



## Progress Report

Management of infections in cirrhotic patients: Report of a Consensus Conference<sup>☆</sup>

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## ABSTRACT

The statements produced by the consensus conference on infection in end-stage liver disease promoted by the Italian Association for the Study of the Liver, are here reported.

The topics of epidemiology, risk factors, diagnosis, prophylaxis, and treatment of infections in patient with compensated and decompensated liver cirrhosis were reviewed by a scientific board of experts who proposed 26 statements that were graded according to level of evidence and strength of recommendation, and approved by an independent jury. Each topic was explored focusing on the more relevant clinical questions. By systematic literature search of available evidence, comparison and discussion of expert opinions, pertinent statements answering specific questions were presented and approved. Short comments were added to explain the basis for grading evidence particularly on case of controversial areas.

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## Introduction

Bacterial infections are a leading cause of acute on chronic liver failure and are associated with high mortality in end-stage liver disease [1]. Dysfunction of the defensive mechanisms against

bacterial or fungal infections makes patients with cirrhosis prone to the development of sepsis [2,3].

By reviewing the studies reporting on the clinical course of cirrhosis after infectious episodes, the overall mortality of infected patients is reportedly around 38% with 30.3% of cases occurring at 1 month and 63% at 12 months, with the pooled odds ratio for death of infected versus non infected of 3.75 (95% confidence interval 2.12–4.23) [4].

Spontaneous bacterial peritonitis represents one of the most common infectious complications in patients with cirrhosis. The median mortality in 7062 such patients was 43.7%, with 31.5% of the cases occurring at 1 month and 66.2% at 12 months [5]. Moreover, severe renal failure is common in patients with spontaneous bacterial peritonitis and is associated with a poor outcome.

The goal of this document was to provide clinical guidelines for the appropriate management of infections in ESLD and liver

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transplantation. Promoter of this “Consensus Guidelines” was the Italian association for the Study of Liver (AISF).

The methods section is listed in Appendix B. Grading and strength of recommendations were applied according to the Centres for Disease control (CDC) grading system (Table S1).

## 1. EPIDEMIOLOGY OF INFECTION IN CIRRHOSIS

### Question 1.a

**What is the prevalence of bacterial infections in cirrhotic patients and which are the risk factors?**

**Comments.** In two studies in patients with liver cirrhosis requiring hospitalization conducted in Italy one in 1995–96 and the other in 2005 bacterial infections occurred respectively in 34 and 38% of hospital admissions [6,7] and an overlapping prevalence was observed in studies performed in other countries [4,8,9]. The occurrence of bacterial infection was associated with higher Child or model for end stage liver disease (MELD) scores. In a retrospective cohort study alcoholic patients with Child–Pugh A/B were more susceptible to infection as compared to non-alcoholics (52/141 vs. 28/122  $p < 0.02$ ) [8]. Previous infection is a general risk factor for new infection [10]. Bacterial infections occur in about 45% of patients admitted with gastrointestinal bleeding [11].

### Statements 1.a

- The prevalence of bacterial infections in hospitalized cirrhotic patients is at least 30% (I).
- The risk of bacterial infection is higher in Child C than in Child A/B cirrhosis or in case with MELD > 15 (I).
- In the setting of Child A/B cirrhosis, alcohol abuse entails a high risk of bacterial infections (II).
- Other risk factors are history of previous infection and gastrointestinal bleeding (II).

### Question 1.b

**What are the clinical manifestations of bacterial infections and what is the mortality associated with bacterial infections in patients with cirrhosis?**

**Comments.** A variable proportion (from 14 to 25%) of infections are classified as spontaneous bacterial peritonitis due to different proportion of patients with ascites in the examined cohorts. Urinary tract infection, pneumonia and bacteraemia represent 20%, 15% and 12% of infections, respectively, while soft tissue infections had a lower and variable prevalence [6,7,10–12].

A systematic review by meta-analysis showed a pooled odds-ratio for death in infected versus non-infected patients with cirrhosis of 3.75 (95% CI 2.12–4.23) [4]. In the two Italian studies the in-hospital mortality in patients with cirrhosis was 16–19% among those with infections and 7–10% among those without, respectively [6,7].

### Statements 1.b

- The most common bacterial infections are spontaneous bacterial peritonitis, urinary tract infections, cellulitis, pneumonia and bacteraemia (II).
- Infections increase mortality by at least 3-fold in cirrhosis; 30% of infected patients will eventually die within 1 month after infection and another 30% by 1 year (I).

### Question 1.c

**What are the most common bacterial agents responsible for infection in cirrhotic patients?**

**Comments.** Bacteria of intestinal origin, particularly *Escherichia coli* are most often involved in community-acquired infections. Multidrug-resistant (MDR) gram-negative bacilli or

MDR gram-positive cocci are increasingly frequent causative organisms in hospital and health care associated infections and in patients receiving quinolone prophylaxis. European epidemiological data show an increasing proportion of resistance to fluoroquinolones and third generation cephalosporins in some species of Enterobacteriaceae, including *E. coli* and *Klebsiella* species. [10–14].

### Statements 1.c

- Bacteria of intestinal origin, particularly *E. coli* are most often involved in community-acquired infections.
- Methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasingly MDR pathogen (II).

### Question 1.d

**How to detect infection in cirrhotic patients?**

### Statements 1.d

- Biological fluid cultures are the basic tests for the diagnosis of bacterial infections in cirrhotic patients and should be done in all patients in whom a bacterial infection is suspected.
- Whenever possible, cultures should be carried out before initiation of antibiotic therapy.
- Collection, analytical phases (direct and indirect identification, confirmation and susceptibility test) must be performed according to standard operating procedures (SOP). Results must be reported within predefined timelines [11] (IIIA).

## 2. EVALUATION OF THE RISK AND THE DIAGNOSIS OF INFECTION IN PATIENTS WITH COMPENSATED AND DECOMPENSATED CIRRHOSIS

### Question 2.a

**Which are the risk factors for specific pathogen and infectious disease syndromes?**

**Comment.** A high risk of Spontaneous Bacterial Peritonitis (SBP) is observed in cirrhotic patients who have recovered from an episode of SBP and/or with a low (<1.5 g/dl) ascites protein [15]. The incidence of bacterial meningitis in cirrhotic patients is higher than in the general population and has a higher mortality rate [16]. Impaired renal function on admission is associated with increased mortality [16]. Bacteriuria is more common and seems to be associated with female gender and the degree of liver insufficiency (Child class C) [17]. Infectious endocarditis was reported in association with cirrhosis [18]; *Streptococcus bovis* endocarditis was associated with advanced liver disease [19]. Procedures such as tracheal intubation and oesophageal tamponade increase the risk of hospital-acquired pneumonia in cirrhotics [20–23]. Transjugular portosystemic shunts (TIPS) can be complicated by primary infection of the device (endotipsitis) or with TIPS-associated bacteraemia [24].

### Statement 2.a

- An increased incidence of infections caused by several pathogens (see Table S2) have been described in case-control studies in cirrhotics (II).

### Question 2.b

**Are there specific risk factors for infections based on disease aetiology or treatment of chronic liver disease?**

**Comments.** Patients with hemochromatosis have been reported to be at higher risk of acquiring *V. vulnificus* and of liver abscess in the presence of *Y. enterocolitica* infection [25–28]. Primary sclerosing cholangitis is a risk factor for ascending cholangitis especially after invasive procedures or in the presence of stones, strictures or cholangiocarcinoma [29,30]. Human immunodeficiency virus

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