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Chapter 5

Ascites: Treatment, Complications, and Prognosis

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http://dx.doi.org/10.5772/intechopen.70384

Abstract

Ascites is the most common complication in patients with cirrhosis. It can lead to several life-threatening complications resulting in a poor long-term survival outcome. Ascites is due to the loss of compensatory mechanism to maintain effective arterial blood volume secondary to splanchnic arterial vasodilatation in the progression of liver disease and portal hypertension. Refractory ascites, spontaneous bacterial peritonitis (SBP), hyponatremia, and hepatorenal syndrome (HRS) are complications that can occur with ascites, all of them leading to a worse quality of life and short-term mortality. When complication appears, liver transplantation as a definitive and curative treatment should be considered. Other common therapeutical approaches to control ascites such as diet, sodium restriction, or the use of diuretics are needed to avoid these complications, although some patients will require further treatments when ascites becomes refractory to standard treatment. This chapter will review the complex treatment of ascites, and its related complications.

Keywords: ascites, hepatorenal syndrome, hyponatremia, portal hypertension, spontaneous bacterial peritonitis

1. Introduction

Decompensated cirrhosis is the end stage of chronic liver disease of any etiology. It has a wide range of different clinical manifestations that are secondary to portal hypertension and/or liver insufficiency. Ascites is the most frequent decompensation, and it is usually the first manifestation of the disease in the majority of the patients [1]. Ascites is the accumulation of liquid inside of the peritoneal cavity, and it is developed in 60% of patients with compensated cirrhosis within 10 years during the natural course of their liver disease [1]. Hippocrates of Kos described ascites a long time ago (ca. 460–ca. 310 BC), and its treatment with large paracentesis was already performed since the ancient Greek physicians. It is still a very common problem in patients

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with liver cirrhosis, malignancy, or cardiovascular disease today. As in Western Europe and the United States of America, liver cirrhosis is the main cause of ascites (75–85%), and we will focus on this disease [2, 3].

The development of ascites is the consequence of the action of several complex mechanisms secondary to severe portal hypertension (i.e., hepatic venous pressure gradient (HVPG) >12 mm Hg) giving place to an impairment of hepatic, circulatory, and renal function. Portal hypertension induces the activation of the endogenous vasoactive systems, which prevent the renal excretion of an adequate amount of sodium, leading to a positive sodium balance [4]. Large evidence suggests that renal sodium retention in patients with cirrhosis is secondary to arterial splanchnic vasodilation. This causes a decrease in effective arterial blood volume with activation of arterial and cardiopulmonary volume receptors, and homeostatic activation of vasoconstrictor and sodium retaining systems (i.e., renin-angiotensin-aldosterone, vasopressin, and the sympathetic nervous systems). Renal sodium retention leads to expansion of the extracellular fluid volume and increases intestinal capillary pressure. The latter is further increased due to both portal hypertension and splanchnic arterial vasodilatation, which also disrupts the intestinal capillary permeability, and thereby contributes to the accumulation of fluid in the abdominal cavity [5]. In addition, certain polymorphisms of the aquaporin-1 gene could predispose to water retention [6].

The development of ascites is associated with a poor prognosis and impaired quality of life in patients with cirrhosis [7]. The probability of survival at 1 and 5 years after decompensation by ascites is about 50 and 20%, respectively [8]. Because of the poor survival, and other complications that will be explained later, patients with ascites should generally be considered for referral for liver transplantation [3].

2. Evaluation and initial investigations

2.1. History and physical examination

The first step in the management of every patient with a new-onset ascites is to reveal its underlying cause. A thorough history and physical examination will help narrow the differential diagnosis and reveal factors that might have been implicated in the development of ascites (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs)). Risk factors for liver disease such as alcohol abuse, metabolic syndrome, or family history of hemochromatosis should be sought. Patients should also be questioned about past history of cancer, heart failure, renal disease, or tuberculosis as they may all be responsible for the development of ascites [3].

The main complaint of patients with ascites is an increase in abdominal girth, often accompanied by lower-extremity edema. Other common manifestations include dyspnea due to increasing abdominal distension and/or accompanying pleural effusions, abdominal pain, anorexia, nausea, and fatigue [9]. The accuracy of the physical examination to detect ascites is highly dependent on the amount of ascites and on the physical constitution of the patient. Accordingly, patients must have approximately 1500 mL of fluid for ascites to be detected reliably by physical

examination and the presence of obesity greatly reduces its diagnostic accuracy [3]. Several signs support the presence of ascites such as the shifting dullness, fluid wave, and puddle signs. The former has 83% sensitivity and 56% specificity in detecting ascites. It is also less cumbersome and performs better than the latter two [3, 10]. The clinician should also look for other physical signs that suggest the presence of a liver disease (e.g., spider angiomas, Dupuytren contracture, palmar erythema, gynecomastia, parotid gland enlargement, or testicular atrophy) or an extrahepatic disease (e.g. jugular venous distension related to heart failure) as the cause of ascites.

2.2. Initial investigations

The essential investigations that should follow the anamnesis and physical examination to confirm the cause of ascites include an abdominal ultrasound (to screen for morphologic evidence of cirrhosis and portal hypertension, tumors, portal vein thrombosis, and hepatic vein thrombosis), laboratory assessment of liver function, renal function, serum and urine electrolytes, and abdominal paracentesis. The latter is compulsory in order to confirm the cause of the ascites and to rule out complications such as spontaneous bacterial peritonitis (SBP). Thus, it should always be performed in a new episode of ascites grades 2 or 3, in patients hospitalized for any complication of the disease or because of worsening of ascites [2, 11]. It is a safe procedure, even in patients with prolonged prothrombin time and low platelets. Indeed, the policy of some physicians to give blood products (fresh frozen plasma and/or platelets) routinely in these patients is not data-supported [3]. Growing evidence from the last two decades has demonstrated that most patients with liver cirrhosis remain in a tenous but balanced state of hemostasis [12]. Accordingly, in a study of 1100 large volume paracentesis, there were no hemorrhagic complications despite no prophylactic correction of platelet counts as low as 19,000 cells/mm^3 (54% < 50,000) and of prolonged international normalized ratios for prothrombin time as high as 8.7 (75% > 1.5 and 26.5% > 2.0) [13]. The most common site for paracentesis is the left lower quadrant of the abdominal wall (3 cm cephalad and 3 cm medial to the anterior superior iliac spine), as in this location the wall is thinner and with a larger pool of fluid than the midline. Visible collateral must be avoided, and in patients with obesity or loculated ascites, an ecoguided paracentesis is commonly needed [3].

The analysis of the ascitic fluid includes cell count and differential, culture, biochemical analysis, and cytology. Current guidelines recommend to routinely perform only cell count and differential, ascitic fluid protein and albumin, and note the gross appearance of the fluid (i.e., water-clear, bilious, purulent, bloody, or chylous) [2, 3]. The former enables to discard SBP or suspect the presence of other type of infection (e.g., high lymphocyte count in patients with tuberculosis). Albumin measurement on the same day in serum and ascitic fluid allows the calculation of the serum-ascites albumin gradient (SAAG), which properly differentiates ascites due to portal hypertension from ascites due to other causes. If the SAAG is greater than or equal to 1.1 g/dL, ascites is ascribed to portal hypertension with an approximate 97% accuracy [14]. Importantly, SAAG accuracy is not influenced by fluid infusion and diuretic use and also remains greater or equal to 1.1 g/dL in patients with both portal hypertension and a second cause for ascites formation [3]. Measurement of SAAG is, therefore, of utmost importance in patients with new-onset ascites, but its repeated measurement is usually not needed in other

scenarios (e.g., worsening or refractory ascites) [3]. **Table 1** shows the etiological classification of ascites according to the SAAG value. Further ascitic testing should be done depending on clinical judgment [3]. In patients in whom a peritoneal carcinomatosis is suspected, an ascitic fluid cytology must be performed, as it has a sensitivity as high as 96.7% if three samples from different paracentesis procedures are analyzed [15]. Bacterial culture is mandatory if infection is suspected. Cultures should be done in aerobic and anaerobic blood cultures inoculated (10 mL) at the bedside to increase their profitability (80% by this method). The utility of lactate

