

Review

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Fluid retention in cirrhosis: pathophysiology and management

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Summary

Accumulation of fluid as ascites is the most common complication of cirrhosis. This is occurring in about 50% of patients within 10 years of the diagnosis of cirrhosis. It is a prognostic sign with 1-year and 5-year survival of 85% and 56%, respectively. The most acceptable theory for ascites formation is peripheral arterial vasodilation leading to underfilling of circulatory volume. This triggers the baroreceptor-mediated activation of renin-angiotensin-aldosterone system, sympathetic nervous system and nonosmotic release of vasopressin to restore circulatory integrity. The result is an avid sodium and water retention, identified as a preascitic state. This condition will evolve in overt fluid retention and ascites, as the liver disease progresses. Once ascites is present, most therapeutic modalities are directed on maintaining negative sodium balance, including salt restriction,

bed rest and diuretics. Paracentesis and albumin infusion is applied to tense ascites. Transjugular intrahepatic portosystemic shunt is considered for refractory ascites. With worsening of liver disease, fluid retention is associated with other complications; such as spontaneous bacterial peritonitis. This is a primary infection of ascitic fluid caused by organisms originating from large intestinal normal flora. Diagnostic paracentesis and antibiotic therapy plus prophylactic regimen are mandatory. Hepatorenal syndrome is a state of functional renal failure in the setting of low cardiac output and impaired renal perfusion. Its management is based on drugs that restore normal renal blood flow through peripheral arterial and splanchnic vasoconstriction, renal vasodilation and/or plasma volume expansion. However, the definitive treatment is liver transplantation.

Introduction

In end stage liver disease (ESLD), accumulation of fluid as ascites, edema or pleural effusion due to cirrhosis is common and results from a derangement in the extracellular fluid volume regulatory mechanisms.¹ In fact, fluid retention is the most frequent complication of ESLD which is occurring in about 50% of patients within 10 years of the diagnosis of cirrhosis.² This complication significantly impairs

the quality of life of cirrhotic patients and it accounts for a notable cost to society. It is associated with poor prognosis and 1-year and 5-year survivals of 85% and 56%, respectively.³

Although several hypotheses have been postulated, key to the understanding of the abnormal fluid retention process in decompensated cirrhosis is the peripheral arterial vasodilation theory. Many

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therapeutic measurements are developed based on this theory; however both, pathophysiology and treatment of the fluid retention complications in ESLD patients are still subjects of dispute. Ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), hepatic hydrothorax and lower extremity edema are major complications in this setting.

This review investigates the scientific literatures about pathophysiology and therapeutic modalities applied for fluid retention and its complications in ESLD patients. In order to do that, a search of articles related to fluid retention and its complications in cirrhosis using MEDLINE/PubMed, Text Books and other scientific publications was accomplished. English-language articles or those with the abstract in English, published until March 2007 were selected. Among these, we have discussed the most common theories along with the new concepts about pathophysiology, diagnosis and management of ascites, SBP, HRS and hepatic hydrothorax.

Ascites

Definition

Ascites is defined as an excessive amount of fluid that develops within the peritoneal cavity. According to the International Ascites Club, it is classified as grade 1, 2 and 3 as far as severity.⁴ Based on associated complications (i.e. SBP or HRS) and therapeutic response, it can also be classified as uncomplicated, complicated and refractory ascites^{5,6} (Table 1).

Table 1 Classification of ascites

Severity ⁴	
Grade 1 (mild)	Not clinically evident, diagnosed on ultrasound
Grade 2 (moderate)	Proportionate sensible abdominal distension
Grade 3 (severe)	Noticeable tense distension of abdomen
Uncomplicated ⁵	Not infected or associated with HRS
Refractory ⁶	Cannot be mobilized, early recurrence after LVP, not prevented satisfactorily with medical treatment (after 1 week)
Diuretic-resistant	No response to intensive diuretic treatment
Diuretic-intractable	Drug-induced adverse effects preclude diuretic treatment

Pathophysiology

The most acceptable theories postulate that the initial event in ascites formation in cirrhotic patients is sinusoidal hypertension (Figure 1).⁷⁻¹⁰ In cirrhotic patients, this is a consequence of distortion of hepatic architecture and increased hepatic vascular tone.⁷ Decreased hepatic bioavailability of nitric oxide (NO), and increased production of vasoconstrictors (e.g. angiotensin, endothelin, cysteinyl-leukotrienes and thromboxane) are responsible for increased tonicity of hepatic vasculature.⁷ Portal hypertension due to increase in sinusoidal pressure, activates vasodilatory mechanisms. These mechanisms, mostly mediated by NO overproduction, lead to splanchnic and peripheral arteriolar vasodilation.^{7,8} In advanced stages of cirrhosis, arteriolar vasodilation causes underfilling of systemic arterial vascular space. This event, through a decrease in effective blood volume leads to a drop in arterial pressure.⁸ Consequently, baroreceptor-mediated activation of renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS) and nonosmotic release of antidiuretic hormone (ADH) occur to restore the normal blood homeostasis.¹ These cause more renal sodium and water retention. On the other hand, splanchnic vasodilation increases splanchnic lymph production exceeding the lymph transportation system capacity and leads to lymph leakage into the peritoneal cavity.¹¹ Persistent renal sodium and water retention, alongside increased splanchnic vascular permeability in addition to lymph leakage into peritoneal cavity play the major role in a sustained ascites formation.

The other mechanism proposed to be involved in ascites formation is based on the hepatorenal reflex. A primary process of sodium and water retention exists before ascites develops; it seems to be mediated mostly through a hepatorenal reflex and causes circulatory volume expansion;⁵ however, Jimenez-Saenz *et al.*¹² observed that only a rapid increase in sinusoidal pressure triggers hepatorenal reflex and ascites formation (e.g. Budd-Chiari syndrome), otherwise a chronically rise of sinusoidal pressure to higher level is usually not associated with ascites formation.

Management

The goals of treatment in the management of ascites are:

- (i) Control of ascites.
- (ii) Prevention or relief of ascites-related symptoms, such as dyspnea or abdominal pain and distension.

