Treatment of cirrhotic ascites

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Abstract

Cirrhosis is the most common cause of ascites and accounts for almost 85% of all cases. It is the most common complication of cirrhosis, after development of ascites only 50% of patients will survive for 2 to 5 years.

Successful treatment is dependent on accurate diagnosis of the cause of ascites.

Because sodium and water retention is the basic abnormality leading to ascites formation, restriction of sodium intake and enhancing sodium excretion is the mainstay of the treatment of ascites. Patients with cirrhosis and ascites must limit sodium intake to 2 gram per day. Enhancement of sodium excretion can be accomplished by usage of oral diuretics. The recommended initial dose is spironolactone 100-200 mg/d and furosemide 20-40 mg/d. usual maximum doses are 400 mg/d of spironolactone and 160 mg/d of furosemide. The recommended weight loss in patients without peripheral edema is 300 to 500 g/d. There is no limit to the daily weight loss of patients who have edema.

About 90% of patients respond well to medical therapy for ascites. Refractory ascites is defined as fluid overload that is unresponsive to sodium restricted diet and high dose diuretic treatment (diuretic resistant) or when there is an inability to reach maximal dose of diuretics because of adverse effects (diuretic-intractable). It has a poor prognosis. Treatment options for patients with refractory ascites are serial therapeutic paracentesis, transjugular intrahepatic stent-shunt (TIPS) or peritoneovenous shunt and liver transplantation. TIPS should be considered in patients who repeatedly fail large-volume paracentesis and have relatively preserved liver functions. Liver transplantation is the only modality that is associated with improved survival. (Acta gastroenterol. belg., **2006**, 69, **217-222**).

1. Introduction

Ascites is an abnormal accumulation of fluid in the peritoneum. The term ascites is derived from the Greek word *άσκος* referring to a bag or sack containing fluid.

Numerous disorders can cause ascites. Most frequently ascites exists in the absence of peritoneal disease, secondary to sinusoidal and post-sinusoidal portal hypertension. Less frequently it is due to diseases involving the peritoneum, mainly peritoneal carcinomatosis and tuberculosis peritonitis.

Liver cirrhosis accounts for 80% of patients presenting with ascites (1). It is the most common complication of cirrhosis and approximately 50% of subjects with compensated cirrhosis will develop ascites over a 10-year period. The onset of ascites is associated with worsened quality of life and increased risk of spontaneous bacterial peritonitis and renal failure (2). The development of ascites is a sign of progressive liver dysfunction and indicates a poor prognosis ; only 50% of patients will survive for 2 to 5 years (3).

The remaining 20% of patients presenting with ascites are due to malignancy (10%), cardiac failure (3%), tuberculosis (2%), pancreatitis (1%) and other more rare causes (4).

Recently there have been several changes in the clinical management and understanding of the pathophysiology.

This review is based on consensus conferences of the International Ascites Club (5), the guidelines published by the AASLD in 2004 (6) and the recently published guidelines in Gut (7).

2. Evaluation of patients with ascites

Successful treatment fully depends on an accurate diagnosis of the origin of the ascites, enabling to initiate an appropriate therapy.

2.1. *Clinical diagnosis*

Clinical diagnosis of ascites is easy when a large amount of fluid is accumulated in the peritoneum. Ascites can present as abdominal distension, flank dullness and protruding umbilical herniation. Flank dullness is only detected when 1500 mL of fluid is present. Ultrasonography can be helpful when the physical examination is not decisive (100 ml ascites can be detected by ultrasonical examination of the abdomen). The ascites accumulates in the most decline parts of the abdomen i.e. flanks and Douglas pouch. In a study comparing physical examination to ultrasound as gold standard, the sensitivity and specificity of the physical examination for detection of ascites ranged from 50% to 94% and 29% to 82% (8).

A clinical grading system for ascites has been proposed by the International Ascites Club (5).

- Grade 1 : mild ascites detectable only by ultrasound
- Grade 2 : moderate ascites manifested by moderate symmetrical distension of the abdomen
- Grade 3 : large or enormous ascites with marked abdominal distension (“tense” ascites).