SAAG	Diseases	Diagnosis
≥1.1	*Liver cirrhosis*	Compatible image test and biopsy, known etiology of liver disease, HVPG > 10 mm Hg, liver stiffness >15 Kpa, proteins in ascites <2.5 g/L
	Budd-Chiari syndrome	Imaging test, proteins in ascites >2.5 g/L
	Sinusoidal obstruction syndrome	Appropriate clinical context (e.g. hemotopoietic stem cell transplantation), proteins in ascites >2.5 g/L
	Portal thrombosis	Imaging test, usually associated with a clinical trigger such as variceal bleeding
	Right heart failure	Right heart failure confirmed by echocardiogram, serum BNP >364 pg/mL, dilated suprahepatic veins, proteins in ascites >2.5 g/L
	Acute liver failure	Appropriate clinical context
	Massive liver metastases	Imaging test, proteins in ascites <2.5 g/L
	Myxedema	Clinical and laboratory findings of severe hypothyroidism
	"Mixed" ascites[*]	Imaging or other test according to clinical suspicion
<1.1	*Peritoneal carcinomatosis*	Positive citology, proteins in ascites >2.5 g/L, WBC >500 with PMNs<250, image test to find primary tumor (most frequent ovarian, gastric, and pancreatic origin)
	Peritoneal tuberculosis	WBC > 500 with PMNs<250 and predominance of lymphocytes, proteins in ascites >2.5 g/L, ADA >40 UI/L, positive culture or PCR, peritoneal biopsy
	Pancreatic ascitis	Ascitic amylase level usually >2000 UI/L, protein concentration in ascites variable, but normally >2.5 g/L, PMN > 250, imaging test to diagnose the underlying disease
	Bilious ascites	Elevated ascitic bilirubin levels and higher than serum, imaging test to diagnose the underlying disease
	Chylous ascites	Ascitic triglyceride level >110–200 mg/dL or higher than serum, imaging test to diagnose the underlying disease
	Nephrotic syndrome	Appropriate clinical context, proteins in ascites <2.5 g/L
	Protein-losing enteropathy	Diarrhea and other clinical symptoms due to the underlying disease, proteins in ascites <2.5 g/L
	Serositis related to connective tissue diseases	Rare manifestación of systemic lupus erythematosus, polyarteritis nodosa and Schölein-Henoch purpura. Appropriate clinical context
	Intestinal ischemia or obstruction	Imaging test

[*]Patients with cirrhosis and other cause (one or more) of ascites formation. Abbreviations: SAAG: serum-ascites albumin gradient; HVPG: hepatic venous pressure gradient; WCC: white blood cell; PMN: polymorphonuclear leukocyte; ADA: adenosine deaminase; PCR: polymerase chain reaction.

Table 1. Etiological classification of ascites according to the serum-ascites albumin gradient value.

dehydrogenase and glucose determination in ascitic fluid to assist in differentiating spontaneous from secondary bacterial peritonitis is supported by limited data and the European Association for the Study of the Liver (EASL) does not recommend its performance [2]. On the contrary, an ascitic fluid carcinoembryonic antigen >5 ng/mL or ascitic fluid alkaline phosphatase >240 units/L has been shown to be accurate in detecting gut perforation into ascitic fluid [16]. Other tests, such as amylase, triglycerides, and polymerase chain reaction (PCR) and culture for mycobacteria should be done only when there is a clinical suspicion of pancreatic disease, chylous ascites, and tuberculosis, respectively. Finally, it is worth mentioning that serum cancer antigen 125 levels are increased in patients with ascites of any cause. Therefore, its measurement is not recommended to guide the differential diagnosis [3].

3. Treatment of ascites

Current guidelines follow the classification of ascites from the International Ascites Club, which divides patients into three groups on the basis of a quantitative criterion. Each group is also linked to a specific treatment strategy (see **Table 2**) [3, 17]. Accordingly, only patients with ascites grade 2 or more should be treated, and they can be treated as outpatients unless they have other complications [2]. The aim of the treatment of ascites is to induce negative sodium balance by reducing sodium intake and increasing sodium excretion by the administration of diuretics.

3.1. Sodium restriction

In approximately 10–20% of patients with cirrhosis and ascites, we can obtain a negative sodium balance only by reducing dietary sodium intake, particularly in those presenting with their first episode of ascites [18]. No predictive factors of response to low sodium diet have been detected. Although the level of dietary restriction should be applied according to the baseline urinary sodium excretion, a moderate restriction of salt intake is generally recommended (intake of sodium of 80–120 mmol/day, which corresponds to 4.6–6.9 g of salt/day). This is generally equivalent to a no-added salt diet with avoidance of preprepared meals. A more severe reduction in dietary sodium content is considered unnecessary and even

Severity and definition	Treatment and strategy
Grade 1 or mild Diagnosed exclusively by ultrasonography.	No treatment is necessary.
Grade 2 or moderate Clinically evident.	Dietary sodium restriction and diuretics. (first spironolactone 50–100 mg/day to reach weight loss: 300–500 mg/day, if needed, add furosemide 20–40 mg/day and increase both every 7 days up to 400 and 160 mg/day, respectively)
Grade 3 or large Clinically evident or tense.	Large-volume paracentesis plus albumin 8 g/L of ascites removed in first place and later dietary sodium restriction (90 mmol/day) and diuretics.

Table 2. Ascites classification and treatment [17].

potentially deleterious since it may impair nutritional status [2, 3]. Fluid restriction is not necessary unless patients have hypovolemic hyponatremia (serum sodium <130 mEq/L together with ascites and/or edema). Fluid loss and weight change are directly related to sodium balance in these patients. It is sodium restriction, not fluid restriction, which results in weight loss, as fluid follows sodium passively [2].

3.2. Diuretics

Evidence demonstrates that renal sodium retention is mainly due to increased proximal as well as distal tubular sodium reabsorption rather than due to a decrease of filtered sodium load [2, 19]. The increased reabsorption of sodium along the distal tubule is mostly related to hyperaldosteronism. As previously mentioned, patients with ascites grade 2 require diuretic treatment if there is no contraindication. The goal of treatment is to achieve an average weight loss of no more than 500 g/day in patients without peripheral edema and no more than 800–1000 g/day in those with peripheral edema.

The efficacy of diuretic therapy in the control of ascites is approximately 90% in patients without renal dysfunction [2, 19]. The diuretics most frequently used are aldosterone antagonists, mainly spironolactone, which selectively antagonizes the sodium-retaining effects of aldosterone in the renal collecting tubules, and loop diuretics, especially furosemide, that inhibit the Na + −K + –2Cl – cotransporter in the loop of Henle. It has been extensively debated whether both types of diuretics should be combined from the beginning or use aldosterone antagonists in a stepwise increase every 7 days with furosemide added only in patients not responding to high doses of aldosterone antagonists. It can be concluded that a diuretic regime based on the combination of aldosterone antagonists and furosemide is the most adequate approach for patients with recurrent ascites but not for patients with a first episode of ascites. These latter patients respond well to spironolactone 50–100 mg/day [2]. Those with recurrent episodes of ascites or peripheral edema should receive a combination of spironolactone 100 mg/day with furosemide 40 mg/day [2, 19]. If there is no response, adherence to a low sodium-diet and diuretic treatment should be confirmed through a good anamnesis and a 24-hour urine sodium excretion measurement. An ascites that is not controlled despite a natriuresis greater than 80–110 mmol/day suggests a non-adherence to a low-sodium diet [3]. Given that full-day collections are cumbersome, the measurement of urine creatinine helps determine if the collection of the 24-hour specimen has been complete. Men with cirrhosis should excrete more than 15 mg of creatinine/kg of body weight per day, and women should excrete more than 10 mg/kg/day. Less creatinine is indicative of an incomplete collection [3]. A random "spot" urine sample is also useful to assess natriuresis and is the preferable test to adjust diuretic treatment in certain scenarios such as the emergency unit. A sodium concentration that is greater than the potassium concentration correlates well with a 24-hour sodium excretion. When the urine sodium/potassium ratio is >1, the patient should be responding to the treatment. The higher the ratio, the greater the urine sodium excretion [20]. In compliant patients with poorly controlled ascites, diuretics may then be increased every 7 days by doubling doses (1:1 ratio) to a maximal dose of spironolactone (400 mg/day) and a maximal dose of furosemide (160 mg/day). Unfortunately, diuretics can also have side effects and cause fluid and electrolytes balance disturbances such as hyponatremia, dehydration, renal impairment, hyperkalemia, or hypokalemia and subsequently, hepatic encephalopathy. For all these

