Treatment of ascites and spontaneous bacterial peritonitis - Part I

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SUMMARY
National guidelines for treatment of ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hyponatremia have been approved by the Danish Society of Gastroenterology and Hepatology. Ascites develops in approximately 60% of patients with cirrhosis during a 10 year period and is frequently associated with complications that determine the course of the disease and the prognosis. These evidence-based guidelines are divided in two parts and consider definitions, pathophysiology, diagnostic aspects, treatment, and prophylaxis.

INTRODUCTION
Ascites is one of the most frequent complications to cirrhosis and portal hypertension. Up to 66% of the patients will develop ascites within a 10 years follow-up period [1, 2]. A cirrhotic patient will only develop ascites if portal hypertension is present and the progression of the disease is closely related to the ability to excrete sodium and free water with the urine [3, 4]. Presence of ascites is a severe complication of the disease that significantly affects the prognosis and increases the risk of developing other complications such as refractory ascites, spontaneous bacterial peritonitis (SBP), hepato-renal syndrome (HRS) and hyponatremia [1, 5-9].The five years survival after the diagnosis of ascites has remained poor and ranges between 30-40% [2].

DEFINITIONS
Uncomplicated ascites

Uncomplicated ascites is defined as presence of free fluid in the peritoneal space, which is reversible to medical treatment and without presence of SBP, hyponatremia, or HRS.
The amount of ascites is graded as follows:

Grade 1: Slight ascites only detectable by ultrasound examination.
Grade 2: Moderate ascites.
Grade 3: Tense ascites [10].

REFRACTORY ASCITES
Refractory ascites is defined as ascites, which cannot be mobilized or will early recur and which cannot be treated satisfactorily or prevented by medical treatment. Refractory ascites can be divided into:
Diuretic-resistant ascites, which means lack of response to a sodium reduced intake and diuretic treatment or
Diuretic-intractable ascites where the patient in total or partly cannot tolerate diuretics due to development of diuretic-induced complications [10].

SPONTANEOUS BACTERIAL PERITONITIS (SBP)
SBP is defined as presence of a neutrophil cell count > 250/µl in ascitic fluid or a positive cell culture with culture of most often only one microbiological agent. If more than 2 organisms are present or in case of a very high neutrophil cell count, secondary bacterial peritonitis should be suspected.

Table 1. Levels of evidence for clinical recommendations.

Diagnosis of ascites	Level of evidence
Ultrasound examination should be performed in all patients	Evidence II A
Diagnostic paracentesis should always be performed in ascites grade 2 and 3 and in case of hospitalization due to liver disease	Evidence II A
SBP should be precluded by assessment of neutrophil cell	Evidence II A

count in ascitic fluid	
Measurement of serum-ascites albumin gradient can be used in case of unclear cause of ascites	Evidence II A
Ascitic protein <15 g/l indicates an increased risk of SBP	Evidence II A

Uncomplicated ascites Medical treatment	Level of evidence
Sodium restriction equal to a daily dose of 80-120 mmol (4.6-6.9 g sodium/d) is recommended	Evidence III A
Fluid restriction is without effect in patients with normal serum sodium	Evidence I A
Patients, who develop ascites for the first time, should be treated with aldosterone antagonist monotherapy with an initial dose of 100 mg daily, which every 3-5 days can be increased with 100 mg daily to a maximum dose of 400 mg/d	Evidence 1 A
Patients with a weight loss < 2 kg/week or in case of development of hyperkalemia increasing doses of furosemide with starting dose of 40 mg/day to a maximum dose of 160 mg/day can be added	Evidence II B
Patients should be monitored clinically and biochemically at least weekly within the first month	Evidence 1 A
In case of recurrent ascites treatment includes spironolacton and furosemide in combination and the doses can be increased until effect to the maximum doses above	Evidence II B
Weight loss during diuretic treatment should be <0.5 kg/d in patients without peripheral oedema and < 1 kg/d in patients with oedema.	Evidence III A
The therapeutic goal of the treatment is to keep the patient free of ascites on the lowest possible dose of diuretics. The dose of diuretics should therefore be titrated to the lowest possible level when the ascites has disappeared	Evidence I A

Paracentesis	Level of evidence
Tense ascites (grade 3) is treated by paracentesis in a single session.	Evidence 1 A
In order to prevent post-paracentesis induced circulatory dysfunction (PICD), human albumin (HA) should be administered with 8 g/l ascites fluid removed.	Evidence I B
Usual diuretic treatment is continued after paracentesis in order to prevent recurrence of ascites.	Evidence I A