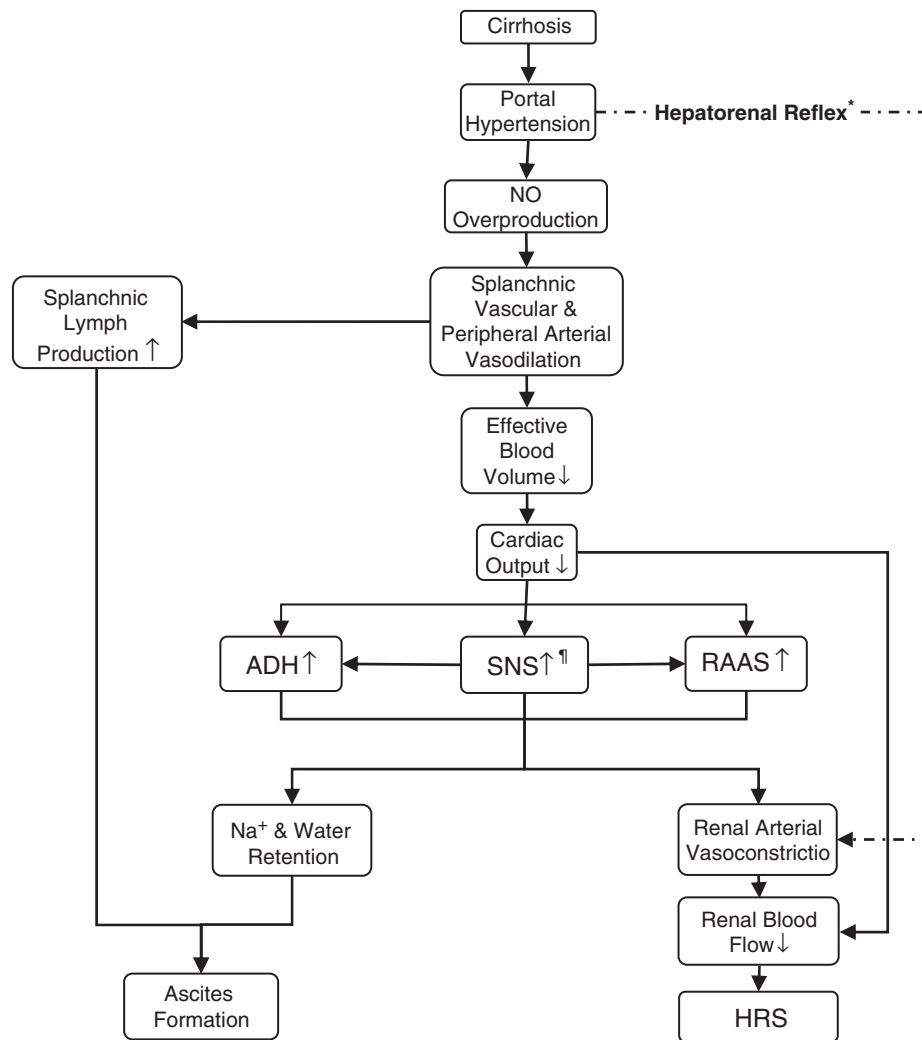


Figure 1. Pathophysiology of ascites and hepatorenal syndrome. Asterisk: adapted from Moller *et al.*⁹ Paragraph symbol: liver regeneration following hepatic injuries is regulated by SNS. Hepatic stellate cells (major fibrogenic cells in the liver) seem to be targets for SNS, and SNS neurotransmitter levels are higher in cirrhotic patients and proportional to hepatic fibrosis. Based on this subject, in HRS, it is not clear whether SNS over activity is primary to the pathogenesis of cirrhosis or secondary to hemodynamic turbulence.¹⁰

(iii) Prevention of life-threatening complications such as SBP and HRS.

In order to achieve them, a number of modalities have emerged. These include bed rest, diet modification, diuretics and more invasive therapeutic measurements such as large volume paracentesis (LVP), transjugular intrahepatic portosystemic shunt (TIPS) and peritoneovenous shunt (PVS).

Therapeutic modalities in the management of ascites are:

- Bed rest: it is shown to inhibit the neurohumoral system (RAAS and SNS) activated chronically in upright position in cirrhotic patients that impairs renal blood perfusion and causes sodium retention. Bed rest reduces the plasma aldosterone level and improves the response to

diuretic therapy in cirrhotic patients.¹³ However, bed rest is not recommended routinely as it is often unpractical and could cause decubitus ulcers and muscle atrophy in malnourished cirrhotic patients.¹⁴

- Water intake restriction: nonosmotic release of ADH due to reduction in effective blood volume in ascitic patients leads to decrease in free water clearance and consequent dilutional hyponatremia. Restriction of water intake is the standard treatment of dilutional hyponatremia (serum Na < 130 mEq/l).^{14,15} But generally there is no proof that water restriction in cirrhotic patients with ascites improves hyponatremia.⁴
- Sodium restriction: the cornerstone of ascites treatment is achievement of a negative sodium balance. This may be obtained through salt restriction in diet. A 2-g/day salt diet is palatable

and an effective means in maintaining a negative sodium balance.¹⁴ However if applied alone, its efficacy is limited to 10% of patients. Further restriction may increase efficacy but less palatable diet increases the noncompliance rates or worsens malnutrition.