http://dx.doi.org/10.5772/intechopen.70384

reasons, patients should be closely followed after the onset of diuretic treatment. Thus, a clinical evaluation and measurements of serum and urine electrolytes must be performed within the first 2 weeks after starting or modifying their dose. When any of the abovementioned side effects appear, diuretics should be stopped or their dose reduced. A particular side effect of spironolactone is tender gynecomastia and muscle cramps in some patients. Amiloride, a diuretic acting in the collecting duct, is less effective than aldosterone antagonists and should be used only in those patients who develop severe side effects with aldosterone antagonists [2].

3.3. Other general measures

Treatment of the underlying disease whenever possible is of great importance as dramatic responses have been described after alcohol abstinence, antiviral, and immunosuppressive therapies in patients with alcoholic, viral and autoimmune liver diseases, respectively [3]. Nutritional therapy can ameliorate nutritional status in cirrhotic patients, reduce infection rates, and decrease perioperative morbidity [11]. Some drugs must be avoided or use with caution in patients with ascites such as NSAID due to the high risk of developing further sodium retention, hyponatremia, and renal failure. In a recent case control study, 37% of the NSAIDs-associated acute kidney injury (AKI) cases were severe and persistent with a very poor short-term outcome [21]. Interestingly, Metamizol use was more common in patients with persistent AKI than in those with transient AKI, and therefore, this drug should also be used with caution. Likewise, angiotensin converting enzyme inhibitors, angiotensin II antagonists, or a1-adrenergic receptor blockers should generally not be used in patients with ascites because of increased risk of renal impairment [2]. Bed rest was previously recommended on the basis that the upright posture could aggravate the already elevated plasma renin levels of patients with liver cirrhosis and ascites. However, it is no longer advocated as there is insufficient evidence to support its use as part of ascites treatment [2]. There is an ongoing debate about the use of nonselective betablockers in patients with refractory ascites. The current guidelines from the American Association for the Study of Liver Diseases recommend to avoid high doses of these drugs (over 160 mg/day of propranolol or over 80 mg/day of nadolol), and in patients with concomitant severe circulatory dysfunction [i.e., systolic blood pressure <90 mm Hg, serum sodium <130 mEq/L, or hepatorenal syndrome (HRS)], their dose should be decreased or the drug temporarily held [22]. Finally, in unblinded randomized clinical trials (RCTs), the long-term albumin infusion (25 g weekly for one year and 25 g every two weeks thereafter) improved survival in patients with new onset ascites [23]. However, further studies are needed before this treatment can be advocated [3].

4. Complications, prognosis, and treatment

Despite the fact that patients with ascites constitute a heterogeneous population with different prognosis depending on the degree of liver insufficiency and circulatory dysfunction, the development of ascites is an ominous sign. The probability of survival at one and five years after the diagnosis of ascites is approximately 50 and 20%, respectively, and long-term

survival of more than 10 years is very rare [8]. In addition, mortality rises up to 80% within 6–12 months in patients who also develop kidney failure [1]. Patients with cirrhosis and ascites are also at high risk for other life-threatening complications of liver disease, including refractory ascites, SBP, respiratory distress, worsening of nutritional status, hyponatremia, or HRS. Accordingly, current guidelines recommend that every patient with ascites should be generally considered for referral for liver transplantation, especially when quality of life is impaired due to refractory ascites, or in the presence of SBE and HRS [2, 3]. Since 2002, the model of end-stage liver disease (MELD) score is used for patient priority in liver transplantation. However, MELD does not reflect the impact of some complications (the so-called Exceptions to MELD score) such as refractory ascites. Indeed, in some patients with this complication the latter score does not accurately reflect their poor prognosis (median survival is approximately 6 months) and their prioritization in the list should be assessed [24].

4.1. Refractory ascites

A nonnegligible number of patients with ascites (10%) develop refractory ascites due to severe sodium retention that cannot be mobilized pharmacologically either because there is no response to high diuretic dose (resistant ascites) or because side effects appear with the use of diuretics (intractable ascites). The term "recurrent ascites" defines an ascites that requires more than three admissions per year because of reaccumulation of ascites [25]. In these patients other therapeutical approaches must be used.

4.1.1. Large volume paracentesis (LVP)

Current guidelines recommend LVP as the first-line treatment in patients with refractory ascites, unless it is loculated [2, 3]. In order to minimize the number of paracentesis (LVP is usually performed every 2–4 weeks), total paracentesis is preferred and diuretic therapy can be maintained if the urine sodium is >30 mmol/day. It is a safe procedure with a complicate rate similar to diagnostic paracentesis, and it can be performed in the outpatient setting [2, 3]. LVP is defined as a volume above 5 L. Although Kao et al. arbitrarily selected this threshold in 1985 based upon the volume required to "adequately decompress the distended abdomen," the intra-individual neurohormonal changes induced by the removal of different ascitic volumes have not been examined [26, 27]. These neurohormonal changes reflect the physiopathological background of the main complication of LP, i.e., postparacentesis circulatory dysfunction (PPCD). Indeed, the removal of large volumes of ascites fluid can further decline the effective circulating volume by causing a significant drop in peripheral vascular resistance by mechanisms not fully elucidated. This hemodynamic derangement is demonstrated by a pronounced reactivation of renin-angiotensin-aldosterone and sympathetic nervous systems that can persist for months. An increase in plasma renin activity of 50% or greater is usually used to define PPCD [27, 28]. Although frequently asymptomatic, PPCD has been associated with significant detrimental effects such as re-accumulation of ascites, development of HRS and dilutional hyponatremia, and shortened survival [2]. It was first demonstrated in the 1980s that adjunctive albumin infusion can prevent PPCD occurrence and since the early 1990s, less costly alternatives to albumin have been sought, such as artificial colloid volume expanders and vasoconstrictors [28]. Despite initial uncertain results, a meta-analysis of

17 trials with a total 1225 patients demonstrated that albumin infusion after LVP is more effective than other plasma expanders (i.e., hypertonic saline, hydroxyethyl starch, and dextran-70, polygeline) for the prevention of PPCD and showed a trend to increased survival. The rate of PPCD was 73% after paracentesis without any re-expansion, 38% when combined with an infusion of dextran or gelatin solutions and only 15–17% when taps were combined with albumin administration. Doses of albumin infusion ranged between 5 and 10 g of albumin per liter of fluid removed [28]. Current guidelines recommend 8 g/L as this has been the dose most commonly used [2, 3]. It is usually administered during or after the paracentesis. Whether lower doses could be used is currently debated as one study comparing doses of 4 vs. 8 g/L showed similar efficacy in preventing PPCD and renal impairment [29]. When less than 5 L of ascites are removed, artificial plasma expanders, saline, and albumin are equally effective [2]. The latter meta-analysis also compared albumin with vasoconstrictors (i.e., midodrine, norepinephrine, and terlipressin). The results were more variable in this subgroup (OR from 0.30 to 5.54) due to the small size of the five included trials and therefore, no definitive conclusions can be made [28]. Further studies that target survival as the primary end-point in patients with truly refractory ascites are needed to fully demonstrate whether albumin or vasoconstrictors can improve survival.

