased sodium excretion is predominantly caused by arterial vasodilation, which triggers neurohumoral responses such as the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS) – responses that cause renal vasoconstriction and sodium retention, and hence development of ascites and edema [Dudley, 1992; Gines *et al.* 1997].

#### Role of portal hypertension

Ascites only develops if moderate portal hypertension is present. Thus, ascites rarely develops if the post sinusoidal pressure gradient is below 12 mmHg [Casado *et al.* 1998]. Portal hypertension leads to increased hydrostatic pressure within the hepatic sinusoids, causing transudation of fluid into the peritoneal cavity [Kravetz *et al.* 2000; Henriksen *et al.* 2005].

Accordingly, the amount of ascitic fluid produced is determined by the magnitude of hydrostatic pressure. Oncotic dynamics (plasma albumin concentration) play only a minor role, if any role, in the rate of ascites formation [Henriksen *et al.* 2001; Moore *et al.* 2006].

Portal hypertension occurs as a consequence of structural changes within the liver in cirrhosis. The degree of portal hypertension is determined by the degree of hepatic vascular resistance and the portal venous inflow. The hepatic vascular resistance is determined by both structural changes such as,

for example, fibrosis and regeneration nodules and dynamic changes [Bosch *et al.* 2003]. The dynamics of the hepatic hemodynamics relate partly to contractile properties of hepatic stellate cells and myofibroblasts [Groszmann *et al.* 2005; Schuppan and Kim, 2013]. These cells may dynamically regulate sinusoidal tone, and hence portal pressure and flow [Rockey, 2001, 2006]. Moreover, data suggest that defective nitric oxide (NO) production and circulation of endogenous vasoconstrictors such as endothelin-1, angiotensin-II, catecholamines and leukotrienes could further aggravate hepatic vascular resistance [Bosch *et al.* 2003; Møller and Henriksen, 2005; Iwakiri and Groszmann, 2006].

#### Role of arterial vasodilation and neurohumoral response

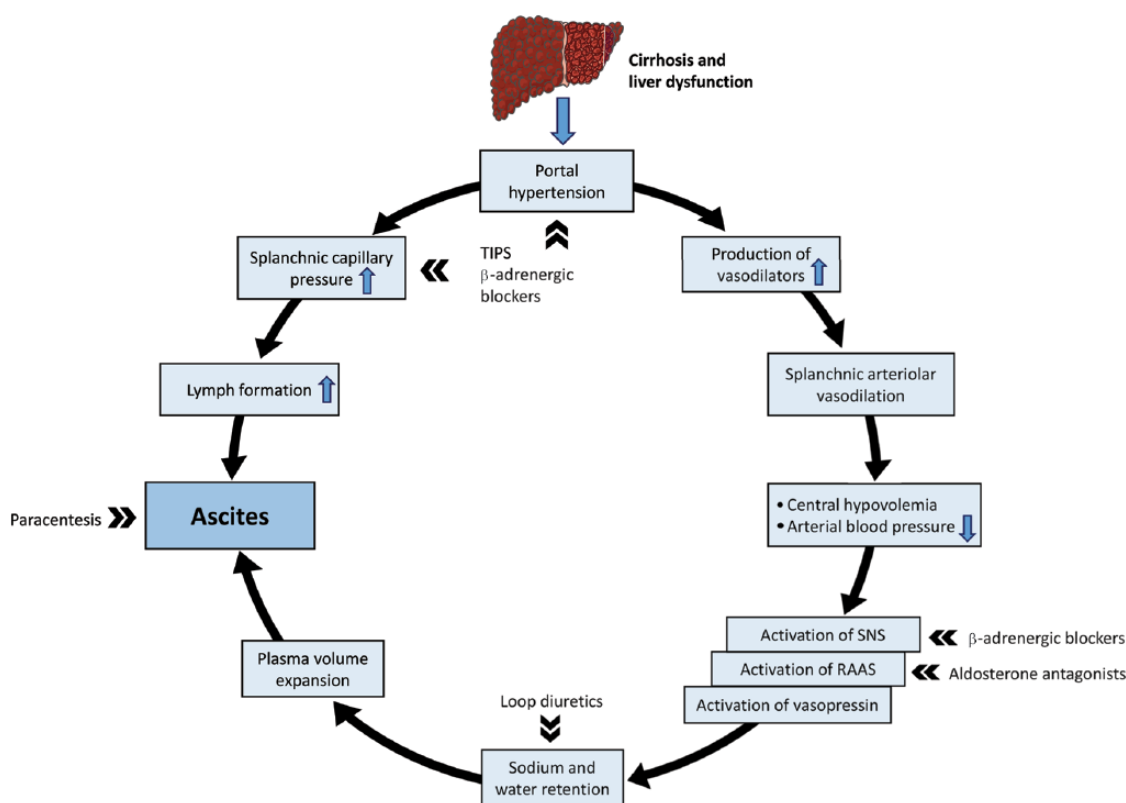
One of the crucial events in the pathogenesis of renal dysfunction and sodium retention is the development of arterial vasodilation. However, the pathophysiological link between portal hypertension and arterial vasodilation still remains to be fully answered. Overproduction of vasodilators due to augmented shear stress in the splanchnic circulation, defective contractile signaling in smooth muscle cells in response to vasoconstrictor stimulation (also termed ‘vascular hypocontractility’) and neurohumoral signals from the liver to the brain are currently the predominant theories [Ferguson *et al.* 2006; Iwakiri and Groszmann, 2007; Hennenberg *et al.* 2008].

The systemic and splanchnic vasodilation seen in cirrhotic patients leads to reduced systemic vascular resistance, decreased effective blood volume, and hence decreased arterial blood pressure.

In order to maintain blood pressure during systemic vasodilation, activation of effective sodium retention and vasoconstricting systems such as the RAAS and SNS are initiated. Nonosmotic release of vasopressin is also commenced [Bernardi and Caraceni, 2001; Møller and Henriksen, 2005; Liu *et al.* 2008].

See Figure 1 for schematic illustration of the pathogenesis behind ascites.

The above-mentioned mechanisms cause hemodynamic changes and result in a hyperdynamic circulation with an increased heart rate and increased cardiac output.



**Figure 1.** Pathogenesis of ascites formation in the cirrhotic patient.

RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TIPS, transjugular intrahepatic portosystemic shunt.