- Diuretic therapy: considering the low efficacy of salt restriction and bed rest, diuretic therapy should not be postponed. Therefore, it is recommended to start diuretic therapy immediately. Spironolactone that acts in renal collecting tubule to inhibit sodium reabsorption, alone or along with furosemide (a loop diuretic) is the first-line therapy in persistent ascites.¹⁶ This regimen is initiated at a dose of 100 mg/day for spironolactone and 40 mg/day for furosemide. To preserve a normokalemic state, maintaining a 100–40 mg ratio of spironolactone and furosemide is advocated. In cases not responding to lower doses, this ratio should be continued through a stepwise-fashion increase in treatment dosage, up to a maximum dose of 400 of spironolactone and to 160 mg/day of furosemide.¹⁴ The dosage will be adjusted based on the patient's daily weight loss.⁴ Weight loss should not go over 0.5 kg/day in the absence of edema and more than 1 kg/day in edematous state. Also, urine sodium concentration should be measured until an appropriate diuretic dose is achieved.¹⁶ Other parameters that may affect dose modifications include: laboratories (serum levels of potassium, sodium and creatinine) and side effects (muscle cramps or gynecomastia).¹⁴ As alternative to spironolactone, amiloride (10–20 mg daily) is commonly used, which has less side effects but is also less effective when compared with other potassium sparing diuretics.¹⁷ Diuretic therapy, in addition to sodium restriction, is an effective therapeutic approach in 80–90% of cirrhotic patients.¹⁸
- Large volume paracentesis: LVP is efficacious in achieving a rapid relief of ascites and alleviating its associated symptoms.³ It can be performed safely in an outpatient setting.¹⁹ It seems more advantageous, when used with diuretics; the recurrence rate of ascites after LVP in addition to diuretic therapy (spironolactone) has been observed to be as low as 18% compared with LVP and placebo (93%).¹⁶ Albumin infusion along with LVP in order to prevent hemodynamic disturbances and renal impairment is highly recommended particularly when the removed fluid volume exceeds 5 l.²⁰ Synthetic plasma volume expanders are advocated if less than 5 l of ascitic fluid removed.¹⁶ Fernandez *et al.*²¹ compared the efficacy of albumin and hydroxyethyl starch (a synthetic volume expander) in two groups of ascitic patients. Their results showed that albumin is more effective in restoring the hemodynamic circulation, possibly by affecting arterial endothelial function as well as increasing the oncotic pressure. In the albumin

group significant suppression of plasma renin activity, increased systolic volume and systemic vascular resistance enhancement were observed. This study as well as the one by Gines *et al.*²² on paracentesis, emphasize the superiority of i.v. albumin as a plasma volume expander in comparison with other synthetic colloids.

- Shunt placement: other treatment modalities such as TIPS and PVS have been explored in order to decrease the need for paracentesis. TIPS has been shown to be more effective than LVP in refractory ascites,^{23–28} but it is associated with frequent complications such as portosystemic encephalopathy^{23,26–28} and worsening liver failure especially in patients with more severe liver dysfunction (Child class C).²⁴ When data are analyzed for survival advantage, TIPS was associated with improved,^{25,28} no difference,^{23,27} or even worsening survival in patients with more advanced disease.²³ Shunt stenosis or dysfunction occur in a significant number of patients.^{23–28} Placement of expandable polytetrafluorethylene-covered TIPS has been recently advocated.²⁹ This has been associated with improved shunt patency and decrease in ascites recurrence without increasing the encephalopathy rate, compared with the traditional type of stents.

PVS, because of its association with a high incidence of occlusion and serious complications, should be reserved for patients who are not orthotopic liver transplantation (OLT) candidates and do not have easy access to a facility that performs LVPs.³⁰ Rosemurgy *et al.*³¹ in a prospective randomized trial compared the relative efficacy of TIPS and PVS. The obtained data showed that control of ascites is achieved more rapidly with PVS, but TIPS has superiority in obtaining long-term free-ascites intervals; longer shunt patency and survival were observed with TIPS.

Based on the severity of ascites appropriate therapeutic modalities may be undertaken.

- (i) Grade 1—Mild ascites: is sub-clinically detected by ultrasound and usually does not need pharmacological treatment; sodium intake restriction along with the follow-up for progression of ascites are adequate.⁵
- (ii) Grade 2—Moderate ascites: treatment should be initiated with diuretics alongside modification in diet sodium.³²
- (iii) Grade 3—Symptomatic tense ascites: irrespectively of response to medical treatment should be managed by LVP plus albumin infusion (if the removed ascitic fluid volume does not exceed 5 l, a synthetic plasma expander may be used instead of albumin).¹⁶ Total volume paracentesis with administration of i.v. albumin at a dose of 6–8 g for each liter of removed ascitic fluid is the preferred modality.⁵

- (iv) Refractory ascites: the standard of care is represented by LVP, with simultaneous administration of intravenous albumin 25% at a rate of about 8 g/l of ascites removed (if LVP > 5 l), in addition to diuretic therapy and salt restriction.³⁰ TIPS placement may be reserved for patients with rapid recurrence of ascites and preserved liver function (bilirubin <3 mg/dl, Child-Pugh score <12), aged <70, without hepatic encephalopathy or cardiopulmonary disease.³³

Spontaneous bacterial peritonitis

Definition

Spontaneous bacterial peritonitis is an ascitic fluid infection that occurs in the absence of any remarkable intraabdominal source of infection; it primarily occurs in patients with advanced cirrhosis.¹⁸ Different studies show that SBP develops in about 1026% of cirrhotic patients. Uncomplicated SBP is defined as spontaneous bacterial peritonitis in the absence of shock, hemorrhage, ileus, severe renal failure and severe encephalopathy.³⁴

Pathophysiology

Translocation of bacteria from their intestinal origin, alterations in systemic immune defense mechanisms and deficiencies in the ascitic fluid antimicrobial activity seem to represent the key events in the pathogenesis of SBP (Figure 2).³⁵

- Bacterial translocation: even if it is not well established, bacterial overgrowth due to impaired intestinal transit in cirrhotic patients seems to be the leading cause of bacterial translocation.³⁵ Some studies showed that prokinetic agents are able to decrease intestinal bacterial overgrowth and its following translocation.³⁶ Increased intestinal mucosal permeability has been considered as an important factor involved in bacterial translocation. It is postulated that portal hypertension through mucosal hypoxia and consequently oxidative damage, in addition to splanchnic vascular stasis and intestinal mucosal congestion, lead to increased intestinal permeability.³⁷ The bacteria migration from lymph nodes to blood and then to ascitic fluid respectively might be the reason of developing peritonitis. It is demonstrated that bacterial translocation is mainly monomicrobial.³⁸
- Alterations in systemic immune defense mechanisms; are mainly represented by impairment of phagocytic activity of the reticuloendothelial system.³⁹
- Deficiencies in the ascitic fluid antimicrobial activity: it is mainly secondary to low ascitic fluid opsonic activity and C3 levels.^{40,41}