4.1.2. Transjugular intrahepatic portosystemic shunt (TIPS)

Another treatment option for patients with refractory ascites is transjugular intrahepatic portosystemic shunt (TIPS). It is a procedure in which an intrahepatic stent is inserted between the hepatic and portal veins with intent for portal decompression to avoid the recurrence of ascites [30]. The optimal portal pressure gradient (PPG) that needs to be obtained to adequately control ascites is not clear, but might be lower than the well-validated 12 mm Hg threshold for the prevention of rebleeding from esophageal varices [30]. Most of randomized clinical trials (RCTs) aimed to reduce PPG below 12 mm Hg by dilating 10-mm diameter stents to 6–8 mm with subsequent calibration up to 10 mm, depending on post-PPG and clinical response [31–34]. By this approach, marked reductions in PPG are avoided, which may be associated with an increased risk of hepatic encephalopathy and liver failure. Until today, seven RCT [31–37] and six meta-analysis [38–43] have assessed the efficacy and safety of TIPS in patients with refractory and recurrent ascites. They have consistently demonstrated that TIPS is effective in the management of this complication, but is associated with higher risk of hepatic encephalopathy compared to LVP. Thus, about 64% (range of 38–84%) had their ascites controlled (although its resolution was slow and most patients required continued administration of diuretics and salt restriction), and hepatic encephalopathy occurred in approximately 51% of patients (39% severe) treated with TIPS. This latter complication is known to increase the rate of mortality and hospitalization and to significantly affect the quality of life [30]. TIPS dysfunction due to pseudointimal hyperplasia within the parenchymal tract or within the outflow hepatic vein was another major drawback in these studies. Indeed, a significant proportion of patients (from 30 to 87%) needed TIPS revision due to malfunction. It must be emphasized that all, but one clinical trial [34], used bare stents instead of the politetrafluoroethylene-covered stents that are used today. These covered-stents have greatly improved shunt patency rates and have also reduced the incidence of hepatic encephalopathy after TIPS placement [30]. There is great controversy over the survival benefit of TIPS in refractory ascites. At the time current guidelines were published, studies had not convincingly proved that TIPS improved survival compared

to repeated LVP, and consequently, it was left as a second-line therapy that had to be considered in patients with very frequent requirement of LVP or with loculated ascites [2, 3]. Among the five trials that had been published at that time, transplant-free survival was significantly improved in two (in one of them only in the multivariate analysis) [33, 36], decreased in one (probably due to technical disability) [35], and not affected in the other two [31, 37]. These discrepancies among studies were likely due to patient selection and data analysis biases. These RCTs excluded patients with advanced liver disease (as defined by serum bilirubin > 5–6 mg/dL, INR > 2, current or chronic HE > 2 by West-Heaven scale), and renal failure (as defined by serum creatinine >3 mg/dL) and thus, only 48% (median, 21–77%) of the screened patients could be included in the RCTs. Meta-analysis also contributed to this controversy. Four conventional meta-analysis did not show any benefit in survival [38–41], whereas a meta-analysis of individual patient data from four RCT showed a significant improvement in transplant-free survival at 1 and 2 years between TIPS and LVP (63 and 49% vs. 53 and 35%, $p = 0.035$) [42]. After the publication of the current guidelines, two RCT [32, 34] and another meta-analysis [43] have been published and concluded that TIPS is more effective in controlling ascites than repeated LVP and improved transplant-free survival in these patients. The RCT of Narahara et al. included 60 patients with refractory ascites treated with bare metal TIPS or LVP. The selection criteria were stricter than the previous RCT and included patients with better preserved renal and hepatic function [32]. The last RCT was recently published and included patients with recurrent ascites treated with covered-stents or LVP with inclusion criteria similar to the former RCT [34]. It can be concluded that pending further RCT with covered stents, TIPS can be recommended in patients with refractory ascites and preserved liver function (Child–Pugh score <13, MELD score <18, bilirubin <5 mg/dL, platelet count >75,000, serum sodium >130 mEq/L), aged <70, no previous episodes of hepatic encephalopathy, and neither central or large hepatocellular carcinoma nor cardiopulmonary disease [19]. In fact, some authors and scientific associations recommend TIPS as the primary therapy for refractory ascites [44–46].

4.1.3. Automated low flow pump system (Alfapump System)

The alfapump is a subcutaneous battery-operated pump to move ascites from the peritoneum to the urinary bladder. One catheter connects the pump to the peritoneal cavity, and another connects it to the urinary bladder. Every 5–10 min small volumes of ascites (generally 5–10 mL) are pumped into the urinary bladder, ranging the daily volume that can be removed between 500 mL and 2.5 L. In order to improve patient's comfort it is deactivated at night. The pump battery is charged via a charging device (Smart Charger, Sequana Medical AG, Zürich, Switzerland) that is placed over the area of the pump twice daily during no more than 20 min. It is at this time when pump function parameters (e.g., volumen transported, pressures in the bladder and abdominal cavity) are automatically transmitted to the charger. This information is forwarded to a central databank and communicated, if needed, to the treating physician, who can remotely program the system to the patient's needs or contact the patient because of possible technical issues. The current price of the device is 22,500 Euros [47].

The alfapump was conceived as an alternative treatment for refractory ascites, especially in those patients who are not candidates for TIPS [47, 48]. This system also requires a good selection process, in which issues such as compliance of the patient, nutritional status, previous abdominal surgery, urinary outlet obstruction, or local skin infections should be carefully evaluated before its

implantation [47]. An initial multicenter, prospective, uncontrolled study (PIONEER) evaluated its safety and efficacy in 40 patients over a period of 6 months. It showed that the pump removed 90% of the ascites and reduced the median number of LVP, but with a significant rate of complications mainly due to infections and catheter dislodgement [49]. However, the number of complications was reduced along the study after including some changes recommended by the data safety monitoring board (i.e., antibiotic prophylaxis with norfloxacin, strict avoidance of NSAID, and the intravenous administration of albumin if ascites was aspired during the surgical intervention) [47]. A recent RCT compared the safety and efficacy of the alfapump system in comparison with LVP in 58 cirrhotic patients with refractory ascites over a 6-month period [48]. The alfapump was more effective reducing and, in many cases, eliminating (more than 50%) the need for paracentesis. It also improved the quality of life and nutritional status of the patients. Survival was similar in both groups, despite the occurrence of more adverse events (96.3 vs. 77.4%, $p = 0.057$), which were also more frequently severe (85.2% vs. 45.2%, $p = 0.002$) in the group treated with alfapump. Adverse events consisted predominantly of AKI in the immediate post-operative period, and re-intervention for pump-related issues. Device deficiencies accounted for seven re-interventions, which are an improvement compared to the results of the PIONEER study and may reflect the continual technological improvements to the alfapump system since commercialization in 2011. After the postoperative period (>7 days), the incidence of AKI and hyponatremia was similar in both groups, but more of these events required hospitalization in the alfapump group. The underlying mechanism for this renal dysfunction and hyponatremia remains unclear. In a recent prospective study that included ten patients with refractory ascites treated with the alfapump system, a marked activation of endogenous vasoconstrictor systems and impairment of kidney function after the device insertion was observed. This finding led the authors to hypothesize that treatment with alfapump might impair effective arterial blood volume mimicking a postparacentesis circulatory dysfunction syndrome and suggested a potential role of albumin in counteracting these effects [50]. Supporting this hypothesis, the authors of the RCT observed an increase in plasma renin activity at 3 months. Finally, total median cost (including implantation procedure and device, scheduled visits, lab test, medications and treatment of adverse events) was significantly higher in the alfapump group (£36970 vs. £12660, $p < 0.0001$). The difference was primarily due to the statistically higher cost of implantation procedure and adverse effects [48]. It can be concluded that further refinements in patient selection, patient care algorithms (including regular albumin administration), and modifications in device design are needed before the alfapump can become a truly alternative treatment for patients with refractory ascites.

