Chapter 1

Introductory Chapter: Treatment of Ascites Associated with Cirrhosis and Its Complications

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Additional information is available at the end of the chapter

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1. Introduction

The presence of ascites is the commonest complication in patients with cirrhosis. Approximately 60% of cirrhotics end up exhibiting it during the course of their disease. The development of ascites indicates a clear decompensation of the disease and is generally associated with a bad prognosis, with an approximately 40% of 1-year mortality [1, 2].

2. Pathophysiology

In patients with cirrhosis of the liver, a circulatory dysfunction is common, characterized by a decrease in systemic vascular resistance secondary to splanchnic arterial vasodilatation, which occurs as a consequence of portal hypertension.

In the early stages, when cirrhosis is compensated for and patients remain asymptomatic, systemic vascular resistance is low and effective blood volume and blood pressure remain normal, due to an increased cardiac output.

In more advanced phases of cirrhosis, there is progressive splanchnic vasodilatation, accompanied by a marked reduction in the effective arterial volume that can no longer be compensated for by an increase in cardiac output.

In this situation, to maintain an effective blood volume and to maintain blood pressure within normal limits, the systemic baroreceptor systems are activated, leading to the activation of the vasoconstrictor systems, including the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS) and, in later stages, the non-osmotic hypersecretion of vasopressin.

Despite these positive effects, these vasoconstricting factors also have negative effects, especially because they facilitate the retention of sodium and water by the kidneys, influencing the appearance and maintenance of ascites, oedemas and dilutional hyponatraemia.

In the later stages of the disease, intense renal vasoconstriction occurs, leading to a significant decrease in glomerular filtration and the development of hepatorenal syndrome (HRS).

At this stage, there is also a notable drop in the cardiac output, probably arising from cirrhosis-associated cardiomyopathy, which further worsens the decrease in effective arterial volume (**Table 1**).