Refractory ascites	Level of evidence
Effect of diuretics and sodium restriction can only be assessed in stable patients without complication such as bleeding or infection.	Evidence III A
Patients with refractory ascites have a poor prognosis and should therefore be evaluated for transplantation.	Evidence II B
Total paracentesis with substitution of albumin (8 g/l removed ascites) is the preferred treatment of refractory ascites. Patients excreting less than 30 mmol sodium/day, may be considered for discontinuation of diuretics.	Evidence I A
Transjugular Intrahepatic Porto-systemic Shunt (TIPS) controls ascites effectively, but induces an increased frequency of hepatic encephalopathy.	Evidence I A
Treatment with TIPS should be considered in patients who need frequent therapeutic paracentesis.	Evidence III B
Mobilisation of ascites after TIPS is often slow, and it is often necessary at least temporally to continue diuretic treatment and sodium restriction.	Evidence II A

Spontaneously bacterial peritonitis (SBP)	Level of evidence
Diagnostic paracentesis with neutrophil cell count and culture should be performed in all patients with ascites. Blood culture should be performed at the same time.	Evidence II B
The diagnosis of SBP is based on neutrophil cell count of >250/µl ascites fluid.	Evidence II B
Treatment with a third generation cephalosporin (cefotaxim 2 g x 2 i.v. in 5 days) is recommended.	Evidence II A
Infusion with HA seems to improve the prognosis in	Evidence II B

patients with compromised renal function.	
Treatment with antibiotics in combination with HA-infusion decreases the risk of hepato-renal syndrome (HRS) and increases the survival rate.	Evidence 1 A
Prophylactic treatment with quinolones after an episode of SBP reduces the risk of recurrent. SBP. Ciprofloxacin 500 mg/d can be used	Evidence I B
Patients with ascitic protein < 15 g/l should prophylactically be treated with a quinolone i.e. Ciprofloxacin 500 mg/d.	Evidence I B

METHODS OF SEARCH

These guidelines were based on studies identified by searching electronic databases and a number of national and international reviews and guidelines, with special emphasis on conclusions from "EASL Clinical Practice Guidelines on the Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome"[11]. Search in Pubmed with the following MeSHs: "Ascites and cirrhosis" retrieved 3274 references and "Spontaneous bacterial peritonitis", 883 references. In total 230 references were included of which 59 are cited in the present guidelines.

ASCITES PATHOPHYSIOLOGY

The development of ascites in cirrhosis is complex. However, presence of portal hypertension is a prerequisite. A peripheral arterial vasodilatation seems to be a pathophysiological hallmark with activation of several vasoactive hormones that contributes to the development of sodium and water retention. According to the peripheral arterial vasodilatation theory splanchnic vasodilatation will lead to development of central hypovolaemia and thereby to a hyperdynamic circulation with increased cardiac output and heart rate [12]. The often pronounced peripheral vasodilatation, which may partially be caused by an increased systemic NO-release in combination with a decreased hepato-splanchnic NO-production, will lead to activation of a number of vasoactive systems, such as the sympathetic nervous system, renin-angiotensin-aldosteron system and an increased non-osmotic release of vasopressin resulting in sodium- and water retention [13, 14]. Furthermore, the balance between an increased local transvascular filtration and a decreased lymphatic drainage may play a role, since the produced amount of ascites is dependent of the increase in transsinusoidal filtration of protein and fluid and the decrease in lymphatic drainage hereof [15]. Ascites is seldom seen in patients with a post sinusoidal pressure gradient <12 mmHg [4].

DIAGNOSTIC EXAMINATIONS IN THE PRESENCE OF ASCITES

Patients with ascites should undergo the following evaluations:
Clinical history and evaluation
Abdominal ultrasound examination
Biochemical tests for liver- and kidney function with serum- and urine electrolytes
Ascitic fluid should be analysed by:
Ascitic puncture with
Cell count and differential count of leucocytes. In case of an increased number of polymorph neutrophil nuclear cells (>250/microliter) SBP is likely
Cultivation of ascites should be performed in all patients with ascites
Determination of serum-ascites albumin gradient (SAAG) can be performed if the aetiology is unclear (10,15)
Patients with portal hypertension will most often have SAAG >11 g per litre
Eventual determination of ascites-total protein. A total protein concentration in acitic fluid is < 15 g/l indicates a high risk of SBP.