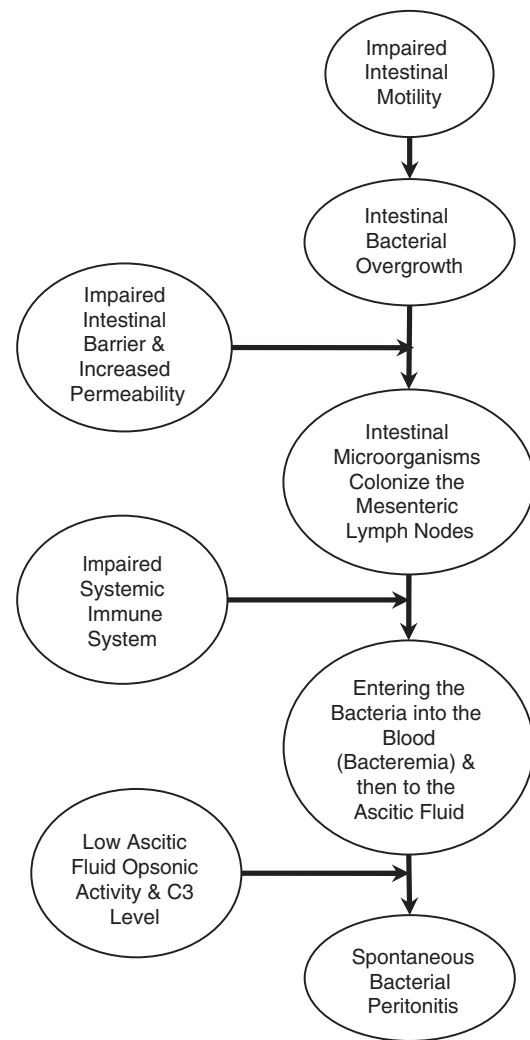


Figure 2. Pathophysiology of spontaneous bacterial peritonitis.

In cirrhotic patients, those with lower levels of C3 in the ascitic fluid are more predisposed to SBP than the group having higher C3 levels.⁴¹ Ascitic fluid protein concentration has a positive correlation with the ascitic fluid opsonic activity so the low level of protein in this fluid (<1 g/dl) is considered as a SBP risk factor.⁴²

Diagnosis

The clinical manifestation of SBP can vary as patients may be asymptomatic or presenting with a single to multiple gastrointestinal symptoms, encephalopathy and/or renal failure.⁴³ Local or systemic signs and symptoms of infection including pain, vomiting, diarrhea, ileus, fever, leukocytosis and septic shock may be accompanying the SBP. The diagnosis is based on the elevated ascitic fluid absolute polymorphonuclear leukocyte (PMN) count (≥ 250 cells/mm³), and usually not associated with a positive ascitic bacterial culture (>60%

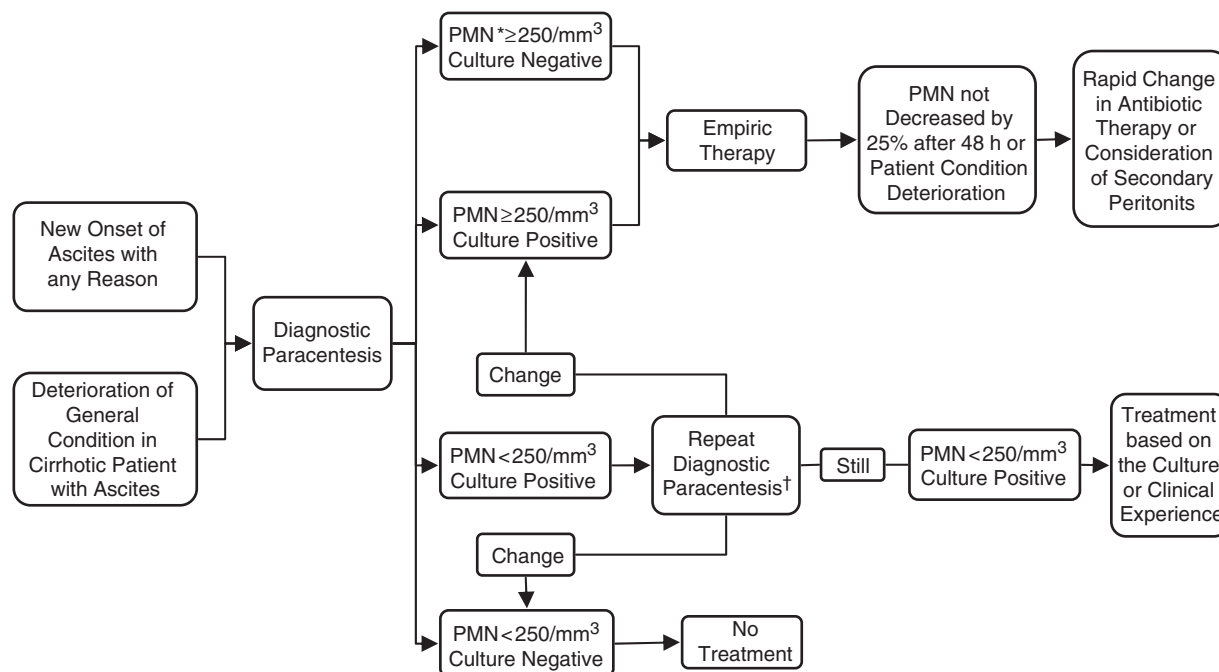


Figure 3. Guidelines for treatment of SBP. Asterisk: if $PMN \geq 250/mm^3$ empiric therapy starts while awaiting the culture results. Dagger: in the presence of signs and symptoms of infection, does not need to be done and treatment must be considered.

of patients); in the presence of hemorrhagic ascites, one PMN is subtracted per 250 red blood cells to adjust for the presence of blood extravasation.⁴³ A prompt diagnosis is important in the management of SBP and in decreasing the incidence of complications, such as HRS.⁴⁴

A consensus in the initial evaluation of a patient with ascites entails a diagnostic paracentesis in the following clinical scenarios:⁴³

- (i) At the time of admission in every patient with ascites whether or not symptoms suggestive of SBP are present.
- (ii) If hospitalized patients with ascites develop abdominal pain, signs of systemic infection, hepatic encephalopathy, worsening renal function without a clear precipitating factor or gastrointestinal hemorrhage.
- (iii) Prior to administration of prophylactic antibiotic in ascitic patients with gastrointestinal bleeding.