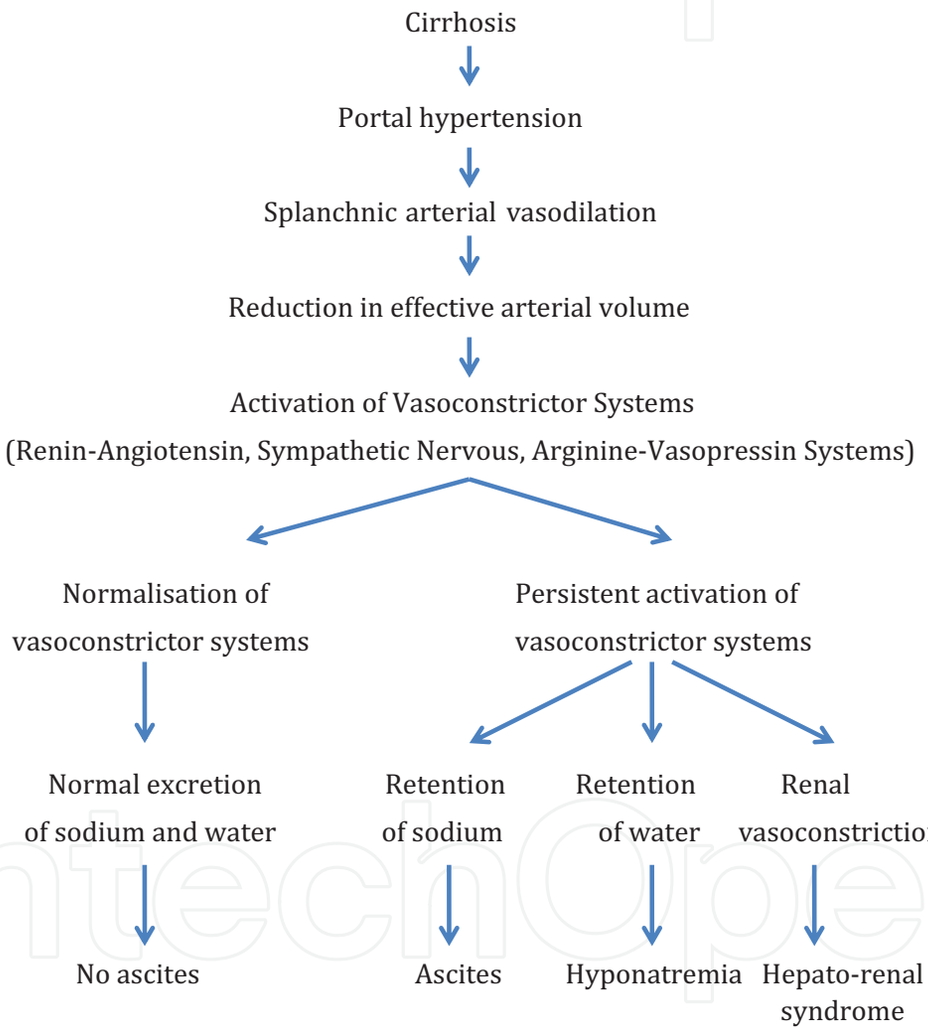

Table 1. Pathophysiology of ascites and its complications in cirrhosis.

3. Diagnosis

For every patient who attends a consultation with suspected ascites, it is essential to confirm, using exploratory paracentesis, that they have a clinical decompensation. This is irrespective

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of whether it is their first occasion or if they have previously had ascites. The analysis of the ascitic fluid makes it possible to rule out other causes of ascites, such as the presence of associated spontaneous bacterial peritonitis (SBP).

The diagnosis of cirrhosis is usually based on clinical, analytical and ultrasound criteria. In case of doubt, the serum albumin/ascites gradient (SAAG) should be determined. When this is greater than 1.1 g/dl, it suggests the existence of portal hypertension. Furthermore, patients with low concentrations of proteins in the ascitic fluid (<1.5 g/dl) have a worse prognosis. Likewise, the polymorphonuclear (PMN) leukocyte count is very useful for ruling out the presence of SBP; in these cases, ascitic fluid cultures must be grown in blood culture bottles.

4. Classification

The International Club of Ascites has a three-grade classification:

Grade 1: Ascites can only be detected by abdominal ultrasound, since it comprises only a small quantity or is of slight degree and is not accompanied by any clinically evident abdominal distension.

Grade 2: Ascites is usually detected by physical exploration and the patient exhibits moderate abdominal distension.

Grade 3: A voluminous ascites is present, giving rise to pronounced abdominal distension.

5. Treatment

In the absence of other, associated complications, patients with uncomplicated ascites can be treated on an outpatient basis.

5.1. Grade 1 ascites

In principle, neither dietary nor pharmacological treatments are required.

At present, there is insufficient information about its natural history and possibilities of progression.

5.2. Grade 2 ascites

This is the most common form of presentation. There is generally a moderate retention of sodium (urinary Na >20 mEq/day), without upsetting the excretion of the solute-free water and with normal glomerular filtration.

The main aim of the treatment is to achieve a negative sodium balance, to which end its oral intake must be reduced and its elimination increased by using diuretics. There is increased

sodium reabsorption at the level of the distal tubule due to the presence of secondary-associated hyperaldosteronism.

Therefore, aldosterone-antagonist diuretics, such as spironolactone, are the drugs of choice and are more effective than loop diuretics.

Patients with primary ascitic decompensation should be treated with spironolactone at a dose of 50–100 mg/day and, in the event of the failure to respond, the dose should be progressively increased week by week until a maximum dose of 400 mg/day is reached.

In patients with recurrent ascites, it is recommended to combine furosemide with aldosterone antagonists. The dose of diuretics should be adjusted in order to yield a weight loss of around 500 g/day in patients who only present ascites and of up to 1 kg/day in those with associated oedemas.

As a maintenance treatment, the minimum dose of diuretics necessary to avoid the development of complications related to the treatment, such as hyponatraemia, hepatic encephalopathy or renal failure, should be recommended (**Table 2**).

5.3. Grade 3 ascites

The first-line treatment for patients with voluminous ascites consists of performing periodic evacuation paracentesis combined with administering intravenous infusions of albumin at a dose of 8 g/l of ascites removed, which is usually carried out under a regime of a short-stay admission in the day hospital.