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2.2. *Analysis of ascitic fluid*

Abdominal paracentesis with appropriate ascitic fluid analysis is the most efficient way to diagnose the cause of ascites and to determine if the fluid is infected. Complications of paracentesis occur rarely (1%) and it is not contraindicated in patients with an abnormal coagulation profile (9).

A diagnostic paracentesis is obligatory for newly diagnosed ascites, every new hospitalisation of a patient with known ascites and every cirrhotic patient presenting with acute renal failure, digestive bleeding, hepatic encephalopathy or sepsis.

The aim of the paracentesis is to detect spontaneous bacterial peritonitis (SBP) (10).

The appearance of the ascitic fluid can be helpful in the differential diagnosis.

- Uncomplicated ascites in the setting of cirrhosis is usually translucent yellow, sometimes water clear if the bilirubin is normal (serous).
- Infected (spontaneously) or malignant fluid is frequently turbid.
- Chylous ascites has a milky appearance due to the higher concentration of triglycerides in ascites than in serum (11).
- Bloody ascites has a concentration of more than 20.000/µL red blood cells and occurs in traumatic paracentesis, malignancy or infections (tuberculous peritonitis rarely presents as bloody ascites). Only a minority of patients with carcinomatous peritonitis present with bloody ascites (12).

2.2.1. Cell count and differentiation

Cell count can be performed on a minimum of fluid. The fluid should be submitted to the lab in a tube containing an anticoagulant to avoid clotting (EDTA tube). In case of cirrhosis the white blood cell count is less than 300/µL. Therapy with diuretics increases the white blood cell count due to reduced peritoneal clearance of those cells compared to fluid. An ascitic fluid neutrophil count of $\geq$ 250 polymorphonuclear cells/ µL is diagnostic of SBP (5).

2.2.2. Bacterial culture

Since ascitic fluid infection is very common in cirrhotic ascites (overall likelihood of development of SBP in a cirrhotic patient with ascites is 10% per year) a diagnostic paracentesis to obtain a bacterial culture is mandatory (13,14,15). The volume of ascitic fluid used for culture has an important impact on the sensitivity in detection of bacterial growth. Culturing of 10 mL of ascitic fluid in blood culture bottles (aerobic and anaerobic culture) led to a significant higher culture positive rate (compared to 1 mL inoculum). This technique provides a sensitivity of culture positivity of 80% (16).

2.2.3. Cytology of ascitic fluid

The overall sensitivity of cytology smears for the detection of malignant ascites is 58% to 75% (17). The explanation for this observation is the fact that only 60% of the patients with malignant ascites have peritoneal metastases, the remaining parts have massive liver metastasis or chylous ascites due to lymphoma. The sensitivity of cytology will be 100% in patients with carcinomatous peritonitis if the samples are sent and processed promptly (18). Hepatocellular carcinomas rarely metastasize to the peritoneum.

2.2.4. Biochemical tests

Previously ascitic fluid has been classified in exudate or transudate, this classification has been replaced by the serum-to-ascites albumin gradient (SAAG). The SAAG is easily calculated by substracting the ascitic fluid albumin value from the serum albumin value (obtained on the same day). This gradient has been proven in prospective studies to categorize ascites better than the total protein exudate/transudate concept (4). If the SAAG is greater than or equal to 1.1 g/dL, the patient has portal hypertension, with approximately 97% accuracy (4). In contrast, a low gradient is associated with abnormalities of the peritoneum including neoplasms, infections and inflammation. Patients who have portal hypertension plus a second cause for ascites also have a SAAG greater than or equal to 1.1 g/dL. The measurement of total protein concentration in the ascitic fluid is a parameter to predict the risk of development of SBP, patients with a value less than 1 g/dL being at high risk (19).

3. Treatment of ascites

Successful treatment of the patient with ascites depends upon an accurate diagnosis regarding its cause. This is particularly true for malignant ascites due to peritoneal carcinomatosis in which diuretic therapy does not reduce fluid production.

In contrast to the other complications of cirrhosis (SBP, variceal bleeding,…), ascites has a relative poor urgency in treatment.

Three reasons for treating ascites

1. Comfort treatment for the patient.
2. Improving cardiac and/or respiratory function (impaired due to massive fluid accumulation).
3. Decrease the risk for SBP, abdominal herniation and hepatic hydrothorax.