To increase the proportion of positive ascitic fluid cultures, studies have shown that culture of ascitic fluid (at least 10 ml) directly into blood culture bottles (aerobic and anaerobic media) at the bedside, significantly increases the yield of bacteria up to 90%.⁴⁵ If ascitic fluid culture is negative despite its PMN count is more than $250/mm^3$ —in the absence of history of antibiotic therapy within 30 days and intraabdominal source

of infection—this state is known as ‘culture negative neutrocytic ascites’.⁴⁶ This is considered a less severe variant of SBP and thus, should be treated in the same manner.⁴⁶ In a special case known as asymptomatic bacterascites in which the ascitic fluid culture is positive but the ascites PMN count is less than $250/mm^3$ and no signs and symptoms of a local or systemic infection are present, specific treatment guidelines have been outlined (Figure 3).⁴³

Polymorphonuclear leukocyte count more than $250/mm^3$ does not appear to be a good criterion in the diagnosis of SBP caused by Gram-positive cocci because this variant of symptomatic SBP presents with PMN count lower than $250/mm^3$.⁴⁷ Symptomatic bacterascites should be treated promptly without repeating diagnostic measurements.⁴³

In addition to blood cultures, routine analysis of the ascitic fluid should include cell count with differential, albumin, bacterial culture and total protein. The clinical settings and lab results suggesting secondary peritonitis are shown in Table 2.⁴⁸ In this situation, diagnostic modalities for secondary peritonitis should be considered.

Leucocytes esterase reagent strips including Nephur-Test and MultistixSG10 are new diagnostic measurements for SBP applied to make a quick diagnosis at the patient bedside.⁴⁹

Table 2 Findings suggesting secondary peritonitis

No decrease in ascitic fluid PMN counts 48 h after treatment initiation.
Ascitic fluid culture result is not monomicrobial.
At least two of the following criteria present:
Ascitic fluid protein >1 g/dl
Ascitic fluid glucose <50 mg/dl
Ascitic fluid lactate dehydrogenase >225 mU/ml

Treatment

Empirical treatment should be initiated while awaiting ascitic fluid culture results and it is based on the most common etiology of SBP.⁴³ The most common causative organisms in community acquired infection are Gram-negative bacteria, mostly Enterobacteriaceae, while among the nosocomial infections, Gram-positive bacteria are the leading cause.⁴⁷ Cefotaxime is currently the antibiotic of choice for the treatment of SBP. This third-generation cephalosporin, is effective against 98% of the flora and differently from the combination of ampicillin plus tobramycin, does not lead to superinfection or nephrotoxicity.⁵⁰ It can be dosed i.v. 2 g every 6–12 h; and five days of treatment are demonstrated to be equally efficacious and more cost-effective than ten days treatment.⁵¹ The use of oral quinolones, such as ofloxacin, may be considered in uncomplicated SBP.³⁴ Other cephalosporins such as cefonicid, ceftriaxone, ceftizoxime and ceftazidime as well as amoxicillin with clavulanic acid could be alternatively used since they have been shown to be as efficacious as cefotaxime.⁵² A study by Sort *et al.*⁵³ suggests that intravenous albumin infusion concomitant to antibiotic administration decreases the incidence of renal dysfunction in SBP and prolongs short- and long-term survival, most notable in patients with abnormal renal function (BUN >30 mg/dl and/or creatinine >1.0 mg/dl). With proper treatment, SBP resolution takes place in 90% of patients; however, if after 48 h of antibiotic therapy the absolute ascitic fluid PMN count does not decrease by 25% or clinical deterioration of the patient's condition is evident within the first few hours of antibiotic therapy, treatment failure should be considered.⁴³ The following steps in the management of this condition should include a rapid modification of antibiotic therapy based on the bacterial culture sensitivity and/or clinical experience. In addition, considering the possibility of secondary peritonitis and thus, appropriate measurements must be undertaken.⁴³

Prophylaxis

Prophylaxis of SBP has been shown to be beneficial in these groups of patients:

- (i) Hospitalized patients with gastrointestinal hemorrhage: the short-term administration of norfloxacin or intravenous ceftriaxone reduces the incidence of SBP or bacteremia as compared with patients not receiving prophylactic antibiotics. In patients with advanced liver disease who are actively bleeding intravenous ceftriaxone is preferred.⁵⁴
- (ii) Nonbleeding cirrhotic patients with prior history of SBP: secondary prophylaxis in patients with prior history of SBP is recommended considering that they have high risk of SBP recurrence (between 40% and 70% risk at 1-year).⁵⁵ Long-term prophylaxis with continuous oral norfloxacin at a dose of 400 mg/day was demonstrated to reduce the recurrence rate of SBP from 68% (placebo group) to 20% (norfloxacin group) in a study by Gines *et al.*⁵⁶ This long-term prophylaxis should be continued until the disappearance of ascites, transplantation or death.¹⁶ Alvarez *et al.*⁵⁷ in a clinical trial showed that trimetoprim-sulfamethoxazole is as efficient as norfloxacin in SBP prophylaxis.
- (iii) Antibiotic prophylaxis also appears to be effective in the prevention of SBP (primary prophylaxis) in patients with low ascitic fluid protein (<15 g/l). They are at high risk of developing the first episode of SBP. Primary prophylaxis with norfloxacin reduces the incidence of SBP, delays the development of HRS and improves survival in patients with advanced cirrhosis.⁵⁸

Hepatorenal syndrome

Definition

Hepatorenal syndrome is defined as a clinical condition of renal failure that occurs in patients with chronic liver disease, advanced hepatic failure and portal hypertension; it is characterized by impaired renal function and marked abnormalities in the arterial circulation and in the activity of the endogenous vasoactive systems.⁵⁹ The following findings are advocating that the liver problem is the underlying disease for HRS and the kidney is not parenchymally involved:

- (i) Renal biopsy reveals no significant parenchymal changes.
- (ii) Liver transplantation completely reverses the renal problem. (Treatment of choice).
- (iii) HRS development is correlated with liver disease severity.