The evacuation of a large quantity of ascitic fluid may be associated with the well-known post-paracentesis circulatory dysfunction syndrome. To prevent this, appearing infusions of albumin are administered, which reduce the incidence of complications during the following month.

After performing evacuation paracentesis with the subsequent replacement of albumin, patients must continue with a diuretic treatment of the minimum dose necessary to prevent reaccumulation of the ascites. It has been confirmed that intravenous albumin is the most effective plasma expander when more than 5 l of ascites is removed [3–5] (**Table 3**).

- Adhere to a low-sodium diet, with an average content of 80–120 mEq/day
- Initiate diuretic treatment with spironolactone (50–100 mg/day) in a single dose
- Control weight on a daily basis, maintaining a loss of approximately 500 g/day without oedema and 500–1000 g/day when there is ascites with oedema
- If there is no response, progressively increase the dose of spironolactone week by week, up to a maximum of 400 mg/day
- In non-responders, add furosemide at an initial dose of 40 mg/day, possibly increasing this up to a maximum of 160 mg/day
- Once the ascites has been controlled, administer the minimum dose of diuretics necessary to prevent the reaccumulation of ascites

Table 2. Treatment of moderate (Grade 2) ascites.

- Adhere to a low-sodium diet, with a content of less than 80 mEq/day
- Perform evacuation paracentesis in conjunction with intravenous administration of albumin at a dose of 8 g/l of ascites removed
- If the patient is not already receiving diuretic treatment, start a combined treatment of spironolactone 100 mg/day with furosemide 40 mg/day
- If the patient has previously been treated with a diuretic, restart it at a higher dose than the former one
- If there is no response, monitor the intake of sodium and increase the dose of diuretics to a maximum of spironolactone 400 mg/day and furosemide 160 mg/day
- Once the ascites has been controlled, maintain a low-sodium diet and the minimum dose of both diuretics to prevent its reaccumulation

Table 3. Treatment of severe (Grade 3) ascites.

6. Refractory ascites

This is defined as the situation in which the ascites cannot be completely eliminated or whose frequent recurrence calls for continuous medical treatment. This form accounts for approximately 10% of cases.

The development of refractory ascites is associated with a poorer short-term prognosis, the median survival being about 6 months. For this reason, all these patients, except the very elderly or those who have serious associated illnesses that contraindicate it, must be considered potential candidates for a liver transplant and should be evaluated to determine their degree of priority in the waiting list.

6.1. Periodic evacuation paracentesis

The commonest treatment indicated for patients with refractory ascites is to perform periodic evacuation paracentesis simultaneously with the administration of intravenous albumin infusions. In most cases, diuretics are not effective under these circumstances, and they must permanently cease to be used in patients who develop complications related to a diuretic treatment.

In the other patients, who maintain a level of urinary excretion of sodium greater than 30 mEq/day, the diuretic treatment may be maintained in order to delay the reaccumulation of the ascites and thereby also the need for periodic evacuation paracentesis to be performed so often [6, 7].

6.2. Portosystemic venous shunts (TIPS)

These consist of an anastomosis and an intravascular prosthesis that is introduced percutaneously by a medical expert in haemodynamic techniques. This establishes a new route of communication, at the intrahepatic level, between the portal system and the general circulation. The insertion is generally achieved by entering through the external jugular vein. This gives rise to the term for the prosthesis, the transjugular intrahepatic portosystemic shunt, and its acronym, TIPS.

After the placement, there is an increase in renal blood flow, accompanied by an increase in renal excretion of sodium, consequently giving rise to an improvement in the control of the ascites. The method is more effective than performing evacuation paracentesis for controlling ascites.

However, the placement of TIPS is associated with a higher incidence of complications, among which the most common is the occurrence of episodes of hepatic encephalopathy, as occurs in 30–50% of cases. The use of TIPS is out of the question for patients with advanced cirrhosis [8].

There are no data concerning improved survival rates, for which reason a second-line treatment is considered. It is considered to be indicated only in patients with preserved hepatic function, or when paracentesis is ineffective or has to be performed frequently (**Table 4**).