### Renal dysfunction and HRS

Another consequence of the activation of RAAS and SNS is renal vasoconstriction, leading to decreased renal blood flow diminishing the glomerular filtration rate and hence to a progressive impairment of renal function [Dagher and Moore, 2001; Stadlbauer *et al.* 2008; Gines and Schrier, 2009].

Even in very early stages of cirrhotic portal hypertension, the capacity of renal sodium excretion is compromised and these early signs of renal dysfunction are seen before the development of ascites [Bernardi *et al.* 1992; Sansoe *et al.* 1999].

In cirrhotic patients, the free water clearance is dramatically reduced – often below 1 ml/min equivalent to intake of only 1.5 liters of fluid/day before fluid accumulation arises, causing a dilutional hyponatremia (serum sodium <130 mmol/l) [Angeli *et al.* 2006]. Hypervolemic hyponatremia is associated with decreased survival [Luca *et al.* 2007; Kim *et al.* 2008]. The clinical use of vaptans, drugs that cause a selective

blockade of  $V_2$  receptors and increase water excretion, is currently not routinely recommended in cirrhotic patients. Although successful in increasing serum sodium levels, questions regarding their safety and use in cirrhotic patients have been raised [Dahl *et al.* 2012].

With more advanced stages of cirrhosis, progressively increasing sodium and water reabsorption and decreasing renal blood flow and glomerular filtration rate (GFR) often happen in parallel with progression of the liver insufficiency [Wensing *et al.* 1997]. The progressive fall in renal blood flow and GFR may lead to the development of HRS [Arroyo *et al.* 2007]. Approximately 20% of cirrhotic patients with refractory ascites progress to HRS. HRS develops in the response to severe liver – and systemic circulatory – dysfunction.

HRS is defined as a functional prerenal failure, unresponsive to volume expansion in the setting of chronic liver disease with ascites. In HRS there are no significant morphological changes in renal histology and these patients display a largely

normal tubular function [Gines and Schrier, 2009; European Association for the Study of the Liver, 2010]. There are two types of HRS. Type 1 HRS is a rapidly progressing acute renal failure often precipitated by triggering factors such as SBP, septic insult or variceal bleeding causing a swift deterioration of liver and circulatory function and hence HRS [Follo *et al.* 1994; Cardenas *et al.* 2001; Ruiz-Del-Arbol *et al.* 2005; Krag *et al.* 2010]. Type 2 HRS is a more chronic form with a more stable renal dysfunction [Arroyo *et al.* 1996; Gines *et al.* 2003].

The diagnostic criteria for HRS are illustrated in Box 1 [Salerno *et al.* 2007b].

#### Box 1.

International Ascites Club criteria for diagnosis of hepatorenal syndrome in cirrhosis [Salerno *et al.* 2007b].

Cirrhosis with ascites

Serum creatinine > 1.5 mg/dl (133 µmol/l)

Absence of shock

Absence of hypovolemia as defined by no improvement of renal function following at least 2 days of diuretic withdrawal (if on diuretics) and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day

No current or recent treatment with nephrotoxic drugs

Absence of parenchymal renal disease as defined by absence of proteinuria (<0.5 g/day), no microhematuria (<50 red blood cells per high power field) and normal renal ultrasonography

#### Diagnosis of ascites

Suspicion of clinical ascites should be confirmed with abdominal ultrasound. Furthermore, the initial evaluation of a patient with ascites should include medical history, physical examination, and laboratory assessment including electrolytes and liver and renal biochemistry.

Based on these findings the underlying cause of ascites is often obvious. However, if it is the first time the patient presents with ascites, more extensive analysis of the ascitic fluid should be carried out with a view to excluding other causes for ascites formation than cirrhosis and excluding complications such as SBP.

Clinical practice includes determination of the serum albumin ascites gradient (SAAG) (serum

albumin concentration–ascites albumin concentration), which can help differentiate between ascites ascribed to portal hypertension and ascites due to other causes. If the SAAG is  $\geq 1.1$  g/dl (or 11 g/l), ascites is most likely due to portal hypertension [Mauer and Manzione, 1988, Runyon *et al.* 1992].

In general, analysis of the ascitic fluid should always be carried out either by diagnostics paracentesis or, if tense ascites is present, in combination with therapeutic large volume paracentesis (LVP). All patients should be screened for the presence of SBP and ascitic fluid investigations should at least include neutrophil cell count, albumin/protein concentration and ascitic fluid inoculation in blood culture bottles.

An ascitic neutrophil cell count of 250 cells/mm<sup>3</sup> ( $0.25 \times 10^9/l$ ) is diagnostic of SBP and is found in approximately 15% of all patients with cirrhotic ascites admitted to hospital [Caly and Strauss, 1993; Tandon and Garcia-Tsao, 2008].

An ascitic albumin concentration <15 g/l in patients with no prior SBP episodes is associated with an increased risk of development of SBP and these patients should therefore receive prophylactic antibiotics to decrease the risk of SBP episodes [Rimola *et al.* 2000; European Association for the Study of the Liver, 2010].

If clinical suspicion to other underlying causes of ascites, cytological examination (cancer suspicion), ascitic and blood amylase concentration (pancreatic disease), polymerase chain reaction (PCR) and culture for mycobacteria (tuberculosis) should be carried out.

#### Treatment of uncomplicated ascites

Patients with cirrhotic ascites often present with concomitant complications such as SBP, hyponatremia and HRS. Patients without these complications are termed as having ‘uncomplicated ascites’ [Salerno *et al.* 1999].

There is no evidence for treatment of patients with mild ascites (grade 1). Patients with grade 2 ascites do often not acquire hospitalization and can be treated in the outpatient clinic [European Association for the Study of the Liver, 2010]. Grading of ascites and treatment overall strategy is depicted in Table 1.

**Table 1.** Grading of ascites and treatment strategy [European Association for the Study of the Liver, 2010].

Grade of ascites	Definition	Treatment
Grade 1	Mild ascites, only detectable by ultrasound	No treatment
Grade 2	Moderate ascites evident by moderate symmetrical distention of the abdomen	Restriction of sodium intake and diuretics
Grade 3	Large ascites with marked abdominal distension	Large volume paracentesis followed by restriction of sodium intake and diuretics (unless refractory ascites)

#### *Dietary salt restriction, restriction of fluid intake*

Generally patients should be advised to follow a low sodium intake diet to create a negative sodium balance and hence increased mobilization of the fluid retention. From a clinical point of view, restriction of daily sodium intake to 80–120 mmol (corresponding to 4.6–6.9 grams of salt/day) is possible through a ‘no added salt diet’ and avoidance of preprepared foodstuffs. A more rigorous salt restriction is often intolerable to the patients and also may further harm the poor nutritional status often seen in these patients.