4.1.4. Vaptans

Vaptans are V2 vasopressin receptor antagonists acting on the kidney and promoting solute-free water diuresis. In patients with cirrhosis, they have been studied in the setting of dilutional hyponatremia (see below section 6) and ascites. In patients with both uncomplicated and refractory ascites, satavaptan did not have a clinical benefit in controlling ascites and even increased mortality, which was related with known complications of liver cirrhosis [51, 52]. Consequently, the drug was withdrawn from development. Tolvaptan has also been used in patients with liver cirrhosis and refractory ascites. Most of the data come from observational studies in which tolvaptan seemed to improve control of

ascites [53–57]. Two RCT also showed that tolvaptan was more effective than placebo for the treatment of ascites-related clinical symptoms. However, in both trials, the drug was given for only 7 days and the follow-up period was no longer than 3 weeks [58, 59]. Both issues are of great concern, given that its efficacy is lost after the discontinuation of the drug [60] and that a black-box warning by the Food and Drug Administration determined that tolvaptan should not be used for longer than 30 days, and limited its use in patients with underlying liver disease. The latter warning came from an increased risk of liver injury in a recent large clinical trial evaluating tolvaptan for a new use in patients with autosomal dominant polycystic kidney disease [61]. Therefore, the use of vaptans in cirrhotic patients with uncomplicated or refractory ascites cannot be recommended at present and required further RCT with a longer follow-up [3, 11].

4.1.5. Vasoconstrictors

Since arterial splanchnic vasodilation plays a major role in the pathogenesis of ascites formation, the use of vasoconstrictors has been evaluated in the treatment of patients with refractory or recurrent ascites. In two preliminary studies both the acute and 7-day administration of Midodrine, an alfa-1-adrenergic agonist, in nonazotemic cirrhotic patients with ascites improved systemic hemodynamics and sodium excretion [62, 63]. Similarly, in another study, the addition of midodrine corrected the deleterious effects on renal function of octreotide and improved systemic hemodynamics [64]. The first study evaluating its effect on patients with refractory or recurrent ascites was a RCT in which 40 patients were randomized to oral midodrine (7.5 mg every 8 h) plus standard medical therapy (sodium restriction plus diuretics) or to standard medical therapy alone. Midodrine significantly improved systemic hemodynamics without significant complications and was superior for the control of ascites at 3 months, but not at 1 and 6 months after therapy. Moreover, the mortality rate in the standard medical therapy group was significantly higher than that in the midodrine group ($p < 0.046$) [65]. A recent pilot study evaluated the efficacy and safety of midodrine in combination with tolvaptan in 50 cirrhotic patients with refractory or recurrent ascites. Their combination controlled ascites significantly better than standard diuretic treatment alone and more rapidly than midodrine alone [66].

Clonidine, a centrally acting α2-agonist and sympatholytic agent, has also been evaluated as an adjunct treatment in patients with cirrhosis and refractory ascites. In two pilot studies, its addition to spironolactone increased natriuresis and body weight loss more efficiently than spironolactone alone in patients with cirrhosis and ascites and activated sympathetic nervous system [67, 68]. Years later, the same group performed a first RCT that included patients with cirrhosis, ascites, and a plasma norepinephrine level of >300 pg/mL. Oral clonidine (0.075 mg b.i.d.) led to an earlier duretic response and was associated with fewer diuretic requirements and complications [69]. A later RCT using the same dose of clonidine for 3 months evaluated its efficacy in 270 patients with refractory ascites. The response rate to the association of clonidine and diuretics was 55–60%. The highest efficacy was obtained in patients who had high serum levels of norepinephine and the presence of two specific polymorphisms of the G-protein and α2-adrenergic receptor gene [70]. The efficacy of the combination of clonidine and midrodine was evaluated in a RCT that included 60 patients with refractory and recurrent ascites. Their combination controlled ascites significantly better than standard diuretic treatment alone over a 1-month period, but was not superior to midodrine or clonidine alone [71].

http://dx.doi.org/10.5772/intechopen.70384

Finally, there is very limited data available with terlipressin. In a small RCT that included 15 patients with nonrefractory ascites and 8 with refractory ascites without HRS, 2 mg of intravenous terlipressin improved renal function and natriuresis in both types of ascites. However, a clinical effect on weight or abdominal girth was not recorded [72]. In a prospective study in which 26 patients with refractory ascites without HRS were treated with maximum diuretic treatment plus albumin and terlipressin, complete and partial response were observed in 62 and 23% of the patients, respectively [73].

With the available evidence, the American Association for the Study of Liver Diseases recommends that the use of oral midodrine should be considered in patients with refractory ascites [3]. On the other hand, the European Association for the Study of the Liver considers that larger RCT with longer follow-up are needed before these drugs can be routinely recommended in the management of these patients [2]. The authors of this chapter are in agreement with this last recommendation.

Figure 1 depicts the pathophysiological rationale for the treatment of patients with ascites and other related complications.