- (iv) HRS resolves in a transplanted kidney, from a donor having HRS to a recipient with normal liver function.

Two different types are suggested for HRS; HRS type 1 is a rapid progressive renal failure (less than 2 weeks) characterized by a 2-fold or more increase of serum creatinine (>221 mol/l) or 50% decrease of creatinine clearance (<20 ml/min); type 2 develops steadily (over months) with a serum creatinine more than 132.6 mol/l or creatinine clearance less than 40 ml/min. The median survival is less than two weeks and about six months for type 1 and 2, respectively.⁶⁰

Pathophysiology

The pathogenesis of HRS has not been completely elucidated but the suggested mechanisms are the same as those involved in ascites pathophysiology (Figure 1).

HRS usually occurs in the setting of severe systemic arterial vasodilation leading to low cardiac output and in advanced stages of cirrhosis.⁶¹ These events are being explained through the peripheral arterial vasodilation theory. NO-mediated vasodilation presents in the early stages of cirrhosis.⁸ Eventually, worsening of the liver disease, followed by blood pooling in splanchnic vascular territory, lead to underfilling of systemic vascular bed and consequently a reduction in the effective blood volume. This causes renal blood flow (RBF) to decrease which is followed by activation of RAAS, SNS and nonosmotic release of ADH.¹ These mechanisms try to reverse the splanchnic vasodilation but the splanchnic vessels are resistant to vasoconstrictor systems. There is a hyporesponsiveness to the vasoactive factors in splanchnic circulation of patients with portal hypertension owing to NO overproduction. This might explain why the vasoactive systems are not able to reverse splanchnic vasodilation and only lead to renal arterial vasoconstriction and further sodium and water retention. Early on in the disease, renal vasodilators can counteract vasoconstrictors. With progression of liver disease, the imbalance between the two opposing mechanisms tilts to the vasoconstrictive mechanism that overcomes the renal vasodilatory one and eventually, results in uncontrolled renal vasoconstriction.¹ Prostaglandins E₂ and I₂ are vasodilators and counteract the vasoconstrictor actions of angiotensin II and norepinephrine and inhibit the tubular effect of vasopressin. This is the reason why patients with ESLD and significant renal impairment should not be treated with nonsteroidal anti-inflammatory drugs, which by

inhibiting prostaglandins synthesis could worsen the renal impairment.⁶² However, it is demonstrated that short-term administration of selective cyclooxygenase-2 (COX-2) inhibitor celecoxib does not impair renal function and the response to diuretics in decompensated cirrhosis.⁶² Decreased RBF because of a reduced effective blood volume and renal arterial vasoconstriction leads to reduction of GFR and finally HRS development.

Ruiz *et al.*⁶¹ confirmed that lower mean arterial pressure and cardiac output in addition to higher level of hepatic venous pressure gradient, plasma renin activity and norepinephrine concentration are significant in patients developing HRS. Among these, the cardiac output and plasma renin activity are considered as the only two self-determining factors for HRS development; in due course, they concluded that severe vasodilation followed by decrease in cardiac output results in HRS.

As in ascites pathophysiology, the role of hepatorenal reflex in development of HRS is proposed. Jalan *et al.*⁶³ by studying the RBF before and after the TIPS stenosis proposed the existence of hepatorenal reflex in man and its essential role in RBF regulation. So it could be proposed that increased hepatic sinusoidal pressure through hepatorenal reflex cause renal arterial vasoconstriction and decreased RBF, ultimately leading to HRS.

The effect of ET-1—a potent vasoconstrictor—in developing HRS is investigated in many studies. ET-1 contracts the renal arterial circulation and cause decrease in RBF. On the other hand, ET-1 by contracting the mesangial cells decreases the glomerular filtration area. These effects reduce the GFR and are reasons for possible role of ET in HRS development. Also increase in concentration of ET-1 associated with amplified hepatic sinusoidal pressure and decrease in RBF suggests a possible role for ET-1 to mediate these hemodynamic changes which is compatible with hepatorenal reflex.⁶⁴

Diagnosis

In a retrospective study, Watt *et al.*⁶⁵ found that approximately 40% of patients with advanced liver disease and renal failure had been mistakenly diagnosed as having HRS. In fact, misdiagnosis was common before 1996, when diagnostic criteria were developed. There are no specific tests for HRS diagnosis but measurements of serum creatinine, BUN and electrolytes along urine analysis are necessary. Imaging modalities including renal ultrasonography and Doppler sonography are indicated to rule out other diagnosis such as obstructive

Table 3 Diagnostic criteria for HRS by the International Ascites Club*Major criteria*

- Chronic or acute liver disease with advanced hepatic failure and portal hypertension
- Low glomerular filtration rate (serum creatinine >1.5 mg/dl (133 mmol/l) or 24-h creatinine clearance <40 ml/min)
- Absence of shock, ongoing bacterial infection, current treatment with nephrotoxic drugs, gastrointestinal fluid losses, renal fluid losses >500 g/day; >1000 g/day (in the case of oedema)
- No sustained improvement in renal function (serum creatinine <1.5 mg/dl (133 mmol/l) or 24-h creatinine clearance <40 ml/min)
- Proteinuria <500 mg/dl
- No ultrasonographic sign of primary renal disease

Minor criteria (additional criteria)

- Urine volume <500 ml/day
- Urine sodium <10 mEq/l
- Urine osmolality > plasma osmolality
- Urine red blood cells <50 per high-power field
- Serum sodium <130 mEq/l

uropathy or parenchymal renal disease. Renal duplex Doppler ultrasonography can also predict the nonazotemic cirrhotic patients vulnerable for developing HRS;⁶⁶ this could be done through measurement of resistive index (RI) which is representing renal interparenchymal vascular resistance.