The main purpose is not the total disappearance of ascites, but to offer the patient a maximum of comfort and a minimum of side effects from the treatment.
The mainstay of treatment of patients with cirrhosis and ascites include :

1. treatment of underlying hepatic disease
2. medical treatment
3. mechanical elimination of ascites
4. lowering the portal hypertension

In order to understand the treatment of portal hypertension induced ascites a brief summary of the pathogenesis of portal hypertension is indispensable.

Principally two main factors are responsible for the development of ascites.

1) Increased lymph production due to elevated sinusoidal pressure. Under normal circumstances, hepatic lymph produced by Starling forces in the hepatic sinusoids is returned easily to the systemic circulation by means of the thoracic duct. When sinusoidal pressure rises in cirrhosis, the lymph production increases, when this production exceeds the ability to return to the lymphatic circulation by the thoracic duct it eventually spills over from surface lymphatics to the peritoneal cavity, causing ascites. The daily resorption capacity of the peritoneum is 900 mL (20, 21).

2) Intravascular refilling
   In cirrhotic ascites there is a marked renal sodium retention and free water retention leading to hypoosmolality and hyponatriemia. Renal sodium retention is determined by three physiologic systems that are triggered in patients with cirrhosis (21-24) :
   1) The renin-angiotensin-aldosterone system
   2) The sympathetic nervous system
   3) The antidiuretic hormone (impairing free water clearance)

3.1. *Medical treatment*

Bed rest has no proven efficacy in the treatment of cirrhotic ascites (25).

Removal of ascites and edema requires a negative sodium balance. This can be achieved by dietary salt (sodium) restriction and/or enhancement of renal sodium excretion.

– Sodium restriction. Severe sodium restricted diets are unpalatable leading to poor compliance and poor nutritional status which can affect the outcomes of a future liver transplant adversely (26). Several studies have compared the efficacy of different dietary regimens (27-30). Severe dietary sodium restriction compared to unrestricted diet did not prove to influence response rate to medical treatment, diuretic drug dosage and costs (hospitalisation time) but the time for complete disappearance of ascites was significantly shorter (29,31). A typical UK diet contains about 150 mmol sodium per day (32). In cirrhotic patients the use of low sodium [2000 mg (80 mmol) per day] diets is now universally recommended (5,6,19). Fluid loss and weight change are directly related to sodium balance. It is sodium restriction, not fluid restriction, which results in weight loss. Dilutional hyponatriemia is a common problem in patients with advanced cirrhosis (prevalence of 30-35% of hospitalized patients with cirrhosis and ascites). Its pathogenesis is directly related to the hemodynamic changes and secondary neurohumoral adaptations that occur in these patients. The presence of dilutional hyponatriemia is associated with a poor survival (33). Fluid intake restriction (1000 mL/d) and minimizing diuretic use is the initial approach to management of patients with dilutional hyponatriemia (sodium < 125 mmol/L). Recently discovered aquaretic drugs might be an additional tool. The surplus value of these drug in the treatment of dilutional hyponatriemia is the increase of solute-free water excretion by antagonizing the action of arginine vasopressine (AVP) by means of blockade of the vasopressine V2 receptor for AVP with specific antagonists or the inhibition of central release of AVP with κ-opioid agonists (34,35). Although good preliminary data exists on the efficacy of these drugs, further large scale efficacy and safety trials are needed in order to consider them a real additional treatment in the management of dilutional hyponatriemia. These drugs are currently under investigation in international phase II/III trials.

– Diuretics. Aldosterone antagonists and loop diuretics are the most frequently used diuretics in cirrhotic ascites.