- Adhere to a low-salt diet, with a sodium content less than 80 mEq/day
- Perform evacuation paracentesis repeatedly, in conjunction with intravenous administration of albumin at a dose of 8 g/l of removed ascites
- Avoid diuretic treatment, except when no complications arise and when the patient maintains a level of renal excretion of sodium of >30 mEq/day
- TIPS can be considered as an alternative treatment for patients with good hepatic function or in whom it is difficult to evacuate the ascites by loculation
- A liver transplant will be considered if there are no contraindications and if they are on the transplant waiting list

Table 4. Treatment of refractory ascites.

7. Hyponatraemia

This is a frequent complication in patients with advanced cirrhosis and is associated with a poor prognosis. It is an important factor related to the deterioration in the quality of life of these patients.

7.1. Definition and differential diagnosis

Hyponatraemia is defined in an arbitrary manner, by the presence of a serum sodium concentration of less than 130 mEq/l. It has a mean prevalence of 22% in patients with cirrhosis and ascites. There are two varieties of hyponatraemia: hypovolaemic and hypervolaemic (or dilutional). The differential diagnosis between the two types is fundamental, since their treatment and prognosis are completely different.

7.1.1. Hypovolaemic hyponatraemia

In general, its origin is related to the loss of extracellular fluid. Patients show signs of dehydration, frequently associated with hepatic encephalopathy. Its most frequent causes are very copious diuresis, secondary to the prolonged or intense administration of diuretics, or the presence

of digestive losses of fluids, in the form of vomiting or diarrhoea. Its treatment is based on controlling the cause, suspending diuretics and administering saline solutions to solve the problem.

7.1.2. Hypervolaemic hyponatraemia

This is predominant in patients with advanced cirrhosis and is characterized by the marked expansion of the extracellular volume. It arises as a direct consequence of the reduction in the capacity of the kidneys to eliminate solute-free water and is secondary to the existing circulatory dysfunction.

Its origin is probably multifactorial, although the most important factor is the presence of a non-osmotic hypersecretion of vasopressin, which acts at the level of the renal collecting tubules, causing a significant increase in the retention of free water [9–11].

7.2. Treatment of hypervolaemic or dilutional hyponatraemia

Treatment is based on increasing the excretion of retained free water, for which several options are available.

7.2.1. Fluid restriction

This remains the first-line treatment in these patients. Clinical experience indicates that such restriction prevents the progressive drop in plasma sodium levels but is not sufficient to reverse hyponatraemia.

7.2.2. Administration of saline solutions

Hypertonic saline infusion has been used, but has proved to be of little value. In addition, it is associated with two types of problem. First, their effect is of short duration and, second, sodium levels fall shortly after the treatment is discontinued. Furthermore, they increase ascites and oedema, so their administration was discontinued rapidly.

7.2.3. Albumin

Infusion of intravenous albumin is usually effective, since, being a good plasma expander, it alleviates circulatory dysfunction. However, because there have been few cases, experience of this recently established method has been very limited so far. Therefore, more studies, with a greater number of patients, are needed to demonstrate its true efficacy [12, 13].

7.2.4. Vaptanes

These are active, orally administered drugs and are selective antagonists of V2 receptors of vasopressin. They have the effect of increasing renal excretion of solute-free water. They are therefore used in different situations, such as in the treatment of patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH), in cases of heart failure and in liver cirrhosis, being effective in 45–80% of cirrhosis cases.

Its most frequent side effect is thirst. Significant increases in plasma sodium levels should be avoided, in order to prevent the appearance of neurological complications, such as central pontine myelinolysis, among others.

Tolvaptan was approved in the United States for the treatment of severe hypervolaemic hyponatraemia (Na <125 mEq/l), whereas in Europe it was only approved for the treatment of SIADH. It is mainly indicated only for cirrhotic patients who are on the waiting list for a liver transplant.

However, the US Food and Drug Administration has drawn attention to the potential risk of liver injury from tolvaptan and recommends this drug not be used in patients with liver disease [14, 15].

8. Spontaneous bacterial peritonitis

This is the most frequent and characteristic bacterial infection of patients with liver cirrhosis and associated ascites.

It is defined as the infection of ascitic fluid in the absence of an intra-abdominal focus. The most frequently associated bacteria are the enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, etc.) and non-enterococcal streptococci (*Streptococcus pneumoniae*, *S. viridans*, etc.).