International Ascites Club has proposed the criteria for HRS diagnosis. Presence of all major criteria for diagnosis is mandatory and minor criteria are supportive (Table 3).⁵

Management

The ideal treatment of HRS is liver transplantation. Prevention of this serious complication is imperative when managing cirrhotic patients with ascites. Most of the treatments of HRS in the past resulted in only transient beneficial effects on renal function and were not able to demonstrate consistently an improvement in survival.⁴ However in recent years, new promising therapeutic modalities have been emerged as more effective treatments of HRS, which may prolong survival in these patients. Different approaches have been adopted, but the aim of most treatments for HRS is to increase RBF. This could be obtained by directly facilitating renal vasodilation or indirectly, through splanchnic vasoconstriction. Administrations of plasma volume expanders along with these therapeutic procedures are recommended (Table 4).

(i) Renal vasodilation:

- Most of the studies showed inability of vasodilators (i.e. dopamine, prostaglandins and prostaglandin analogs-misoprostol) in improving renal perfusion. However, high doses of misoprostol alongside albumin seem to be effective in HRS reversal.⁶⁷

Dopamine used in subpressor doses has shown none or only minor effect on GFR.⁶⁸

(ii) Vasoconstriction of the splanchnic circulation:

- Several studies have shown that the administration of agonists of the vasopressin (V1) receptors, ornipressin or terlipressin (both are active predominately in the splanchnic vessels and have little effect on the renal circulation) improve renal function and reverse HRS.^{69,70} Recently, Fabrizi *et al.*⁷¹ with a meta-analysis of the clinical trials performed on terlipressin therapy in HRS, advocated the safety and efficacy of terlipressin; nevertheless, a significant number of relapse after treatment termination was observed. Guevera *et al.*⁶⁹ demonstrated that a 3-day treatment with ornipressin, administered in a continuous intravenous infusion, at doses ranging from 1 to 6 IU/h, along albumin was associated with a normalization of the overactivity of the vasoactive systems and a marked increase in atrial natriuretic peptide levels but only a trivial improvement in renal function. However, a prolonged treatment of 15 days resulted in a remarkable improvement in renal function, with normalization of serum creatinine concentration, marked increase in RBF and GFR, and persistent suppression in the activity of vasoconstrictor systems. HRS did not recur in patients in whom normalization of serum creatinine was achieved.⁶⁹
- Ortega *et al.*⁷² showed that terlipressin (0.5–2 mg/4 h intravenously until serum creatinine level <1.5 mg/dl or for 15 days) is an effective treatment for HRS type 1, with an uncommon recurrence after complete response (17%). This efficacy was significantly enhanced by concomitant albumin infusion. An increased survival rate following

Table 4 Summary of the most promising treatment options for HRS

Type of treatment		Dose	Duration
Pharmacological			
<i>Mechanism</i>			
Vasoconstriction of splanchnic circulation	Octreotide	100–200 µg s.c. t.i.d.	Maximum of 2 months
	Midodrine Albumin 20%	7.5–12.5 mg p.o. t.i.d. 20–40 g i.v. daily	
	Ornipressin Albumin 20%	2–6 IU/h i.v. 20–60 g daily	3 days
	Terlipressin Albumin 20%	0.5–2 mg i.v. every 4 h every 3 days 20–40 g i.v. daily	Maximum of 15 days
Renal vasodilation	Misoprostol	0.4 mg p.o. t.i.d.	Maximum of 40 days
	Adenosin-1 receptor antagonist (FK 352)	10 mg i.v.	one bolus
Selective angiotensin II type I receptor antagonist	Losartan	25 mg p.o. daily	7 days
Nonpharmacological			
Liver transplantation			

a complete response was observed. Ischemic complications requiring discontinuation of the drug can occur, more commonly seen in patients treated with ornipressin than those treated with terlipressin.^{69,72}

- Octreotide and midodrine (an alpha-adrenergic agonist) have been used with promising results:

In an observational European study, Angeli *et al.*⁷³ demonstrated that a combined long-term administration of midodrine, albumin and octreotide, improved renal failure after 10 days and almost complete normalization after 20 days. This therapy was compared with the traditional administration of dopamine at nonpressor doses. All the patients received albumin to improve the effective circulating volume. None of the patients with the dopamine therapy showed improvement in renal function. The octreotide plus midodrine treatment therapy proved to be safe with no remarkable side effects.

- Systemic vasoconstrictors, such as alpha-adrenergic agonist (i.e. norepinephrine and metaraminol) and agonists of the angiotensin I receptors fail to demonstrate any significant benefit in the treatment of HRS.⁷⁴

(iii) The use of saralasin, a nonselective angiotensin receptor antagonist resulted in arterial hypotension;⁷⁵ so further impairment in renal function may occur. However, a recent study by Yang *et al.*,⁷⁶ found that one-week treatment with losartan, a highly selective angiotensin II type I receptor antagonist, increases sodium excretion in association with an improvement of renal function in cirrhotic patients with and without ascites. Further studies need to be done to confirm these findings and evaluate if there is a role in the treatment of HRS with losartan.

(iv) The role of TIPS in the management of HRS has not yet been established. Some studies suggest that TIPS may improve renal perfusion and GFR and reduce the activity of RAAS and SNS in cirrhotic patients with type 1 HRS.⁷⁷ Wong *et al.*⁷⁸ showed that applying TIPS following medical therapy with midodrine, octreotide and albumin in HRS is an effective therapeutic modality. A more recent study that included both HRS I and HRS II patients, demonstrated that TIPS was associated with a better survival compared with nonshunted individuals. Patients with Child Score >12, bilirubin level >15 mg/dl, and severe encephalopathy were excluded from the study.⁷⁹ Although the results

of these studies are promising, but larger and controlled trials need to be done before TIPS is a recommended treatment for HRS considering its significant side effects (i.e. hepatic encephalopathy, and further impairment in liver function).

- (v) The molecular adsorbent recirculating system (MARS), which enables the selective removal of albumin-bound substances accumulating in the liver failure, may represent a relatively safe, alternative therapy in high risk HRS I patients.⁸⁰
- (vi) The ideal treatment of HRS is liver transplantation. The OLT outcome in cirrhotic patients having HRS is poor compared with those lacking HRS. Restuccia *et al.*⁸¹ proposed treatment of HRS prior to OLT. They showed that OLT outcome in the patient with HRS treated with vasopressin analogs before OLT is similar to the result in those not having HRS.