  • Aldosterone antagonists
    Spironolactone acts by competitively inhibiting the binding of aldosterone to a specific receptor protein in the cytoplasm of the cortical and medullary collecting ducts. Sodium entry in these ducts occurs through aldosterone-sensitive sodium channels. Spironolactone decreases the number of open sodium channels by competitively inhibiting the mineralocorticoid receptor (36). Since increased aldosterone levels contribute to sodium retention and development of ascites, aldosterone antagonists are the rational treatment for ascites.
    The diuretic effect of spironolactone usually is observed after 48 hours, the peak effect might be delayed for up to 7 to 10 days (37).
    Both controlled and uncontrolled trials have proven that spironolactone is the drug of choice for the initial treatment of cirrhotic ascites (28,29, 37). The dosage of aldosterone antagonists depends of the degree of hyperaldosteronism.
  • Loop diuretics
    Loop diuretics, such as furosemide, are frequently used as an adjuvant to spirinolactone in the treatment of cirrhotic ascites. They inhibit active chloride reabsorption at the ascending limb of the loop of Henle, causing an increase of the amount of sodium, chloride and water delivered to the distal tubule. Loop diuretics are fast acting ; the diuretic effect appears in 30 minutes after oral administration, peaks at 1 to 2 hours and weans off by 3 to 4 hours (38). Loop diuretics are very potent in the absence of hyperaldosteronism. The presence of secondary hyperaldosteronism decreases the potential of these diuretics in cirrhosis.

Complications of diuretic therapy

- Renal insufficiency (defined by a serum creatinine higher than 2 mg/dL) induced by diuretic therapy, occurring in cirrhotic patients with fluid diminution under diuretic therapy. Normally this insufficiency is modest and the renal function recovers rapidly after interruption of the diuretics.
- Loop diuretics cause hypokalemia. These drugs must be stopped immediately if potassium levels reach under 3,5 mM.
- Hyperkalemia is a common complication of aldosterone antagonists. Special caution should be taken in case of renal failure. Dosage of these antagonists should be decreased if potassium reaches 5,5 mM. They should be stopped if potassium level is higher than 6 mM.
- Diuretic induced hyponatriemia is defined by a decrease of serum sodium to less than 125 mM (39). Diuretic therapy should be interrupted if serum sodium levels decrease less than 120 mM. Spontaneous hyponatremia is a result of a decrease of free water excretion and is a negative prognostic factor.
- Metabolic acidosis is a secondary effect of treatment with spironolactone.
- Hepatic encephalopathy can be induced by diuretic treatment. Diuretics should be interrupted temporarily when encephalopathy presents (40).
- Muscle cramps
- Spironolactone is occasionally associated with painful gynecomastia.

Since secondary hyperaldosteronism is the main efferent factor promoting renal sodium retention, antimineralocorticoid drugs are the first line diuretics (27). A European survey demonstrated that antimineralocorticoids indeed represented the starting therapeutic regime most used in practice (42). Their efficiency has been clearly demonstrated by controlled clinical trials (28,43, 44). The recommended initial dose is 100-200 mg/day once daily due to its prolonged half-life. The dose needed to enhance natriuresis is proportional to the degree of hyperaldosteronism. When severe hyperaldosteronism is present the dosage of spirinolactone has to be increased progressively to a maximum advisable dosage of 400 mg/day (45-48). Single agent use of spironolactone was previously advocated, but hyperkalemia and the long half-life of the drug resulted in its use as a single agent only in patients with mild volume ascites (49). Recent guidelines propose a diuretic regimen consisting of single morning doses of oral spironolactone and furosemide beginning with 100 mg of the former and 40 mg of the latter (5,7,45,46,48). The doses of both oral diuretics can be increased simultaneously every 3 to 5 days (maintaining the 100 mg/40 mg ratio to reduce side effects such as electrolyte disturbances) if weight reduction or natriuresis are inadequate. The recommended weight loss in patients without peripheral edema is 300-500 g/day. There is no limit to the daily weight loss of patients who have massive edema (50).

In patients with a poor diuretic response, urinary sodium levels provide useful data to guide management of ascites. As only 10 mEq/d of sodium is lost by nonurinary sources, urinary sodium excretion should be greater than sodium intake (2 g or 80 mmol sodium). If the urinary sodium excretion is higher than the prescribed sodium intake in a subject with a poor diuretic response, compliance with the low sodium diet should be questioned. An increase in diuretic dose is often helpful in inducing natriuresis if urine sodium is very low (46,47).

In the outpatient clinic the 24-hours collections are sometimes cumbrous. A practical alternative is the determination of urine sodium and potassium concentration on a spot urine. If urine sodium concentration is greater than the potassium concentration, the 24-hour sodium excretion is higher than 78 mmol per day with approximately 90% accuracy (51).