In its initial stages, the patient may be asymptomatic, but characteristic symptoms, such as abdominal pain, fever, nausea, vomiting and diarrhoea, soon appear. Patients may also suffer from paralytic ileus, hepatic encephalopathy, digestive haemorrhage or renal failure.

To confirm its diagnosis, it is necessary to perform diagnostic paracentesis and undertake a cell count of the ascitic fluid.

The finding of more than 250 polymorphonuclear leukocytes/cm^3 of ascitic fluid is considered diagnostic of SBP, irrespective of the results obtained from bacterial cultures.

Once the diagnosis has been made, an antibiotic treatment should be instituted as soon as possible. Third-generation cephalosporins continue to be the empirical treatment of choice for community-acquired SBPs. In nosocomial episodes and potentially in those related to the health system, antibiotic coverage should be broader and adapted to the local pattern of resistance. The duration of the treatment is adjusted with respect to the results obtained from the paracentesis control diagnostics, continuing for up to 24–48 h after confirmation of the resolution of the infection (<250 PMN/cm^3).

It should also be remembered that patients presenting with renal and/or hepatic dysfunction at the time of diagnosis should receive intravenous albumin in order to prevent the development of renal failure and to improve short-term survival [16–18].

8.1. Primary SBP prophylaxis

Patients with a low protein concentration in the ascitic fluid (>10–15 g/dl) have a higher risk of developing a first episode of SBP, in comparison with those in whom the protein concentration

remains high. In the absence of additional risk factors, the probability of developing it during the course of 1 year is less than 20%.

Evidence of advanced hepatic impairment (Child-Pugh >9 points), with bilirubin >3 mg/dl, or circulatory dysfunction (creatinine >1.2 mg/dl or a plasma sodium level of <130 mEq/l) in patients with low levels of proteins in the ascites increases the risk of developing an SBP by up to 60%.

Administration of norfloxacin at a dose of 400 mg/day in these patients reduces the probability of infection to 7%, prevents the development of hepatorenal syndrome and improves short-term survival. For this reason, it is appropriate for this subgroup of patients to make long-term use of norfloxacin, especially if they are on the waiting list for a liver transplant [19].

9. Hepatorenal syndrome

Hepatorenal syndrome is a frequent cause of renal failure in patients with advanced liver cirrhosis and is associated with poor short-term prognosis. It is a functional renal failure that develops as a consequence of intense renal vasoconstriction.

9.1. Diagnosis

There are two types of HRS: 1 and 2.

Type 1 HRS presents as rapidly progressing acute renal failure, with blood creatinine values increasing sharply to a level greater than 2.5 mg/dl. It is associated with very poor short-term prognosis, with a median survival without treatment of only 2 weeks.

Type 2 HRS is characterized by more moderate and stable renal failure, with plasma creatinine values generally ranging from 1.5 to 2.5 mg/dl. It typically occurs in patients with refractory ascites; their median survival is 6 months.

During follow-up, patients with type 2 HRS may develop type 1 HRS, either spontaneously or due to the presence of a precipitating factor, usually an associated bacterial infection [20–22].

9.1.1. Differential diagnosis

The diagnosis of HRS involves excluding other causes for the development of renal failure in a cirrhotic patient, since they can present different causes, such as hypovolaemia, bacterial infections, acute tubular necrosis, administration of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, antibiotics such as gentamicin, etc.) and parenchymal nephropathy.

There are no objective variables by which these causes of renal failure can be distinguished, which sometimes make differential diagnosis complicated, especially when trying to discriminate between HRS and acute tubular necrosis. Their diagnostic criteria are described subsequently [23, 24] (**Table 5**).

- Presence of cirrhosis with ascites
- Serum creatinine >1.5 mg/dl
- No improvement in serum creatinine levels, at least 2 days after discontinuing diuretics and then expanding the blood volume by infusions of albumin at a dose of 1 g/kg of body weight/day, up to a maximum of 100 g/day
- Absence of shock
- No evidence of recent intake of nephrotoxic drugs
- Absence of renal parenchymal disease as evidenced by the presence of proteinuria (>500 mg/day), microhaematuria (>50 red cells/high-magnification field) and/or an abnormal renal ultrasound result.