Restriction of fluid intake is generally considered an obsolete treatment possibility in patients with uncomplicated ascites. However, water restriction in patients with ascites and hyponatremia has become standard clinical practice in many centers, although controversy remains as to what is the best treatment of these patients. Fluid intake can rarely be restricted to <1 l/day, which is insufficient to cause fluid loss [Gines *et al.* 2008] and furthermore the efficacy of water restriction may depend on the level of hyponatremia [Moore and Aithal, 2006]. Thus, more studies are needed to find the best approach and, until then, water restriction should only be used in few, if any, patients.

#### *Diuretics*

Diuretics remain the standard treatment of cirrhotic ascites. The effect of the diuretics should in the beginning of treatment be assessed with daily control of bodyweight and close monitoring of creatinine and electrolytes to avoid serious electrolyte disturbances and to reduce the risk of diuretic-induced renal failure.

The diuretic treatment should always be initiated with the administration of spironolactone, an aldosterone receptor antagonist.

Spironolactone counteracts the effects of the high circulating levels of aldosterone, facilitating the increased reabsorption of sodium in the distal tubules of the kidneys. Thus, spironolactone accelerates the natriuresis and is more effective than loop diuretics in patients with cirrhotic ascites [Eggert, 1970; Perez-Ayuso *et al.* 1983]. The initial dose should start at 100 mg/day gradually increasing with 100 mg/week until adequate natriuresis is achieved. The effect of spironolactone is seen after 3–5 days of treatment and the maximum recommended dose of spironolactone is 400 mg/day.

Patients with a first episode of grade 2 ascites should initially only be treated with an aldosterone antagonist [Santos *et al.* 2003; Bernardi, 2010]. However, it is often necessary to add loop diuretics (e.g. furosemide) to counteract the potassium sparing effects of aldosterone antagonists resulting in hyperkalemia.

Also, in case of an insufficient response (defined by reduction in bodyweight of <2 kg/week) to spironolactone alone, loop diuretics should be added in a stepwise manner every 2–3 days to a maximum of 160 mg/day.

In patients with recurrent ascites, studies have concluded that the combination of an aldosterone antagonist and loop diuretics is the preferred regimen since the combination therapy increases the natriuretic effect [Angeli *et al.* 2010; Bernardi, 2010].

Furosemide alone is not recommended since efficacy in cirrhotic patients is low [Perez-Ayuso *et al.* 1983].

To avoid intravascular volume depletion and risk of renal impairment, hepatic encephalopathy and hyponatremia, diuretic dosage should be adjusted



**Table 2.** Definition and diagnostics criteria for refractory ascites in cirrhosis [Salerno *et al.* 2010].

Diuretic-resistant ascites	Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of 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.
Fundamentals	
1. Treatment duration	Patients must be on intensive diuretic therapy (spironolactone 400 mg/day and furosemide 160 mg/day) for at least 1 week and on a sodium-restricted diet of <90 mmol/day.
2. Lack of response	Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake.
3. Early ascites recurrence	Reappearance of grade 2 or grade 3 ascites within 4 weeks of initial mobilization.
4. Diuretic-induced complications	<ul style="list-style-type: none"> <li>- Diuretic-induced hepatic encephalopathy: the development of encephalopathy in the absence of any other precipitating factor</li> <li>- Diuretic-induced renal impairment: increase in serum creatinine by &gt;100% to a value of &gt;2 mg/dl (177 µmol/l) in patients with ascites responding to treatment</li> <li>- Diuretic-induced hyponatremia: decrease of serum sodium by &gt;10 mmol/l to a serum sodium level of &lt;125 mmol/l</li> <li>- Diuretic-induced hypo- or hyperkalemia: change in serum potassium to &lt;3 mmol/l or &gt;6 mmol/l despite appropriate measures</li> </ul>

to a daily weight loss of no more than 500 g/day in patients without peripheral edema and 1 kg/day in patients with peripheral edema [Shear *et al.* 1970; Pockros and Reynolds, 1986; Gines *et al.* 2004].

After mobilization of ascites, the least effective dosage of diuretics should be sought to reduce the risk of diuretic-induced complications and to minimize side effects. Furthermore, total alcohol abstinence is a key element in avoidance of recurrence of ascites in alcoholic cirrhosis.

Patients with ascites that cannot be mobilized despite intensive diuretic treatment and sodium restriction diet are termed 'diuretic resistant'. Approximately, 10% become refractory to diuretic treatment and other treatment modalities should be considered [Moore and Aithal, 2006]. Diuretic intractable ascites is characterized by diuretic-induced complications such as encephalopathy and hyponatremia that preclude the use of an effective diuretic dosage. See Table 2 for the definition and diagnostic criteria for diuretic-resistant ascites and diuretic intractable ascites.

#### Therapeutic paracentesis

In patients with large grade 3 ascites or refractory ascites, LVP rapidly removes tense ascites and is the treatment of choice. A patient with tense ascites is seen in Figure 2. LVP should be completed in a single session, with the needle preferably inserted in the left iliac fossa under strict sterile conditions. LVP can often be managed in the outpatient clinic.

Several controlled clinical studies have demonstrated that LVP with albumin substitution is rapid, safe and effective [Quintero *et al.* 1985; Gines *et al.* 1987b; Salerno *et al.* 1987]. In general LVP is a low-risk procedure and local complications such as hemorrhage (even though coagulopathy is often evident) or perforation of the bowel are low [Pache and Bilodeau, 2005]. Coagulopathy is not a contraindication for LVP and there are no data supporting the use of prophylactic fresh frozen plasma and platelets before or during LVP.

LVP >5 l should always be followed by intravenous administration of human albumin (HA) to



**Figure 2.** Patient with tense ascites.

reduce the risk of development of postparacentesis circulatory dysfunction (PPCD) due to rapid decrease in effective arterial blood volume [Gines *et al.* 1988; Pozzi *et al.* 1994]. PPCD can cause rapid reappearance of ascites, renal failure and HRS, dilutional hyponatremia and increased mortality risk [Gines *et al.* 1988, 1996; Sola *et al.* 1994]. To prevent development of PPCD, 20% HA infusion is recommended after paracentesis at a dose of 8 g/l ascites removed [Runyon, 2009; European Association for the Study of the Liver, 2010]. HA is generally preferred over other plasma expanders, since it is more effective when more than 5 l of ascites is removed [Gines *et al.* 1996].