In the largest, multicenter, randomised controlled trial performed in patients with ascites, treatment with sodium restriction and diuretics has been shown to be effective in more than 90% of patients in reducing the volume of ascites to acceptable levels (52). The remaining 10% of patients have refractory ascites which is defined as fluid overload that is nonresponsive to sodium restricted diet and high-dose diuretic treatment (400 mg per day of spirinolactone and 160 mg per day of furosemide) or when there is inability to reach the maximal dose of diuretics because of adverse effects (diuretic-intractable) (39,53). Remaining options for these patients include serial therapeutic paracentesis, liver transplantation, transjugular intrahepatic stent-shunt or peritoneovenous shunt or liver transplantation (45,46, 52,54). Once refractory ascites develops the survival prognosis is poor, approximately 50% of patients die within 12 months (55).

3.2. *Therapeutic paracentesis*

For many centuries paracentesis was the only treatment that could be offered to patients with cirrhosis and ascites. Currently it is reserved for patients with refractory or tense ascites. Since paracentesis is a treatment (removal) of ascites but not of sodium retention, patients should not interrupt diuretics. Remaining diuretic treatment leads to reduction of the frequency of paracentesis (48,56). Since the renin-aldosterone system, which is already activated in cirrhotic patients, is extremely sensitive to changes in circulating blood, administration of i.v. albumin after large volumes paracentesis is recommended (57,58). When less than 5 L of ascites is removed, substitution can be given with synthetic plasma expanders. For paracentesis in whom more than 5 L is removed administration of albumin at a dose of 8 g/L is generally recommended (58). Application of plasma volume expansion makes it safe to remove all of the

ascitic fluid in a single session, even when a large amount of ascites is present.

Frequency of paracentesis provides insight into the patient's degree of compliance with the sodium restriction. Paracentesis performed every two weeks must control ascites, even in patients with no sodium excretion (45). The sodium concentration of ascitic fluid is approximately equivalent to that of plasma in cirrhotic patients (130 mmol/L). A 10 L paracentesis removes 1300 mmol sodium. Patients consuming 88 mmol of sodium per day, excreting approximately 10 mmol per day in nonurinary losses, and excreting no urinary sodium retain a net of 78 mmol per day. Therefore a 10-L paracentesis removes approximately 17 days of retained sodium in patients with no renal sodium excretion. If paracentesis of approximately 10 L is needed more often than twice a month the patient is clearly not complying with the sodium restricted diet.

3.3. *Reduction of portal sinusoidal hypertension*

Elevated portal vein pressure is a main factor in the pathogenesis of portal hypertension. Reduction of the pressure can be achieved by surgical creation of a peritoneovenous shunt or transjugular intrahepatic portosystemic shunt (TIPS). Both procedures have shown to decrease ascites production.

Four large scale, multicenter randomized controlled trials comparing TIPS to sequential large-volume paracentesis have been published (54,60-62). These studies report a better control of ascites in the TIPS group. Contraindications for the procedure are congestive heart failure with cardiac ejection fraction < 50% in order to cope with the volume returned from the splanchnic circulation immediately after TIPS insertion (61), preexisting hepatic encephalopathy (TIPS is associated with a 30% incidence of hepatic encephalopathy) and Child-Pugh score more than 12 points. The currently widely used model of end-stage liver disease (MELD) was originally developed to predict 3-month mortality after TIPS (63). TIPS usually converts diuretic-resistant patients into diuretic-sensitive patients, by decreasing the activity of sodium retaining mechanisms (64). Up to now discordant data have been published about the effect on mortality of TIPS placement (54,60,61,62), therefore TIPS is currently reserved for patients who do not tolerate repeated paracentesis or patients with loculated ascites (65).

Peritoneovenous shunt (LeVeen or Denver) was popularized in the 1970s and has shown in controlled trials to decrease the dose of diuretics (66,67). However, poor long-term patency, excessive complications, and no survival advantage compared to medical therapy in controlled trials have led to near abandonment of this procedure (66,67).

3.4. *Liver transplantation*

Since the survival of patients with ascites (and especially with refractory ascites) is poor (55), they should be evaluated for liver transplantation, being the only modality that is associated with improved survival (survival rate at five years for patients with cirrhotic ascites is 30%-40%, versus 70-80% among patients who have undergone transplantation) (68).

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