Secondary to liver transplantation, prevention of HRS entails avoiding the precipitating factors of HRS. A study by Sort *et al.*,⁵³ illustrated that the development of HRS in patients with SBP can be effectively prevented by the administration of albumin (1.5 g/kg intravenously at the time of diagnosis of the infection and 1 g/kg intravenously 48 h later) together with antibiotic therapy. Treatment with albumin in addition to the standard antibiotic therapy resulted in a significant decrease in HRS incidence and improvement in survival.⁵³ This beneficial effect of albumin is likely related to its capacity to counteract the effects of the activation of vasoconstrictor systems, which probably result from a reduction in effective arterial blood volume, associated with infection.

Hepatic hydrothorax

Definition

Hepatic hydrothorax is defined as a notable pleural effusion, usually greater than 500 ml, in patient with cirrhosis and no cardiopulmonary disease. The estimated prevalence of this uncommon but often debilitating complication is 4–10%.⁸²

Pathophysiology

Movement of ascitic fluid as a result of negative intra-thoracic pressure and positive intraabdominal pressure from the peritoneal cavity into the pleural space through diaphragmatic defects seems to result in hepatic hydrothorax formation. These defects are mostly in the tendinous portion of the diaphragm that is normally covered with pleuroperitoneum. The gradient of pressure between

Table 5 Treatments for hepatic hydrothorax

Type of treatment	Dose/modality of treatment
Pharmacological	
Octreotide	25–100 µg/h i.v.
Terlipressin	4 mg i.v. one bolus, every 6 h
Albumin	40 g i.v. daily
Nonpharmacological	
Thoracentesis	
TIPS	If thoracentesis is more frequent than once every 2–3 weeks
Liver transplantation	

the thorax and peritoneal cavity creates blebs of the peritoneum, accumulated with the ascitic fluid, through these defects. Eventually, rupture of these blebs into the thoracic space cause repositioning of ascitic fluid leading to hydrothorax formation. Rarely, hepatic hydrothorax can be present in the absence of ascites.⁸²

Diagnosis and management

The pleural effusion leads to symptoms ranging from exercise intolerance to shortness of breath and in some cases, respiratory failure. An examination of the pleural fluid is part of the initial evaluation to establish the diagnosis of hepatic hydrothorax; in addition to a history, physical examination and radiological imaging. Pleural effusions associated with ascites are mostly right-sided and transudative with the following laboratory features:⁸²

- Cell count less than 250 PMN/mm³.
- Total protein concentration is less than 2.5 g/dl.
- Pleural fluid to serum ratio of total protein is less than 0.5.
- Pleural fluid to serum ratio of lactate dehydrogenase is less than 2:3.

Likewise ascitic fluid, hydrothorax in cirrhotic patients contains low complement level and opsonic activity. These patients are prone to spontaneous bacterial empyema (SBEM) while plural effusions of other causes are not known to predispose to SBEM.⁸³ Same as ascitic fluid analysis in SBP diagnosis, pleural fluid analysis with reagent strip is a rapid diagnostic method for SBEP and the positive result indicates antibiotic therapy.⁸⁴

The same principles for the management of cirrhotic ascites are applied to hepatic hydrothorax (Table 5). For most patients, symptomatic relief can be obtained with dietary sodium restriction (90 mEq/day) combined with diuretic therapy.⁸²

Dyspnea can be promptly relieved with a therapeutic thoracentesis; however, no more than 2 l of pleural fluid should be removed at each session because of the risk of unilateral re-expansion pulmonary edema.⁸⁵ When treatment with sodium restriction and maximal diuretics fails and patients are requiring more than one session of thoracentesis every 2 to 3 weeks for symptomatic relief, TIPS is indicated.⁸⁶ In these refractory cases, TIPS can be an effective alternative treatment modality but the same complications associated with TIPS placement (most notably hepatic encephalopathy) seen in refractory ascites are also seen here.⁸⁶ Thoracoscopic pleurodesis is proposed for refractory hepatic hydrothorax,⁸⁷ but OLT remains the only definitive treatment for hepatic hydrothorax.

Conclusion

Ascites is the most prevalent complication of cirrhosis. The most acceptable theory for ascites development in cirrhotic patient is arterial vasodilation and consequently sodium and water retention. Most of the treatment modalities are based on this theory. Bed rest, salt restriction, diuretics and LVP are among these modalities. TIPS and PVC are indicated in the setting of cirrhosis and refractory or recurrent ascites. Short of the OLT, none of the other therapeutic procedures are the ideal treatment of ascitic patients.

SBP is a common complication of ascites occurring in the setting of bacterial translocation from intestine to the ascitic fluid in the peritoneal cavity. Diagnostic paracentesis of ascitic fluid is needed. PMN count more than 250/mm³ is diagnostic. Treatment initiation must be, while we are awaiting the lab result, based on the common causative organisms. Cefotaxime is the treatment of choice. Quinolones are indicated in case of uncomplicated SBP. Concomitant albumin infusion could prevent HRS development. Prophylactic regimen is advocated in cirrhotic patient with gastrointestinal hemorrhage, prior history of SBP and low ascitic fluid albumin level. Quinolones are mostly administered as prophylactic agents.

HRS is suggested to develop in the setting of arterial vasodilation leading to low cardiac output and decrease in RBF respectively. Renal arterial vasoconstriction is contributing in RBF reduction; so therapeutic approaches are directed to restore the normal RBF through reversing the systemic vasodilation or directly renal arterial vasodilation. Among these, combination of octerotide, midodrine plus albumin, vasopressin V1 receptor analogs and highly selective angiotensin II type I receptor

antagonist are used with promising result. Patients with HRS might benefit from TIPS insertion, but further studies are needed to prove its efficacy. Like ascites, OLT is the only unambiguous treatment.

Hepatic hydrothorax is the relocation of ascitic fluid from high-pressure peritoneal cavity to low pressure thoracic space. Treatment modalities are the same as ascites. Thoracentesis and thoracoscopic pleurodesis are performed in symptomatic and refractory hydrothorax respectively. Same as the other complications of cirrhosis OLT is the only definitive treatment.

Conflict of interest: None declared.

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