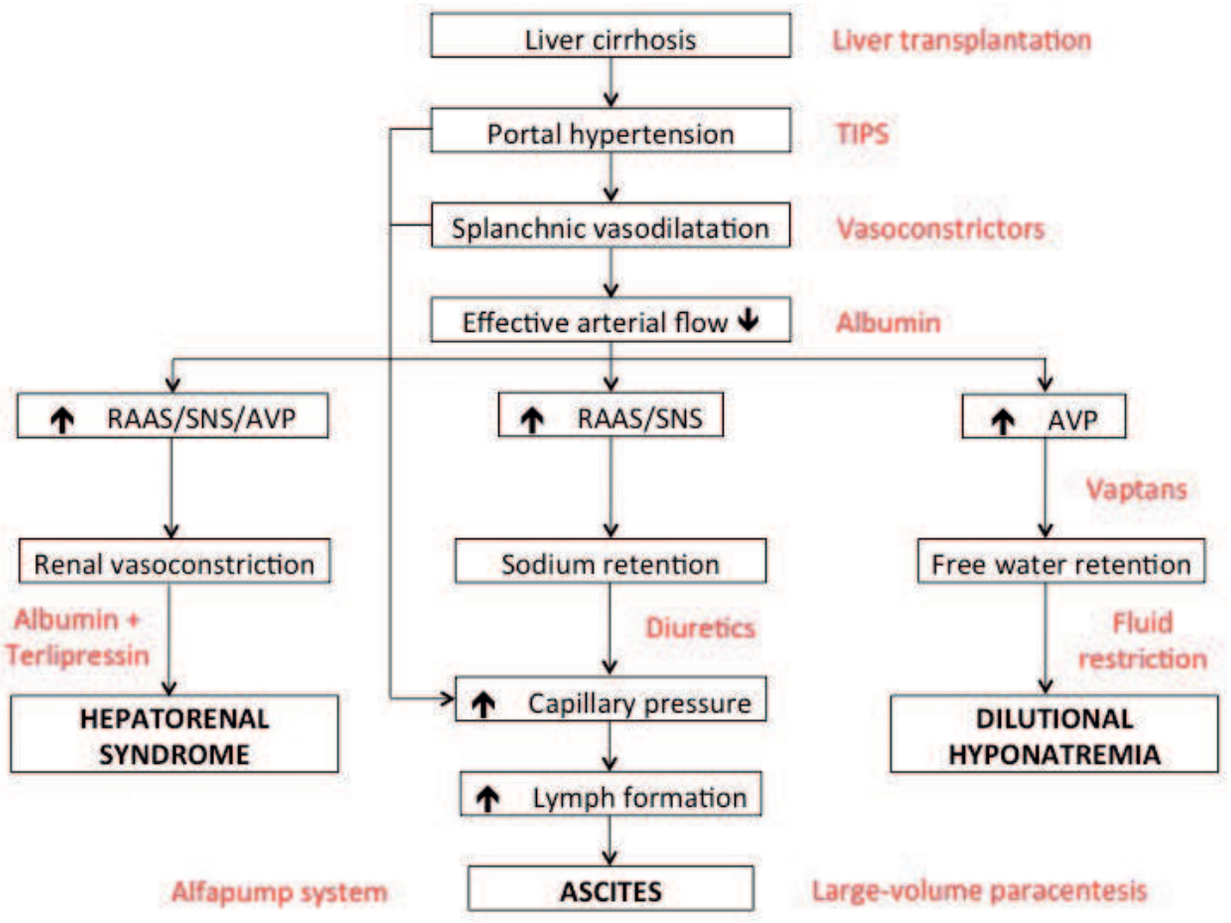

Figure 1. Physiopathology and treatment of patients with ascites and other related complications. Splanchnic vasodilatation driven by portal hypertension leads to an arterial underfilling that is counteracted by the activation of antinatriuretic and vasoconstrictor factors (RAAS, SNS, and AVP) that may lead to development of ascites, dilutional hyponatremia, and hepatorenal syndrome. Current therapies act at different levels of this pathophysiological cascade. Abbreviations: TIPS: transjugular intrahepatic portosystemic shunt; RAAS: renin-angotensin-aldosterone system; sympathetic nervous system; AVP: arginine vasopressin.

5. Spontaneous bacterial peritonitis (SBP)

Compared to general population, patients with cirrhosis have an increased risk of developing bacterial infections and sepsis, for this reason, SBP has a remarkable importance. SBP is a common infection of ascitic fluid developed in patients in the absence of an intra-abdominal genesis of infection. SBP was described for the first-time long time ago, approximately in the 1970s by Harold Conn [74], who pointed out the high in-hospital mortality in patients with this complication. The mechanisms leading to SBP include bacterial translocation, the reduced gut motility giving place to intestinal bacterial overgrowth, altered structure, and function of the intestinal mucosal barrier, and shortage in local immune response systems [75]. Patients with cirrhosis and SBP frequently develop an exaggerated inflammatory response with a severe impairment in renal, cardiovascular, or other organs functions. This syndrome is called acute or chronic liver failure and implies a high rate of hospital mortality [76].

SBP is the most frequent bacterial infection in hospitalized patients with cirrhosis [77]. It occurs in approximately 15–30% of hospitalized patients. Approximately 70% of the episodes of SBP is present when patients are admitted to the hospital, and the rest, 30%, is acquired during hospitalization [78]. The clinical manifestations in patients with SBP are usually symptoms such as abdominal pain, diarrhea, fever, chills, and hepatic encephalopathy, but in approximately 25% of cases of SBP, there are no apparent symptoms. Subclinical manifestations could occur as, for example, deterioration in renal function without other cause or development of tense and refractory ascites in a patient previously responsive to diuretics.

The prognosis in patients with SBP is very poor. The mortality during hospitalization is still remarkably high (20–40%) and is due to other complications that could appear because of the advanced liver disease. The most determinant prognostic factor in patients with SBP is the development of HRS [79]. The development of type-1 HRS and the poor short-term prognosis in these patients mostly depends on the degree of liver and renal impairment at diagnosis of SBP. There are several related-factors to an increased risk of type 1 HRS in patients with SBP; serum bilirubin levels ≥4 mg/dL, serum creatinine levels ≥1 mg/dL, and BUN ≥30 mg/dL [80–83]. In addition, SBP may trigger severe life-threatening complications, as for example, renal impairment, gastrointestinal bleeding, and deterioration of hepatic insufficiency, which are responsible for the associated high mortality.

The importance of an early diagnosis and the use of an adequate treatment are crucial in the survival. As previously mentioned, its diagnosis requires a polymorphonuclear leukocyte count greater than 250 cells/mm^3 [2]. The most common organisms isolated in SBP are *Escherichia coli, Klebsiella pneumoniae,* and *Streptococcus pneumoniae* [19]. The organism responsible for the infection is isolated in 60–70% of the cases. The remaining cases without the isolation of the organism are considered to have a culture-negative SBP and are treated in the same way as those with a positive culture. In the diagnostic procedure of SBP, must be a differentiation between SBP and secondary peritonitis. Secondary peritonitis is defined because it follows a primary abdominal infection such as gallbladder infection, diverticulitis, or gut perforation. Patients' general conditions rapidly deteriorates in those with secondary peritonitis, for this reason, the diagnosis must be quick, and can be confirmed by a laboratory workup, showing at least two of the following

conditions: low glucose concentration levels in ascitic fluid (<50 mg/mL), ascites lactate dehydrogenase higher than serum lactate dehydrogenase, and finally, ascites concentration of proteins >1.5 g/dL. Other typical characteristics in secondary peritonitis are positive cultures with different bacteria, very high count of neutrophils in blood and ascitic fluid. When these conditions appear, a CT scan is recommended to localize the source of the infection [84, 85].

Current guidelines recommend the onset of the empirical treatment immediately after the diagnosis of the infection, and it should be performed with broad-spectrum antibiotics such as a third-generation cephalosporin [2, 3]. Until the last 10 years, the use of third-generation cephalosporins has been shown to be highly effective in the treatment of SBP. Gram-negative bacteria (particularly enterobacteriaceae) were responsible for the majority of the episodes of SBP [86]. However, the etiology and epidemiology in patients with cirrhosis and SBP have changed in the last years, and the efficacy of the third-generation cephalosporins as well as that of alternative therapies such as amoxicillin-clavulanic or quinolones has decreased [78]. It has been speculated that prophylaxis with norfloxacin and invasive procedures could have caused these changes [87].

Patients with nosocomial SBP have a high incidence of multidrug resistant (MDR) bacteria and have a poor response to third-generation cephalosporin in up to 25–66% of cases [78, 88]. Patients with an ineffective first-line treatment for SBP have been associated with very poor survival [86]. A group of experts suggested in 2014 a modification of the current guidelines in patients with nosocomial SBP by using a broader-spectrum of antibiotics, but it was not until last year, when a randomized controlled trial of 32 patients in Padua compared different antibiotic treatment of nosocomial SBP. Patients were randomized to receive meropenem plus daptomycin vs. cetazidime. After 48 hours of treatment, a paracentesis was performed and if the neutrophil count of the ascitic fluid decreased less than 25% compared to pretreatment value, it was considered a treatment failure. The main outcome was the resolution of SBP after 7 days of treatment. The arm with the combination of meropenem plus daptomycin was markedly more effective than the arm of only the third-generation cephalosporin (87 vs. 25%, respectively) with a p value of <0.001. In the study, 90-day transplant-free survival was also evaluated without significantly different values between both arms of treatment, and the last important issue to be described of the study, in the multivariate analysis of 90-day transplant-free survival. The independent predictive factors or survival were ineffective response to first-line treatment (hazard ratio: 20.6; $p < 0.01$), development of AKI throughout the hospitalization (HR: 23.2; $p < 0.01$), and baseline mean arterial pressure (HR: 0.92; $p < 0.01$) [89].

Different broad-spectrum of antibiotics have been proposed, but carbapenems should be used in order to widely cover the spectrum of Gram-negative MDR bacteria. Regarding Gram-positive bacteria, linezolid, lipo, or glycopeptides should be used, but there are some concerns about the high risk of nephrotoxicity and the high rate of vancomycin-resistant enterococci in patients with cirrhosis and nosocomial infections treated with glycopeptides. Duration of therapy should be a minimum of 5–7 days. In patients who develop renal impairment, it is recommended to use intravenous albumin (1.5 g/kg at diagnosis, followed by 1 g/kg on day 3) along with ceftriaxone [90]. The SBP resolution rate ranges between 70 and 90%. Despite the resolution of the infection, patients recovering from an episode of SBP should be considered as potential candidates for liver transplantation.