TREATMENT OF UNCOMPLICATED ASCITES

Grade 1 ascites or slight ascites
There is no specific treatment recommendation for this condition.
Ascites grade 2 or moderate ascites
Patients with grade 2 ascites can be treated in the outpatient clinic, unless they have other complications to cirrhosis. These patients are characterised by a reduced sodium excretion in relation to sodium intake and a positive sodium balance. The aim of the treatment of ascites in patients with cirrhosis is to counterbalance the renal sodium retention. Sodium intake should therefore be reduced to achieve this goal by a decrease of the content of sodium in the food (in practice this means no addition of sodium to food and minimizing sodium intake in beverages etc.) and/or increase the excretion of sodium by the kidneys with diuretic treatment.
A negative sodium balance is achieved in 10-20% of patients with cirrhosis solely by a reduction of sodium in the food intake, especially in patients with newly diagnosed ascites [16, 17]. To achieve a negative sodium balance, it is recommended to reduce sodium intake moderately equally to 90 mmol/d in patients who need diuretic treatment. Salts with potassium used in combination with an aldosterone antagonist may induce hyperkalaemia [10]. Fluid restriction can only be recommended to patients with hypervolemic (dilutionary) hyponatraemia and has even then often limited effect.

TREATMENT WITH DIURETICS

In cirrhosis, sodium retention is caused by an increased proximal and distal tubular sodium reabsorption in the kidneys [18, 19]. Diuretic treatment of ascites in cirrhosis follows two principles: The sequential treatmen strategy, where the treatment with an aldosterone antagonist is maximised before a loop-diuretic is added or the combination treatment strategy where the treatment with an aldosterone antagonist and a loop-diuretic are increased in parallel.
According to the sequential principle strategy, the dose of spironolactone is increased depending on the effect by doses of 100 mg every 3-5 days with a maximal daily dose of 400 mg spironolactone [17]. If natriuresis is not achieved with a maximal dose of an aldosterone antagonist, the diuretic treatment is increased stepwise by an addition of i.e. furosemide from 40 mg/day up to a maximum dose of 160 mg/day. The sequential principle strategy may be the preferred treatment in uncomplicated ascites. Applying the combination treatment strategy, treatment is initiated with 100-200 mg spironolactone daily in combination with 40 mg furosemide daily. In case of no response after 4-5 days of treatment, the spironolactone dose is increased to 200-300 mg/day and the furosemide dose to 80 mg (as single dose), and the dose can be increased by lack of response to maximum daily doses of 400 mg spironolactone and 160 mg furosemide (divided into two

doses), respectively. The combination treatment seems to be optimal in patients with recurrent ascites and in particular in the precense of peripheral oedema. The diuretic dose should be increased stepwise in both the sequential and combination treatment strategies, and the diuretic response is defined as being insufficient by a weight loss of less than 1 kg within the first week and less than 2 kg/week hereafter. The upper limit for weight loss is controversial, but most authors agree upon obtaining a weight loss of less than 0.5 kg/d in patients without peripheral oedema and maximally 1 kg/d in patients with oedema [20]. Patients should be motivated to daily weighing. After weight loss, the diuretic treatment can often be reduced in order to avoid diuretic-induced complications. Treatment with drugs such as non-steroidal anti-inflammatory drugs, which may negatively interfere with the diuretic treatment, should be avoided.
Diuretic treatment of patients with cirrhosis and ascites is associated with several complications:
Renal insufficiency due to intravascular volume depletion. The condition is often reversible after volume therapy and reduction of diuretics
Hepatic encephalopathy
Derangement of electrolytes and acid base balance. Hyperkalaemia is a frequent problem to treatment with potassium-sparing diuretics while hypokalaemia is seen in patients treated with loop diuretics. In case of hyperkalaemia during treatment with an aldosterone antagonist addition of furosemide may solve the hyperkalaemia. Hyponatriaemia is another frequent complication to treatment with diuretics. Discontinuation should only happen when serum-sodium is below 122-125 mmol/l.
Gynaecomastia is among the most frequent complications to treatment with spironolactone. Amiloride may be used as an alternative treatment.
Muscular cramps may extensively impair patients quality of life [21]. Diuretic treatment should be reduced or stopped in patients with invalidating muscular cramps. In this case infusion of HA should be considered [22].

