EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis

European Association for the Study of the Liver [1]

Ascites is the most common complication of cirrhosis, and ~60% of patients with compensated cirrhosis develop ascites within 10 years during the course of their disease [1]. Ascites only occurs when portal hypertension has developed [2] and is primarily related to an inability to excrete an adequate amount of sodium into urine, leading to a positive sodium balance. A large body of 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., the sympathetic nervous system and the renin–angiotensin–aldosterone system). Renal sodium retention leads to expansion of the extracellular fluid volume and formation of ascites and edema [3–5]. The development of ascites is associated with a poor prognosis and impaired quality of life in patients with cirrhosis [6,7]. Thus, patients with ascites should generally be considered for referral for liver transplantation. There is a clear rationale for the management of ascites in patients with cirrhosis, as a successful treatment may improve the outcome and symptoms.

A panel of experts was selected by the EASL Governing Board and met several times to discuss and write these guidelines during 2008–2009. These guidelines were written according to published studies retrieved from Pubmed. The evidence and recommendations made in these guidelines have been graded according to the GRADE system (Grading of Recommendations Assessment Development and Evaluation). The strength of evidence has been classified into three levels: A, high; B, moderate; and C, low-quality evidence, while that of the recommendation into two: strong and weak (Table 1). Where no clear evidence existed, the recommendations were based on the consensus advice of expert opinion(s) in the literature and that of the writing committee.

1. Uncomplicated ascites

1.1. Evaluation of patients with ascites

Approximately 75% of patients presenting with ascites in Western Europe or the USA have cirrhosis as the underlying cause. For the remaining patients, ascites is caused by malignancy, heart failure, tuberculosis, pancreatic disease, or other miscellaneous causes.

1.2. Diagnosis of ascites

The initial evaluation of a patient with ascites should include history, physical examination, abdominal ultrasound, and laboratory assessment of liver function, renal function, serum and urine electrolytes, as well as an analysis of the ascitic fluid.

The International Ascites Club proposed to link the choice of treatment of uncomplicated ascites to a classification of ascites on the basis of a quantitative criterion (Table 2). The authors of the current guidelines agree with this proposal.

A diagnostic paracentesis with an appropriate ascitic fluid analysis is essential in all patients investigated for ascites prior to any therapy to exclude causes of ascites other than cirrhosis and rule out spontaneous bacterial peritonitis (SBP) in cirrhosis. When the diagnosis of cirrhosis is not clinically evident, ascites due to portal hypertension can be readily differentiated from ascites due to other causes by the serum–ascites albumin gradient (SAAG). If the SAAG is greater than or equal to 1.1 g/dl (or 11 g/L), ascites is ascribed to portal hypertension with an approximate 97% accuracy [8,9]. Total ascitic fluid protein concentration should be measured to assess the risk of SBP since patients with protein concentration lower than 15 g/L have an increased risk of SBP [10].

A neutrophil count should be obtained to rule out the existence of SBP [10]. Ascitic fluid inoculation (10 ml) in blood culture bottles should be performed at the bedside in all patients. Other tests, such as amylase, cytology, PCR and culture for mycobacteria should be done only when the diagnosis is unclear or if there is a clinical suspicion of pancreatic disease, malignancy, or tuberculosis [8–11].

Recommendations **A diagnostic paracentesis should be performed in all patients with new onset grade 2 or 3 ascites, and in all patients hospitalized for worsening of ascites or any complication of cirrhosis (Level A1).**

Received 25 May 2010; accepted 25 May 2010

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Clinical Practice Guidelines

Table 1. Grading evidence and recommendations (adapted from the GRADE system).

	Notes	Symbol
Grading of evidence		
High quality evidence	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality of evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C
Grading recommendation		
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption	2

Neutrophil count and culture of ascitic fluid (by inoculation into blood culture bottles at the bedside) should be performed to exclude bacterial peritonitis (Level A1).

It is important to measure ascitic total protein concentration, since patients with an ascitic protein concentration of less than 15 g/L have an increased risk of developing spontaneous bacterial peritonitis (Level A1) and may benefit from antibiotic prophylaxis (Level A1).

Measurement of the serum–ascites albumin gradient may be useful when the diagnosis of cirrhosis is not clinically evident or in patients with cirrhosis in whom a cause of ascites different than cirrhosis is suspected (Level A2).

1.3. Prognosis of patients with ascites

The development of ascites in cirrhosis indicates a poor prognosis. The mortality is approximately 40% at 1 year and 50% at 2 years [7]. The most reliable factors in the prediction of poor prognosis include: hyponatremia, low arterial pressure, increased serum creatinine, and low urine sodium [7,12]. These parameters are not included in the Child-Turcotte-Pugh score (CTP score) and among them, only serum creatinine is included in the Model for end-stage liver disease (MELD score). Furthermore, since serum creatinine has limitations as an estimate of glomerular filtration rate in cirrhosis [13], these scores probably underestimate the mortality risk in patients with ascites [14]. Since allocation for liver transplantation is based on the MELD score in several countries, patients with ascites may not receive an adequate priority in the transplant lists. Therefore, there is need a for improved methods to assess prognosis in patients with ascites.

Recommendations **Since the development of grade 2 or 3 ascites in patients with cirrhosis is associated with reduced survival, liver transplantation should be considered as a potential treatment option (Level B1).**

1.4. Management of uncomplicated ascites

Patients with cirrhosis and ascites are at high risk for other complications of liver disease, including refractory ascites, SBP, hyponatremia, or hepatorenal syndrome (HRS). The absence of these ascites-related complications qualifies ascites as uncomplicated [11].

1.4.1. Grade 1 or mild ascites

No data exist on the natural history of grade 1 ascites, and it is not known how frequently patients with grade 1 or mild ascites will develop grade 2 or 3 ascites.

1.4.2. Grade 2 or moderate ascites

Patients with moderate ascites can be treated as outpatients and do not require hospitalization unless they have other complications of cirrhosis. Renal sodium excretion is not severely impaired in most of these patients, but sodium excretion is low relative to sodium intake. Treatment is aimed at counteracting renal sodium retention and achieving a negative sodium balance. This is done by reducing the sodium intake and enhancing the renal sodium excretion by administration of diuretics. Whilst the assumption of the upright posture activates sodium-retaining systems and slightly impairs renal perfusion [15], forced bed rest is not recommended because there are no clinical trials assessing whether it improves the clinical efficacy of the medical treatment of ascites.

1.4.2.1. Sodium restriction. A negative sodium balance can be obtained by reducing dietary salt intake in approximately 10–20% of cirrhotic patients with ascites, particularly in those presenting with their first episode of ascites [16,17]. There are no controlled clinical trials comparing restricted versus unrestricted sodium intake and the results of clinical trials in which different regimens of restricted sodium intake were compared are controversial [17,18]. Nevertheless, it is the current opinion

Table 2. Grading of ascites and suggested treatment.

Grade of ascites	Definition	Treatment
Grade 1 ascites	Mild ascites only detectable by ultrasound	No treatment
Grade 2 ascites	Moderate ascites evident by moderate symmetrical distension of abdomen	Restriction of sodium intake and diuretics
Grade 3 ascites	Large or gross ascites with marked abdominal distension	Large-volume paracentesis followed by restriction of sodium intake and diuretics (unless patients have refractory ascites)