However, paracentesis does not address the underlying cause of ascites (renal sodium and water reabsorption) and ascites will re-occur in 93% of patients if treatment with diuretics is not reinstated [Fernandez-Esparrach *et al.* 1997].

### Treatment of refractory ascites

Refractory ascites is defined as ‘ascites that cannot be mobilized or the early recurrence of which (i.e. after LVP) cannot be satisfactorily prevented by medical therapy’ [Moore *et al.* 2003]. These patients are primarily treated with repeated LVPs. Once ascites has become refractory to diuretics,

the median survival is poor – approximately 50% die within the next 6 months. Emerging data suggest that use of nonselective beta-blockers (prevention of oesophageal variceal bleeding) in cirrhotic patients with refractory ascites is associated with poorer outcome and caution regarding nonselective beta-blocker indication and dosage should probably be considered thoroughly in these patients [Sersté *et al.* 2010; Krag and Madsen, 2014].

Patients with refractory ascites should in general be considered for liver transplantation.

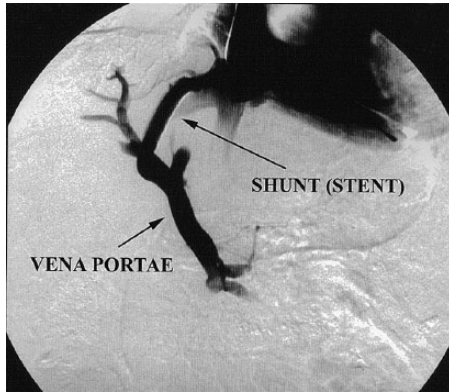
It is a frequent asked question whether diuretics should be continued in patients with refractory ascites. However, discontinuation or at least reduction of diuretics should happen in all patients with diuretic-induced complications such as severe electrolyte disturbances, renal impairment and development of overt hepatic encephalopathy. In the remaining patients, measuring the urine sodium concentration will determine if the diuretic therapy should be discontinued. If the urinary sodium excretion under diuretic therapy is below 30 mmol/day, the natriuretic effect is not sufficient and diuretics might as well be discontinued [Moore *et al.* 2003].

### TIPS

In case of recurrent ascites and requirement of frequent LVPs (>3/month), insertion of TIPS should be considered. TIPS functions as a side-to-side portocaval anastomosis between the high pressure portal vein side and low pressure hepatic vein side, and effectively decompresses the portal system. The decrease in portal hypertension results in a secondary decrease in the activation of RAAS, leading to an increased sodium excretion [Rossle *et al.* 1998]. Figure 3 depicts a TIPS.

Compared with repeated LVP, TIPS is considered a more effective treatment option for the control of ascites [Rossle *et al.* 2000; Gines *et al.* 2002; Salerno *et al.* 2007a] and complete resolution of ascites is seen in up to 75% of patients [Ochs *et al.* 1995].

However, the effect of TIPS on survival in patients with refractory ascites has not been clearly demonstrated. Three meta-analyses have all failed to demonstrate a difference in survival between TIPS and LVP groups [Albillos *et al.* 2005; Deltenre *et al.* 2005; Saab *et al.* 2006]; one meta-analysis



**Figure 3.** Transjugular intrahepatic portosystemic shunt. The shunt (stent) is inserted between the vena portae and the hepatic vein.

showed a trend towards reduced mortality for TIPS patients and one showed increased transplant-free survival in the TIPS groups [D'Amico *et al.* 2005; Salerno *et al.* 2007a]. Post-TIPS mortality is predicted by the indication for the TIPS procedure; patients with refractory ascites have decreased survival compared with the group of patients with variceal bleeding as the main indication for the TIPS procedure [Angemayr *et al.* 2003]. In general post-TIPS mortality risk is primarily predicted by high bilirubin levels ( $>3$  mg/dl) [D'Amico *et al.* 2005; Gerbes *et al.* 2005] and high MELD score (Model of Endstage Liver Disease) [Angemayr *et al.* 2003].

An important challenge with the insertion of TIPS is the increased risk of development of hepatic encephalopathy which occurs in 25–30%, the risk increasing with age [Sanyal *et al.* 1994; Casado *et al.* 1998]. Previous episodes of hepatic encephalopathy are a contraindication for insertion of TIPS. TIPS can be considered in patients with refractory ascites with  $>3$  LVPs/month, but appropriate risk assessment prior to TIPS is essential.

### Treatment of complicated ascites

Complicated ascites is defined as ascites with complications of one or more of the following: SBP, HRS and Hyponatremia. Management of Hyponatremia has previously been mentioned briefly.

### SBP

All patients with cirrhosis and ascites are at risk of developing SBP. A routine cell count from the

ascitic fluid obtained either at diagnostic or therapeutic paracentesis should always be done to rule out SBP.

Symptoms of SBP include abdominal pain, fever and vomiting. Diagnosis should also be suspected in patients with worsening of liver function, hepatic encephalopathy, renal failure and/or gastrointestinal bleeding but SBP is frequently asymptomatic.

Previously, mortality exceeded 90% but with early diagnosis and current treatment strategies mortality has been reduced to approximately 20% [Garcia-Tsao, 2001; Tandon and Garcia-Tsao, 2008].

Inoculation of ascitic fluid in blood culture bottles often display *Escherichia coli* and *Streptococcus* species [Tandon and Garcia-Tsao, 2008], although ascites culture is negative in as many as 60% of patients, despite both clinical signs of SBP and neutrophil cell count  $>250$  cells/ $\mu$ l. These patients should still be treated as having SBP [Rimola *et al.* 2000].

### Treatment of SBP

Since antibiotic resistance is an increasing challenge, ascitic fluid and blood inoculation + assessment regarding susceptibility to antibiotics prior to antibiotic treatment should always be performed. Empiric antibiotic treatment should be started immediately after diagnosis of SBP. Third generation cephalosporins such as cefotaxim cover most causative organisms and are often the treatment of choice [Felisart *et al.* 1985; Rimola *et al.* 1995]. Administration of 2 g intravenously twice a day is often preferred; a 5-day therapy is as effective as a 10-day therapy [Runyon *et al.* 1991]. Alternatively piperacillin/tazobactam could be considered [Novovic *et al.* 2012].