PARACENTESIS

Patients with tense ascites (grade 3) should be treated by paracentesis. Because paracentesis only removes the excess volume without preventing recurrence of ascites the procedure should be followed by sodium restriction and diuretics as described above [23]. Paracentesis should be performed under aseptic condition after clinical evaluation of presence of ascites. It is recommended to verify ascites by ultrasound examination in order to secure that the ascites is not localized in pockets. In that case ultrasound-guided paracentesis should be performed.
Paracentesis does not increase the risk of peritonitis in patients with cirrhosis [24], but the draining tube should be removed within 24 hours. Paracentesis is not contraindicated in patients with coagulation disturbances since the available literature does not describe any increased bleeding risk in patients with coagulopathia (INR >1.5, thrombocytes < 50 x 109 /l) [25, 26]. Paracentesis should not be performed in patients with disseminated intravascular coagulation. There is an increased risk of development of post-paracentesis induced circulatory dysfunction (PICD) during paracentesis. PICD is defined as >50% increase in plasma renin one week after paracentesis [27]. Without treatment, this condition is irreversible and followed by an increased mortality [27]. PICD can be seen in up to 75% of performed paracentesis and can be prevented by volume expansion [28]. Development of PICD is related to a quick drop in intraabdominal pressure during paracentesis together with a reduction in the intrathoracal pressure, thereby leading to an increased venous blood velocity to the heart, and increased cardiac output and decreased systemic vascular resistance [29, 30].

Paracentesis combined with infusion of HA has generally shown to be:
more effective and shortens the hospital stay
decreases the risk of development of hyponatraemia, renal failure and hepatic encephalopathy
effective even by paracentesis of large volume of ascites. A lower number of liver-related complications is seen by infusion of HA compared to synthetic plasma expanders within 30 days after paracentesis. HA infusion is thereby overall cheaper and more effective than alternative plasma expanders [31].

"The International Club of Ascites" and EASL therefore recommends in patients with an expected paracentesis volume of >5 litre to give HA 8 g/l drained ascites [11].

REFRACTORY ASCITES

Refractory ascites is defined as patients, who do not respond with natriuresis to a maximum diuretic treatment: 400 mg spironolactone and 160 mg furosemide daily for at least one week and sodium restriction of less than 90 mmol sodium/d. These patients should especially avoid intake of liquorice with sodium. A weight loss < 0.8 kg and a negative sodium balance with urinary excretion of sodium below sodium intake reflects a lack of response. Early recurrence of ascites is defined as development of ascites grade 2 or 3 within 4 weeks after the initial paracentesis. In cases where the patients respond to the diuretic treatment, but develop diuretic-induced complications such as encephalopathy, increase in serum creatinin >100%, hyponatremia (decrease in serum sodium > 10 mmol/l or to a level of serum sodium < 125 mmol/l) or hypo- and hyperkalaemia (serum potassium < 3 mmol/l or >6 mmol/l) are defined as diuretic intractable ascites [10,32].

Transition from an uncomplicated stage of ascites to the refractory stage is associated with an increased mortality with a median survival rate of approximately 6 months [32]. Paracentesis or insertion of af a transjugular intrahepatic porto-systemic shunt (TIPS) do not seem to significantly influence survival [10, 33]. Treatment options in refractory ascites are paracentesis with albumin substitution, continued diuretic treatment, TIPS and liver transplantation. Diuretics should be discontinued in patients with refractory ascites, who excrete less than 30 mmol sodium daily [20].

TIPS reduces the postsinusoidal pressure gradient and thereby modify the mechanisms of the development of ascites [34, 35]. TIPS is effective to control recurrent ascites and to increase the sodium excretion and glomerular filtration rate [36]. A major problem with TIPS is the increased risk of developing hepatic encephalopathy, which transiently may be observed in 30-50% of the patients and chronically in 5-10%. Other complications to TIPS are thrombosis and stenosis of the shunt; which however, is seen less frequently after the introduction of coated stents [37]. Recent large randomized controlled trials and meta-analyses have shown that the recurrence of ascites is less frequent in TIPS-treated patients compared to patients solely treated by paracentesis [34, 36]. A single meta-analysis has furthermore shown a trend towards improved survival in TIPS-treated patients [38]. It

should, however, be emphazised that TIPS is a demanding procedure, which should only be performed in specialised centers. Repeated paracentesis with substitution of albumin is the first choice of treatment in patients with refractory ascites. TIPS is effective to control refractory ascites but is associated with an increased risk of hepatic encephalopathy. TIPS can be considered in patients with need of frequent paracenteses (more than monthly). Some patients may after TIPS still need diuretic treatment and sodium restriction to avoid regeneration of asctes. Contraindications to TIPS performance are severe liver dysfunction (Child –Pugh-score >11), definite hepatic encephalopathy (>grade 2), bacterial infections, progressively renal failure, pulmonary hypertension, heart or lung failure, and high age [39].