In patients who have had one episode of SBP, the recurrence rate within 1 year is 70% [91]. Long-term norfloxacin administration (400 mg/day p.o) decreases the recurrence within the first year after SBP from 68% in the placebo group to 20% in the treated group. Therefore, with these results, all patients with a previous episode of SBP should be treated with norfloxacin indefinitely until liver transplantation, death, or resolution of ascites [90, 92].

Prevention of SBP should always be considered especially in high-risk patients, including those with acute gastrointestinal hemorrhage, low ascitic fluid protein concentration (<10–15 g/L), survivors of a previous episode of SBP, and advanced cirrhosis [2]. A RCT showed that the administration of primary prophylaxis with norfloxacin in patients with low protein ascites (<15 g/L), advanced liver disease (Child Pugh score ≥9, serum bilirubin ≥ 3 mg/dL), or deterioration of kidney function (serum creatinine ≥1.2 mg/dL or serum sodium <130 mEq/L) significantly reduce several complications such as 1 year probability of developing SBP (from 61 to 7%), HRS (from 41 to 28%), and improved 3-month survival (from 62 to 94%) [83]. In addition, Soriano et al. demonstrated that intestinal decontamination with norfloxacin was useful to prevent SBP in hospitalized patients with low ascitic fluid protein levels (23 vs. 0%) [91]. Although prophylaxis strategies are beneficial in several aspects, long-term administration of antibiotics leads to the emergence of MDR bacteria as previously explained. However, due to the problem of antibiotic resistance, clinical judgment must guide the use of antibiotic prophylaxis [93]. Rifaximin has been recently proposed as a possible alternative treatment in prophylaxis of SBP. A case control study published many years ago showed that rifaximin was beneficial in the prevention of SBP in patients with hepatic encephalopathy [94]. Since then two studies have compared the efficacy of rifaximin vs. conventional prophylaxis (i.e., norfloxacin) and have provided contradictory results. In a prospective study including patients with and without previous SBP, rifaximin did not lead to a reduction of SBP occurrence in hospitalized patients with advanced liver disease, despite a greater proportion of patients with previous SBP in the norfloxacin group (89 vs. 15%, $p < 0.001$) [95]. Conversely, in a RCT including 260 patients with ascites and a previous episode of SBP, rifaximin was more effective than norfloxacin in reducing the recurrence of SBP (3.9% vs. 14.1%; $p = 0.04$) and even improved survival (13.7% vs. 24.4%; $p = 0.044$) during an 18 month of follow-up [96].

6. Hyponatremia

Furthermore, ascites is very often complicated by a disability of solute-free water excretion. In this setting, the antinatriuretic pathway involves the oversecretion of arginine vasopressin (AVP) that enhances the function of the vasopressin 2 (V2) receptors in the renal distal collecting tubules, inhibiting solute-free water excretion [97]. In this scenario, the AVP production is increased, and there is a lack of clearance of AVP due to cirrhosis itself. In addition, V2 is excessively bound by AVP, triggering more free water retention in kidney tubules by the creation of more aquaporin-2 channels to retain more water. Therefore, these patients cannot remove enough water and results in worsening serum dilution and hypoosmolarity [98]. All this mechanism gives place to dilutional hyponatremia, which is the commonest form of hyponatremia in patients with cirrhosis.

http://dx.doi.org/10.5772/intechopen.70384

In patients hospitalized with cirrhosis and ascites, the prevalence of hyponatremia, defined by sodium <135 mEq/L, is about 22%, which rises to 49% if the cut-off point is 130 mEq/L. The presence of hyponatremia implies a poor prognosis. It has been demonstrated that hyponatremia is an independent predictive factor to have an increased morbidity and mortality and has been added to the MELD score (Sodium-MELD) for liver donor allocation in the United States [99]. When there is a decrease of 1 unit of sodium below 135 mEq/L, the mortality risk increases by over 10% in patients who are in the list for liver transplant [100]. In addition, it has been demonstrated that hyponatremia is a common event in patients with cirrhosis that may lead to hepatic encephalopathy, with implies a significant decline in quality of life and increased neurological complications throughout liver transplantation. Several transplant centers require correction of hyponatremia prior to liver transplantation, but there is no standard algorithm.

There are several types of hyponatremia. On the one hand, hypervolemic or dilutional hyponatremia as explained previously, and on the other hand, hypovolemic hyponatremia, which is usually secondary to excessive fluid losses from the kidney (overdiuresis secondary to diuretic treatment) or from gastrointestinal tract due to diarrhea. If there is an evidence of dehydration or prerenal azotemia, the treatment in these patients consists in solving the cause with fluid volume expansion replacement. Otherwise, if there is a hypervolemic hyponatremia in the setting of volume overload, it is much more difficult to correct the hyponatremia and for patients to tolerate properly the correction. The therapy consists mainly in water restriction and the increase of free water renal excretion. Daily dietary fluid restriction is recommended to 1.5 L, particularly when the serum sodium is below 130 mEq/L. The main drawback of this strategy is the poor patient's compliance and low response. Another point in the treatment is the diuretic adjustment or withdrawal if it is required.

A study of 997 patients with cirrhosis and ascites demonstrated that serum sodium is less than or equal to 120 mmol/L in only 1.2% of patients and less than or equal to 125 mmol/L in only 5.7% [101]. Attempts to rapidly correct hyponatremia in this setting with hypertonic saline can lead to more complications than the hyponatremia itself [2]. Fluid restriction (i.e., 1–1.5 L of water per day) is seldom effective in improving hyponatremia, but prevents a further decrease in sodium levels [2, 3].

There are other strategies under investigation such as increasing the effective arterial blood volume with intravenous albumin with or without vasoconstrictors as, for example, midodrine. These studies are nonrandomized, and there is a need of further studies before their incorporation into clinical practice [102]. Another interesting treatment option for dilutional hyponatremia is the use of vaptans. They induce the release of solute-free water into urine and improve hyponatremia in patients with cirrhosis [103, 104]. Vaptans result useful and effective in improving sodium levels in 45–82% of patients with dilutional hyponatremia. However, the effect is short and goes back to baseline hyponatremia after the withdrawal of the drug, and they do not improve survival. The side effects of this drug are dehydration, thirst, AKI, and overcorrection of sodium levels. Experts in the issue recommend the use of vaptans for a short period of time in patients with hyponatremia below 125 mEq/L who are hospitalized waiting for a liver transplant. Although they have been approved by the Food and Drug Administration and the European Medication Agency for the management of hypervolemic hyponatremia, their widespread use in cirrhosis warrants further long-term studies [2].

7. Hepatorenal syndrome (HRS)

Finally, the last important complication related with ascites is the development of a harmful event such as HRS. HRS is a late manifestation of extreme circulatory dysfunction with a marked vasoconstriction of the kidney arteries trying to compensate splanchnic vasodilatation secondary to portal hypertension. HRS usually appears in patients with cirrhosis and advance stage of liver dysfunction, and it is always accompanied by ascites and usually hyponatremia [105].