Patients with SBP and signs of hepatic dysfunction (bilirubin  $> 66$   $\mu$ mol/l) or signs of renal impairment should further be given HA at 1.5 g albumin/kg in the first 6 hours followed by 1 g/kg on day 3 since HA infusion reduces the risk of HRS [Sort *et al.* 1999]. Furthermore, the beneficial effect of administering HA to the cirrhotic patient is probably also attributable to the albumin binding capacity of circulating pro-inflammatory and bacterial products such as prostaglandins (PGE<sub>2</sub>) and lipopolysaccharide. Consequently HA may play an important role as modulator of



the systemic and organ related inflammation evident in patients with decompensated cirrhosis [Arroyo *et al.* 2014; O'Brien *et al.* 2014].

The risk of re-infection is high and secondary prophylaxis with, for example, oral norfloxacin 400 mg daily, significantly reduces the risk of future SBP episodes [Gines *et al.* 1990].

Patients with low ascitic albumin concentration <15 g/l and severe liver disease without previous SBP episodes should be considered for primary prophylactic treatment with, for example, norfloxacin 400 mg daily, which reduces risk of SBP and improves survival [Fernandez *et al.* 2007].

### Hepatorenal failure

Type 1 HRS is a rapidly progressing acute renal failure evolving in the setting of a precipitating factor, further augmenting circulatory dysfunction, whereas type 2 HRS is a more slowly progression of renal failure seen in patients with refractory ascites.

Early diagnosis of HRS 1 is important to improve short-term survival, which untreated is of only 1 month. Median survival of type 2 HRS is 6 months [Alessandria *et al.* 2005]. See Table 1 for diagnostic criteria.

#### Treatment of hepatorenal failure

Patients with suspicion of HRS 1 should be monitored closely by urine output, fluid balance, arterial blood pressure and vital surveillance. Infections should be treated and diuretics should be discontinued.

The specific treatment of HRS 1 should be aimed at decreasing splanchnic arterial vasodilation, decreasing central hypovolemia and increasing renal blood flow. Administration of vasoconstrictor drugs such as terlipressin, which acts as a vasopressin analogue, stimulates the splanchnic vasopressin  $V_{1a}$  receptors. Terlipressin induces constriction of the extremely dilated splanchnic vascular bed, thereby improving the central underfilling and increasing the arterial blood pressure [Moreau and Lebrec, 2006; Gines *et al.* 2007]. Terlipressin can only be administered intravenously and is started at a dose of 1 mg/4–6 hours and increased to a maximum of 2 mg/4 hours, if there is no reduction in serum creatinine of at least 25% on day 3 compared with serum

creatinine baseline value. Treatment is effective in 40–50% of patients and is associated with increased short-term survival [Gines and Schrier, 2009; Gluud *et al.* 2010]. Patients receiving terlipressin should be monitored for development of cardiac arrhythmias, acute myocardial infarction, and signs of splanchnic or digital ischemia.

HA should in addition be administered with 1 g/kg the first day followed by 20 g twice a day [Ortega *et al.* 2002]. Treatment with terlipressin and albumin should be continued until normalization of serum creatinine (below 133  $\mu\text{mol/l}$ ) is achieved. If HRS 1 redevelops, treatment can be repeated [European Association for the Study of the Liver, 2010].

Hemodialysis (in combination with terlipressin) is frequently used to control azotemia and electrolyte balance before eventual liver transplantation, which should be considered in all patients with HRS who have no contraindications to the procedure [Runyon, 2009].

Terlipressin does not seem to have a sustained effect in type 2 HRS [Gluud *et al.* 2012].

Use of albumin dialysis [molecular adsorbent recirculating system (MARS)] in patients with ACLF has failed to show improved survival in randomized controlled trials [Banares *et al.* 2013].

Despite treatment, the prognosis of HRS remains poor with a median survival of all patients with HRS of only 3 months [Gines and Schrier, 2009].

### Perspectives and conclusion

Management of cirrhotic ascites and its complications remain an everyday clinical challenge for hepatologists. Although advances in medical therapy have been made, the development of ascites is still associated with poor prognosis and markedly increased mortality.

Adequate management of ascites is important since this not only improves quality of life in these patients, but also decreases risks of complications such as SBP. Several up-to-date clinical guidelines are available [Runyon, 2009; European Association for the Study of the Liver, 2010].

Future strategies should approach target different aspects of the pathophysiological process resulting in splanchnic arterial vasodilation, central

hypovolemia and decreased arterial blood pressure. Development of long-acting systemic vasoconstrictors should be encouraged. Optimization of the treatment strategies will hopefully result in better management of ascites with fewer side effects and complications leading to an improved survival.

All patients with ascites should be considered as liver transplant candidates, since liver transplantation still remains the ultimate treatment for these patients.

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The authors declare no conflict of interest in preparing this article.