SPONTANEOUS BACTERIAL PERITONITIS

Patients with decompensated cirrhosis and ascites exhibit a variable degree of immunologic incompetence with an increased risk of bacterial infections, especially SBP [40]. Typically, patients with SBP do not present symptoms of infection but some patients may show signs of sepsis and shock, hepatic encephalopathy, or deterioration of the liver function. The mortality without treatment is >50%, but it can be reduced to <20% with early diagnosis and treatment [41]. SBP is seen in approximately 12% of the patients who are hospitalized with cirrhosis and ascites [42]. Newly hospitalized patients with ascites should therefore immediately undergo a diagnostic puncture of ascites.

SBP is defined by

presence of neutrophil cells in the ascitic fluid (≥250/µl) or

a positive ascitic fluid culture.

SBP is distinguished from secondary bacterial peritonitis by abscence of an intraabdominal focal infection. Diagnostic paracentesis should be performed in all hospitalized patients with cirrhosis and ascites and during hospitalization by suspicion of infection resulting in deterioration of the liver or kidney function. The diagnosis is based on an increased count of neutrophil cells of ≥250/µl by microscopy. Cell count performed with automatized equipments such as a flow cytometer seems to be as effective. Analysis should be accessible twenty-four hours a day with a response time not exceeding 6 hours by acute analysis. Culture of ascites fluid should be done simultaneously.

TREATMENT

In case of an increased neutrophil cell count (>250/µl), treatment with antibiotics should immediately be initiated. Cefotaxim or other third generation cephalosporins are the best documented antibiotics and have been shown more effective than for example treatment with ampicillin in combination with tobramycin [43]. Cefotaxim should be used in a dose of 2 g intravenously twice daily for a minimum of five days. In case of SBP with increased serum creatinine and/or serum bilirubin >67 µmole/l infusion with HA (1.5 g/kg body weight) should be administered immediately at diagnosis and repeated on day 3, with HA 1 g/kg body weight.

Alternatively, intravenously administered Ciprofloxacin can be used the first day followed by seven days of oral treatment (500 mg x 3). A single study has shown similar effect of intravenous Cefotaxim in patients, who have not previously been treated with quinolones and without signs of upper gastrointestinal symptoms. A randomised controlled study in patients with severe SBP has shown an increased survival rate in patients treated with HA 1.5 g albumin/kg body weight at the time of diagnosis followed by 1 g/kg day 3 in combination with treatment with cefotaxim compared to cefotaxim alone [44]. Administration of albumin seems preferentially to improve prognosis in patients with impaired renal function or jaundice. Some patients may present with a combination of a normal count of leucocytes in the ascitic fluid and a positive culture, named “bacter-ascites”. In presence of systemic infection or repeated positive ascites cultures, antibiotics should be administered. In case of repetitive negative cultures the patients should be surveyed.

PREVENTION OF SBP

Primary prophylaxis

Patients with cirrhosis and a low amount of protein in the ascitic fluid (< 15 g/l) have an increased risk of development of SBP [45]. Treatment with quinolones reduces the risk of development of infection such as SBP in case of low protein content in the ascitic fluid, but the effect on mortality is only marginal [46]. Patients without previous SBP but with ascitic protein <15 g/l should be treated prophylactically with a quinolone such as ciprofloxacin 500 mg daily as long ascites is present.

Secondary prophylaxis

A new diagnostic paracentesis with cell count and cultures should be performed in patients with SBP after termination of antibiotic therapy. Seventy percent of the patients, who recover after SBP, develop recurrence within the first year. Prophylactic treatment with quinolones after the first episode of SBP reduces the risk of a new SBP episode from 68% to 20% without clear effect on mortality [47]. Several randomized studies have shown a decrease in hospitalizations and fewer recurrences of SBP in patients treated prophylactically. Patients with previous SBP should therefore be offered long-term prophylaxis with ciprofloxacin 500 mg daily. Alternatively, weekly treatment with 500-1000 mg ciprofloxacin could be considered.

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