Table 5. Diagnostic criteria for hepatorenal syndrome.

9.2. Treatment

HRS treatment depends on the severity of renal failure and its associated complications. Patients with type 1 HRS who are on a liver transplant waiting list should be treated in an intensive or intermediate care unit, with close monitoring to detect any intercurrent complications at an early stage.

By contrast, patients with type 2 HRS without associated complications can be controlled on an outpatient basis. Therefore, we describe the therapeutic options available to patients with type 1 HRS.

9.2.1. Vasoconstrictors

The use of vasoconstrictors in conjunction with the intravenous administration of albumin is considered the first-line treatment in the management of patients with type 1 HRS.

Vasoconstrictors used include vasopressin analogues, especially terlipressin and alpha-adrenergic agonists, such as noradrenaline and midodrine.

Treatment with terlipressin and albumin produces a significant improvement in renal function in 40–50% of patients and is accompanied by improved survival.

Treatment usually starts at a dose of 1 mg/4 h in the form of intravenous boluses, increasing to 2 mg/4 h after 3 days if there is no response (defined as a decrease in creatinine by more than 25% of the baseline level).

Relapse after treatment is infrequent; if it occurs, it is advisable to repeat the same treatment [25–27].

Patients being treated with vasoconstrictors and albumin should be monitored closely in order to detect the presence of possible side effects. These are mainly of an ischaemic and cardiovascular nature and can appear in 10–15% of cases. The treatment is also effective and safe in patients with associated bacterial infections.

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9.2.2. Other vasoconstrictors

The wider availability and lower cost of noradrenaline and midodrine, both in combination with albumin, make them an attractive alternative to treatment with terlipressin. The efficacy and safety of noradrenaline are similar to those of terlipressin in the treatment of patients with type 1 HRS. The same is true of midodrine, although clinical experience of its use is more limited.

Norepinephrine is given at a dose of 0.5–3.0 mg/h in continuous intravenous infusion, with the aim of increasing the mean blood pressure to 10 mm Hg. Treatment is continued until the level of blood creatinine drops below 1.5 mg/dl.

9.2.3. TIPS

TIPS may be considered an alternative treatment to that with vasoconstrictors, since it also improves renal function in this type of patient. Its clinical application under these circumstances is rather limited, since many patients with type 1 HRS present contraindications for its implementation, of which the most frequent and serious is advanced liver failure.

9.2.4. Renal substitution therapy (hepatic dialysis)

This treatment modality is only indicated in patients with type 1 HRS who do not respond to treatment with vasoconstrictors and albumin, and who develop criteria requiring urgent dialysis, such as hypervolaemia, hyperkalaemia, metabolic acidosis, and so on. Fortunately, however, these situations are rare in this group of patients.

Other dialysis methods include the use of the molecular adsorbent recirculation system (MARS) and Prometheus, a dialysis machine to which a module is added for fractional plasma separation and adsorption. However, their usefulness is very limited in these patients.

9.2.5. Liver transplant

Liver transplant is the definitive treatment and therefore the first choice for patients with types 1 and 2 HRS. Therefore, every patient who presents an HRS should be referred to a reference centre where the operation can be performed.

Its functional nature makes HRS potentially reversible after orthotopic liver transplantation (OLT) without associated renal transplantation. Double transplantation (liver and kidney) should only be considered in patients who have required prolonged renal support for 6–8 weeks, because the probability of their HRS reverting is very low.

Patients with type 1 HRS should be prioritized on the transplant waiting list, since they are at a high risk of early mortality. The use of the model for end-stage liver disease (MELD) scoring method as an organ distribution system has made it possible to prioritize these patients, since it includes serum creatinine in the scoring.

It should be noted that although the renal function of patients with type 1 HRS improves after treatment with vasoconstrictors, the creatinine used to calculate the MELD score in

these patients should be that obtained beforehand, at the beginning of treatment, so that they remain as priorities in the waiting list [28].

Treatment with vasoconstrictors and albumin before the liver transplant is recommended, since prior improvement of renal function may improve the prognosis during the post-transplant period.

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