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### References

- Albillos, A., Banares, R., Gonzalez, M., Catalina, M. and Molinero, L. (2005) A meta-analysis of transjugular intrahepatic portosystemic shunt versus paracentesis for refractory ascites. *J Hepatol* 43: 990–996.
- Alessandria, C., Ozdogan, O., Guevara, M., Restuccia, T., Jimenez, W., Arroyo, V. *et al.* (2005) Meld Score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology* 41: 1282–1289.
- Angeli, P., Fasolato, S., Mazza, E., Okolicsanyi, L., Maresio, G., Velo, E. *et al.* (2010) Combined versus sequential diuretic treatment of ascites in non-azotaemic patients with cirrhosis: results of an open randomised clinical trial. *Gut* 59: 98–104.
- Angeli, P., Rodriguez, E., Piano, S., Ariza, X., Morando, F., Solà, E. *et al.* (2014) Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. *Gut*. DOI: 10.1136/gutjnl-2014-307526.
- Angeli, P., Wong, F., Watson, H., Gines, P; CAPPS Investigators (2006) Hyponatremia in cirrhosis: results of a patient population survey. *Hepatology* 44: 1535–1542.
- Angemayr, B., Cejna, M., Karnel, F., Gschwantler, M., Koenig, F., Pidlich, J. *et al.* (2003) Child-pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt. *Gut* 52: 879–885.
- Arroyo, V., Garcia-Martinez, R. and Salvatella, X. (2014) Human serum albumin, systemic inflammation and cirrhosis. *J Hepatol* 61: 396–407.
- Arroyo, V., Gines, P., Gerbes, A., Dudley, F., Gentilini, P., Laffi, G. *et al.* (1996) Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology* 23: 164–176.
- Arroyo, V., Terra, C. and Gines, P. (2007) Advances in the pathogenesis and treatment of type-1 and type-2 hepatorenal syndrome. *J Hepatol* 46: 935–946.
- Banares, R., Nevens, F., Larsen, F., Jalan, R., Albillos, A., Dollinger, M. *et al.* (2013) Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: The RELIEF trial. *Hepatology* 57: 1153–1162.
- Bernardi, M. (2010) Optimum use of diuretics in managing ascites in patients with cirrhosis. *Gut* 59: 10–11.
- Bernardi, M. and Caraceni, P. (2001) Pathogenesis of ascites and hepatorenal syndrome: altered haemodynamics and neurohumoral systems. In: Gerbes, A., Beuers, U., Jünger, D., Pape, G., Sackmann, M. and Sauerbruch, T. (eds), *Falk Symposium 117. Hepatology 2000. Symposium in Honour of Gustav Paumgartner*, Munich, 6–8 May 2000. Dordrecht: Kluwer Academic Publishers, pp. 185–203.
- Bernardi, M., Di Marco, C., Trevisani, F., De Collibus, C., Fornale, L., Baraldini, M. *et al.* (1992) The hemodynamic status of preascitic cirrhosis: an evaluation under steady-state conditions and after postural change. *Hepatology* 16: 341–346.
- Bosch, J., Abraldes, J. and Groszmann, R. (2003) Current management of portal hypertension. *J Hepatol* 38(Suppl. 1): S54–S68.
- Caly, W. and Strauss, E. (1993) A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol* 18: 353–358.
- Cardenas, A., Gines, P., Uriz, J., Bessa, X., Salmeron, J., Mas, A. *et al.* (2001) Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. *Hepatology* 34: 671–676.
- Casado, M., Bosch, J., Garcia-Pagan, J., Bru, C., Banares, R., Bandi, J. *et al.* (1998) Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. *Gastroenterology* 114: 1296–1303.
- D’Amico, G., Luca, A., Morabito, A., Miraglia, R. and D’Amico, M. (2005) Uncovered transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis. *Gastroenterology* 129: 1282–1293.

- Dagher, L. and Moore, K. (2001) The hepatorenal syndrome. *Gut* 49: 729–737.
- Dahl, E., Gluud, L., Kimer, N. and Krag, A. (2012) Meta-analysis: the safety and efficacy of vaptans (tolvaptan, satavaptan and lixivaptan) in cirrhosis with ascites or hyponatraemia. *Aliment Pharmacol Ther* 36: 619–626.
- Deltenre, P., Mathurin, P., Dharancy, S., Moreau, R., Bulois, P., Henrion, J. *et al.* (2005) Transjugular intrahepatic portosystemic shunt in refractory ascites: a meta-analysis. *Liver Int* 25: 349–356.
- Dudley, F. (1992) Pathophysiology of ascites formation. *Gastroenterol Clin North Am* 21: 215–235.
- Eggert, R. (1970) Spironolactone diuresis in patients with cirrhosis and ascites. *Br Med J* 4: 401–403.
- European Association for the Study of the Liver (2010) EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 53: 397–417.
- Felisart, J., Rimola, A., Arroyo, V., Perez-Ayuso, R., Quintero, E., Gines, P. *et al.* (1985) Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology* 5: 457–462.
- Ferguson, J., Dover, A., Chia, S., Cruden, N., Hayes, P. and Newby, D. (2006) Inducible nitric oxide synthase activity contributes to the regulation of peripheral vascular tone in patients with cirrhosis and ascites. *Gut* 55: 542–546.
- Fernandez, J., Navasa, M., Planas, R., Montoliu, S., Monfort, D., Soriano, G. *et al.* (2007) Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 133: 818–824.
- Fernandez-Esparrach, G., Guevara, M., Sort, P., Pardo, A., Jimenez, W., Gines, P. *et al.* (1997) Diuretic requirements after therapeutic paracentesis in non-azotemic patients with cirrhosis. A Randomized double-blind trial of spironolactone versus placebo. *J Hepatol* 26: 614–620.
- Fernandez-Esparrach, G., Sanchez-Fueyo, A., Gines, P., Uriz, J., Quinto, L., Ventura, P. *et al.* (2001) A prognostic model for predicting survival in cirrhosis with ascites. *J Hepatol* 34: 46–52.
- Follo, A., Llovet, J., Navasa, M., Planas, R., Forns, X., Francitorra, A. *et al.* (1994) Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 20: 1495–1501.
- Garcia-Tsao, G. (2001) Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology* 120: 726–748.
- Gentilini, P., Vizzutti, F., Gentilini, A., Zipoli, M., Foschi, M. and Romanelli, R. (2002) Update on ascites and hepatorenal syndrome. *Dig Liver Dis* 34: 592–605.
- Gerbes, A. and Gülberg, V. (2005) Benefit of TIPS for patients with refractory ascites or recidivant ascites: serum bilirubin may make the difference. *Hepatology* 41: 217.
- Gines, A., Fernandez-Esparrach, G., Monescillo, A., Vila, C., Domenech, E., Abecasis, R. *et al.* (1996) Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 111: 1002–1010.
- Gines, A., Escorsell, A., Gines, P., Salo, J., Jimenez, W., Inglada, L. *et al.* (1993) Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. *Gastroenterology* 105: 229–236.
- Gines, P., Arroyo, V., Quintero, E., Planas, R., Bory, F., Cabrera, J. *et al.* (1987b) Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites. Results of a randomized study. *Gastroenterology* 93: 234–241.
- Gines, P. and Cardenas, A. (2008) The management of ascites and hyponatremia in cirrhosis. *Semin Liver Dis* 28: 43–58.
- Gines, P., Cardenas, A., Arroyo, V. and Rodes, J. (2004) Management of cirrhosis and ascites. *N Engl J Med* 350: 1646–1654.
- Gines, P., Fernandez-Esparrach, G., Arroyo, V. and Rodes, J. (1997) Pathogenesis of ascites in cirrhosis. *Semin Liver Dis* 17: 175–189.
- Gines, P. and Guevara, M. (2007) Therapy with vasoconstrictor drugs in cirrhosis: the time has arrived. *Hepatology* 46: 1685–1687.
- Gines, P., Guevara, M., Arroyo, V. and Rodes, J. (2003) Hepatorenal syndrome. *Lancet* 362: 1819–1827.
- Gines, P., Quintero, E., Arroyo, V., Teres, J., Bruguera, M., Rimola, A. *et al.* (1987a) Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 7: 122–128.
- Gines, P., Rimola, A., Planas, R., Vargas, V., Marco, F., Almela, M. *et al.* (1990) Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 12: 716–724.
- Gines, P. and Schrier, R. (2009) Renal failure in cirrhosis. *N Engl J Med* 361: 1279–1290.
- Gines, P., Tito, L., Arroyo, V., Planas, R., Panes, J., Viver, J. *et al.* (1988) Randomized comparative