HRS may appear with or without precipitating factors, and there are several predictive factors for the development of HRS. The development of bacterial infections, particularly SBP, is the most important risk factor for HRS (30%) [106]. Other important causes include infections, hypovolemia, paracentesis, and bleeding and nephrotoxic medication. HRS is a potentially reversible functional renal impairment in patients with cirrhosis. It may be rapidly progressive (type I HRS) or may develop gradually (type II HRS), which is usually associated with refractory ascites [106]. HRS is diagnosed with clinical and analytical data and its definition has been updated recently. Since the first definition of HRS type 1 in 1994, there have been slight changes, the last one being in 2015 in the revised consensus recommendations of the International Club of Ascites (ICA) [93]. This last change has been made adopting the concept of AKI originally developed in general critically ill patients and has removed the high cut-off value of serum creatinine (2.5 mg/dL or 220 μmol/L) to start pharmacological treatment with vasoconstrictors. HRS type 1 is defined when AKI stage 2 or more is fulfilled with the rest of HRS criteria (see **Table 3**) [80]. In this way, vasoconstrictors and albumin can be administrated earlier and thus potentially achieving a better efficacy. Although this new definition could have benefits in the efficacy, there is still a lack of biomarkers to differentiate between HRS and parenchymal kidney disease such as acute tubular necrosis. The adequate differentiation could select patients with a real functional damage to start the correct treatment as soon as possible. Recently, there are several urine biomarkers under study, trying to help in this hard work.

The prognosis of HRS remains poor, with an average median survival time of nearly 3 months. High MELD scores and type 1 HRS are associated with very poor prognosis. Median survival of patients with untreated type 1 HRS is approximately 1 month [107]. Current guidelines from the European Association for the Study of the Liver emphasize the early detection and treatment of HRS and give priority to liver transplantation [2].

- Diagnosis of cirrhosis with the presence of ascites
- Acute kidney injury stage 2 or more following the International Ascites Club—Acute kidney criteria
- No response to the withdrawal of diuretics and albumin expansion for 48 h
- Absence of shock
- Absence of nephrotoxic drugs in the recent days
- Absence of structural kidney damage evaluated with hematuria >50 hematites/camp, proteinuria >500 mg/day, and normal kidney ultrasonography

Table 3. Hepatorenal syndrome criteria [93].

7.1. Clinical and pharmacological treatment

7.1.1. Terlipressin and norepinephrine

Diuretics should be removed and albumin expansion (1 g/kg) for 48 hours must be administrated if there is no contraindication. If there is no response and the rest of HRS criteria are fulfilled, these patients should be admitted to an intensive care unit. Fluid balance, arterial pressure, vital signs, and central venous pressure are ideally required to prevent volume overload. Current standard treatment involves the use of vasoconstrictors therapy: Terlipressin (1 mg/4–6 hours intravenous bolus) with albumin (20–40 g/day) should be considered as the first-line treatment, and if not available, norepinephrine is a valid alternative. A recent study demonstrated that the administration of terlipressin in continuous infusion instead of boluses had the same rate of response and less side effects [108]. Seventy-eight patients were randomly assigned to receive either continuous intravenous infusion (2 mg/day) or intravenous boluses (0.5 mg/4 h), and if there was no response, the dose was progressively increased to a final dose of 12 mg/day in both groups. The rate of side effects was lower in the infusion than in the boluses (35.29 vs. 62.16%, respectively, $p < 0.025$). The rate of HRS reversal (total and partial) was not significantly different in both groups (76.47 vs. 64.85%). This standard treatment with vasoconstrictor and albumin is effective in 40–50% approximately, although in the last study explained previously it was about 70%. The recurrence of HRS after stopping the vasoconstrictor is about 40%. There are a few studies assessing independent predictive factors of response to terlipressin, and these studies showed a relationship between the improvement in systemic hemodynamics and the effectiveness of treatment. In a study performed in Barcelona, patients with an increase in mean arterial pressure (MAP) of at least 5 mm Hg at day 3 after the beginning of terlipressin, had a higher rate of response. In addition to the improvement in hemodynamics, the degree of liver dysfunction, evaluated with bilirubin greater than 10 mg/dL, was related to a poor response to terlipressin [109]. Another study performed in United States showed that baseline serum creatinine before the beginning of terlipressin predicted the resolution of HRS, and with this information they suggested that an earlier start of treatment would be more effective [110].

A recent RCT compared norepinephrine with terlipressin and demonstrated that reversal of HRS was similar to terlipressin (43 vs. 39%, respectively). Furthermore, there was no statistical difference in survival in both arms: 39% in norepinephrine group and 48% in terlipressin group ($p = 0.461$) [111]. In addition, a recent meta-analysis of 152 patients suggested that norepinephrine is also an effective option for the treatment of HRS as good as terlipressin, when is used in combination with albumin [112].

7.1.2. Midodrine and octreotide

Other therapeutic option is the combination of midodrine and octreotide plus albumin. This therapeutic option has been used widely in countries where terlipressin is not available. A RCT has demonstrated a worse response rate in patients treated with midodrine and octreotide compared to the arm treated with terlipressin (5 vs. 56%, respectively. $p < 0.001$). Ninety-day survival was also lower in the midodrine and octreotide group (29 vs. 56%, $p < 0.06$) [113].

To summarize all these data, although norepinephrine requires an intensive care unit for its use, it is an effective alternative to terlipressin for the treatment of HRS. On the other side, the combination of midodrine and octreotide is not an effective treatment.

7.1.3. Transjugular intrahepatic portosystemic shunt (TIPS)

Transjugular intrahepatic portosystemic shunt (TIPS) may be considered as a second-line therapy, although there is weak evidence to support its use in this complication [2]. TIPS is usually contraindicated in patients with HRS because the syndrome appears in the setting of advanced liver dysfunction. Few small trials have shown renal function improvement and a decrease in renin, aldosterone, and norepinephrine levels after the TIPS insertion [114, 115]. However, data is not strong enough to recommend its use in clinical practice.

7.1.4. Renal replacement therapy

Renal replacement therapy is recommended in guidelines when everything fails, but implies an even worse prognosis [2, 3, 107]. In clinical practice, it is used in patients awaiting liver transplantation, whose renal function did not respond to vasoconstrictor treatment.

7.1.5. Molecular adsorbent recirculating system (MARS)

Liver support with molecular adsorbent recirculating system (MARS) has been used in studies with small sample size in patients who did not respond to standard treatment and it was not effective in changing systemic hemodynamics and kidney function [116]. Only one trial showed a decrease in serum creatinine and bilirubin levels in the arm treated with MARS in comparison to hemodialysis arm [117].

All these invasive treatments are controversially recommended to use in patients without the possibility of liver transplantation and should only be assessed in patients awaiting liver transplant.

7.2. Prevention of HRS

As previously, HRS can be avoided in several situations. The first situation that HRS could be avoided is in large volume paracentesis (LVP). We must give 6-8g of albumin/liter of ascites removed. This action will prevent worsening of circulatory dysfunction, and second, renal impairment, in addition, it also improves survival [2].

The second situation to prevent HRS is in the scenario of SBP. It could be prevented with primary prophylaxis with norfloxacin. Fernandez et al. showed that norfloxacin administration reduced the development of HRS (28 vs. 41%, $p < 0.001$) and 3-month mortality (94 vs. 62%, $p = 0.003$). In addition, norfloxacin administration reduced the 1-year probability of developing a SBP (7 vs. 61%, $p < 0.001$) compared to placebo [83]. Therefore, primary prophylaxis with norfloxacin has an outstanding impact in the clinical course of patients with cirrhosis, reduces the incidence of SBP, delays de development of HRS, and improves survival. This effect is probably secondary to the reduction of bacterial products in the gut, and hence reducing bacterial translocation.

As explained previously, SBP can trigger a kidney failure, which implies a fatal prognosis. In this situation, the utilization of intravenous albumin infusion may improve the effect on circulatory dysfunction in this setting. The study in the Hospital Clinic of Barcelona showed a better 3-month-survival (41 vs. 22%, $p = 0.03$) and lower incidence of kidney failure in patients treated with albumin. (10 vs. 33%, $p = 0.002$). There are ongoing studies, and others done previously recommending the use of albumin expansion in patients with other infections different from SBP, but there is no enough evidence to recommend it in the current guidelines [118].

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