- study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology* 94: 1493–1502.
- Gines, P., Uriz, J., Calahorra, B., Garcia-Tsao, G., Kamath, P., Del Arbol, L. *et al.* (2002) Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. *Gastroenterology* 123: 1839–1847.
- Gluud, L., Christensen, K., Christensen, E. and Krag, A. (2010) Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 51: 576–584.
- Gluud, L., Christensen, K., Christensen, E. and Krag, A. (2012) Terlipressin for hepatorenal syndrome. *Cochrane Database Syst Rev* 9: CD005162.
- Groszmann, R. and Abraldes, J. (2005) Portal hypertension: from bedside to bench. *J Clin Gastroenterol* 39: S125–S130.
- Guarner, C. and Soriano, G. (2005) bacterial translocation and its consequences in patients with cirrhosis. *Eur J Gastroenterol Hepatol* 17: 27–31.
- Guevara, M., Cárdenas, A., Uriz, J. and Ginès, P. (2005) Prognosis in patients with cirrhosis and ascites. In: Ginès, P., Arroyo, V., Rodés, J. and Schrier, R., (eds), *Ascites and Renal Dysfunction in Liver Disease: Pathogenesis, Diagnosis, and Treatment*, 2nd edn. Malden, MA: Blackwell Publishing, Chapter 21.
- Hennenberg, M., Trebicka, J., Sauerbruch, T. and Heller, J. (2008) Mechanisms of extrahepatic vasodilation in portal hypertension. *Gut* 57: 1300–1314.
- Henriksen, J. and Møller, S. (2005) *Alterations of Hepatic and Splanchnic Microvascular Exchange in Cirrhosis: Local Factors in the Formation of Ascites*. Malden, MA: Blackwell Publishing.
- Henriksen, J., Siemssen, O., Krintel, J., Malchow-Møller, A., Bendtsen, F. and Ring-Larsen, H. (2001) Dynamics of albumin in plasma and ascitic fluid in patients with cirrhosis. *J Hepatol* 34: 53–60.
- Iwakiri, Y. and Groszmann, R. (2006) The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology* 43: S121–S131.
- Iwakiri, Y. and Groszmann, R. (2007) Vascular endothelial dysfunction in cirrhosis. *J Hepatol* 46: 927–934.
- Kim, W., Biggins, S., Kremers, W., Wiesner, R., Kamath, P., Benson, J. *et al.* (2008) Hyponatremia and mortality among patients on the liver-transplant waiting List. *N Engl J Med* 359: 1018–1026.
- Krag, A., Bendtsen, F., Henriksen, J. and Møller, S. (2010) Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. *Gut* 59: 105–110.
- Krag, A. and Madsen, B. (2014) To block or not to block in advanced cirrhosis: that is the question. *Gut*. DOI: 10.1136/gutjnl-2014-308424.
- Kravetz, D., Bildoza, M., Argonz, J., Romero, G., Korula, J., Munoz, A. *et al.* (2000) Patients with ascites have higher variceal pressure and wall tension than patients without ascites. *Am J Gastroenterol* 95: 1770–1775.
- Liu, H., Schuelert, N., Mcdougall, J. and Lee, S. (2008) Central neural activation of hyperdynamic circulation in portal hypertensive rats depends on vagal afferent nerves. *Gut* 57: 966–973.
- Luca, A., Angermayr, B., Bertolini, G., Koenig, F., Vizzini, G., Ploner, M. *et al.* (2007) An integrated meld model including serum sodium and age improves the prediction of early mortality in patients with cirrhosis. *Liver Transplant* 13: 1174–1180.
- Mauer, K. and Manzione, N. (1988) Usefulness of serum-ascites albumin difference in separating transudative from exudative ascites. Another look. *Dig Dis Sci* 33: 1208–1212.
- Møller, S. and Henriksen, J. (2005) *The Systemic Circulation in Cirrhosis*. Malden, Ma: Blackwell Publishing.
- Moore, K. and Aithal, G. (2006) Guidelines on the management of ascites in cirrhosis. *Gut* 55(Suppl. 6): vi1–vi12.
- Moore, K., Wong, F., Gines, P., Bernardi, M., Ochs, A., Salerno, F. *et al.* (2003) The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 38: 258–266.
- Moreau, R. and Lebrec, D. (2006) The use of vasoconstrictors in patients with cirrhosis: type 1 HRS and beyond. *Hepatology* 43: 385–394.
- Novovic, S., Semb, S., Olsen, H., Moser, C., Knudsen, J. and Homann, C. (2012) First-line treatment with cephalosporins in spontaneous bacterial peritonitis provides poor antibiotic coverage. *Scand J Gastroenterol* 47: 212–216.
- O'Brien, A., Fullerton, J., Massey, K., Auld, G., Sewell, G., James, S. *et al.* (2014) Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. *Nat Med* 20: 518–523.
- Ochs, A., Rossle, M., Haag, K., Hauenstein, K., Deibert, P., Siegerstetter, V. *et al.* (1995) The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. *N Engl J Med* 332: 1192–1197.




- Ortega, R., Gines, P., Uriz, J., Cardenas, A., Calahorra, B., De Las Heras, D. *et al.* (2002) Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology* 36: 941–948.
- Pache, I. and Bilodeau, M. (2005) Severe haemorrhage following abdominal paracentesis for ascites in patients with liver disease. *Aliment Pharmacol Ther* 21: 525–529.
- Perez-Ayuso, R., Arroyo, V., Planas, R., Gaya, J., Bory, F., Rimola, A. *et al.* (1983) Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-aldosterone system. *Gastroenterology* 84: 961–968.
- Pockros, P. and Reynolds, T. (1986) Rapid diuresis in patients with ascites from chronic liver disease: the importance of peripheral edema. *Gastroenterology* 90: 1827–1833.
- Pozzi, M., Osculati, G., Boari, G., Serboli, P., Colombo, P., Lambrugh, C. *et al.* (1994) Time course of circulatory and humoral effects of rapid total paracentesis in cirrhotic patients with tense, refractory ascites. *Gastroenterology* 106: 709–719.
- Quintero, E., Gines, P., Arroyo, V., Rimola, A., Bory, F., Planas, R. *et al.* (1985) Paracentesis versus diuretics in the treatment of cirrhotics with tense ascites. *Lancet* 1: 611–612.
- Rimola, A., Garcia-Tsao, G., Navasa, M., Piddock, L., Planas, R., Bernard, B. *et al.* (2000) Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol* 32: 142–153.
- Rimola, A., Salmeron, J., Clemente, G., Rodrigo, L., Obrador, A., Miranda, M. *et al.* (1995) Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. *Hepatology* 21: 674–679.
- Ripoll, C., Groszmann, R., Garcia-Tsao, G., Grace, N., Burroughs, A., Planas, R. *et al.* (2007) Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 133: 481–488.
- Rockey, D. (2001) Hepatic blood flow regulation by stellate cells in normal and injured liver. *Semin Liver Dis* 21: 337–349.
- Rockey, D. (2006) Hepatic fibrosis, stellate cells, and portal hypertension. *Clin Liver Dis* 10: 459–479, vii–viii.
- Rossle, M., Ochs, A., Gulberg, V., Siegerstetter, V., Holl, J., Deibert, P. *et al.* (2000) A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med* 342: 1701–1707.
- Rossle, M., Siegerstetter, V., Huber, M. and Ochs, A. (1998) The first decade of the transjugular intrahepatic portosystemic shunt (TIPS): state of the art. *Liver* 18: 73–89.
- Ruiz-Del-Arbol, L., Monescillo, A., Arocena, C., Valer, P., Gines, P., Moreira, V. *et al.* (2005) Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology* 42: 439–447.
- Runyon, B. (2009) Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 49: 2087–2107.
- Runyon, B., McHutchison, J., Antillon, M., Akriviadis, E. and Montano, A. (1991) Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. *Gastroenterology* 100: 1737–1742.
- Runyon, B., Montano, A., Akriviadis, E., Antillon, M., Irving, M. and Mchutchison, J. (1992) The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. *Ann Intern Med* 117: 215–220.
- Saab, S., Nieto, J., Lewis, S. and Runyon, B. (2006) TIPS versus paracentesis for cirrhotic patients with refractory ascites. *Cochrane Database Syst Rev*: CD004889.
- Salerno, F., Angeli, P., Bernardi, M., Laffi, G., Riggio, O. and Salvagnini, M. (1999) Clinical practice guidelines for the management of cirrhotic patients with ascites. Committee on Ascites of the Italian Association for the Study of the Liver. *Ital J Gastroenterol Hepatol* 31: 326–334.
- Salerno, F., Badalamenti, S., Incerti, P., Tempini, S., Restelli, B., Bruno, S. *et al.* (1987) Repeated paracentesis and i.v. albumin infusion to treat ‘tense’ ascites in cirrhotic patients. A safe alternative therapy. *J Hepatol* 5: 102–108.
- Salerno, F., Camma, C., Enea, M., Rossle, M. and Wong, F. (2007a) Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. *Gastroenterology* 133: 825–834.
- Salerno, F., Gerbes, A., Ginés, P., Wong, F. and Arroyo, V. (2007b) Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut* 56: 1310–1318.
- Salerno, F., Guevara, M., Bernarid, M., Moreau, R., Wong, F., Angeli, P. *et al.* (2010) Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. *Liver Int* 30: 937–947.



- Sansoe, G., Ferrari, A., Baraldi, E., Castellana, C.N., De Santis, M. and Manenti, F. (1999) Renal distal tubular handling of sodium in central fluid volume homeostasis in preascitic cirrhosis. *Gut* 45: 750–755.
- Santos, J., Planas, R., Pardo, A., Durandez, R., Cabre, E., Morillas, R. *et al.* (2003) Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety. *J Hepatol* 39: 187–192.
- Sanyal, A., Freedman, A., Shiffman, M., Purdum, P., 3rd, Luketic, V. and Cheatham, A. (1994) Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study. *Hepatology* 20: 46–55.
- Schuppan, D. and Kim, Y. (2013) Evolving therapies for liver fibrosis. *J Clin Invest* 123: 1887–1901.
- Sersté, T., Melot, C., Francoz, C., Durand, F., Rautou, P., Valla, D. *et al.* (2010) Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology* 52: 1017–1022.
- Shear, L., Ching, S. and Gabuzda, G. (1970) Compartmentalization of ascites and edema in patients with hepatic cirrhosis. *N Engl J Med* 282: 1391–1396.
- Sola, R., Vila, M., Andreu, M., Oliver, M., Coll, S., Gana, J. *et al.* (1994) Total paracentesis with dextran 40 vs diuretics in the treatment of ascites in cirrhosis: a randomized controlled study. *J Hepatol* 20: 282–288.
- Sort, P., Navasa, M., Arroyo, V., Aldeguer, X., Planas, R., Ruiz-Del-Arbol, L. *et al.* (1999) Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 341: 403–409.
- Stadlbauer, V., Wright, G., Banaji, M., Mukhopadhyaya, A., Mookerjee, R., Moore, K. *et al.* (2008) Relationship between activation of the sympathetic nervous system and renal blood flow autoregulation in cirrhosis. *Gastroenterology* 134: 111–119.
- Tandon, P. and Garcia-Tsao, G. (2008) Bacterial infections, sepsis, and multiorgan failure in cirrhosis. *Semin Liver Dis* 28: 26–42.
- Wensing, G., Lotterer, E., Link, I., Hahn, E. and Fleig, W. (1997) Urinary sodium balance in patients with cirrhosis: relationship to quantitative parameters of liver function. *Hepatology* 26: 1149–1155.
- Wiest, R. and Garcia-Tsao, G. (2005) Bacterial translocation (Bt) in cirrhosis. *Hepatology* 41: 422–433.
- Wiest, R., Lawson, M. and Geuking, M. (2014) Pathological bacterial translocation in liver cirrhosis. *J Hepatol* 60: 197–209.

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