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Management of bacterial infection in the liver transplant candidate

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Abstract

Bacterial infection (BI) is a common cause of impairment of liver function in patients with cirrhosis, especially in the liver transplant candidates. These patients share an immunocompromised state and increased susceptibility to develop community and hospital-acquired infections. The changing epidemiology of BI, with an increase of multidrug resistant strains, especially in healthcare-associated settings, represents a critical issue both in the waiting list and in the post-operative management. This review focused on the role played by BI in patients awaiting liver transplantation, evaluating the risk of drop-out from the waiting list, the possibility to undergo liver transplantation after recovery from infection or during a controlled infection.

Key words: Cirrhosis; Portal hypertension; Bacterial infection; Liver transplantation

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Core tip: Bacterial infection (BI) is a common cause of impairment of liver function in patients with cirrhosis, especially in the liver transplant candidates. BI may play a detrimental role in patients awaiting liver transplantation, increasing the risk of drop-out from the waiting list.

Ferrarese A, Zanetto A, Becchetti C, Sciarrone SS, Shalaby S, Germani G, Gambato M, Russo FP, Burra P, Senzolo M.

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INTRODUCTION

The liver is actively involved in inflammatory response against bacteria, and plays a central role in the regulation of immune defense, bacterial clearance, acute-phase protein, cytokine production and metabolic adaptation to inflammation^[1]. Conversely, sepsis-induced hypoxic hepatitis and cholestasis make hepatic dysfunction an independent predictor of mortality during bacterial infection (BI)^[2,3].

Cirrhosis is *per se* an immunocompromised state which predisposes to the development of BI, and sepsis-related death^[4]. It's characterized by an immunodeficient state due to an impaired response to pathogens at different levels of the immune system, involving innate and adaptive cell dysfunction^[5]; this condition coexists with a persistent stimulation of immune system, with enhanced serum levels of pro-inflammatory cytokines^[6,7]. The severity of this inflammatory state correlates with severity of liver dysfunction^[8,9]. Moreover, other superimposed conditions - such as impaired gut microbiota and intestinal barrier dysfunction - further increase the risk of BI^[10]. In a study by Rasaratnam *et al*^[11], when patients were treated with selective intestinal decontamination, their hepatic venous pressure gradient decreased by a mean of 2.43 mmHg, further strengthening the hypothesis that bacteria contribute to the hyperdynamic circulation and portal hypertension in cirrhosis.

Sepsis-related organ damage in cirrhosis is characterized by both an excessive inflammatory response and a decrease in the hepatic capacity of tolerance^[12]. This further increases circulatory dysfunction, with splanchnic vasodilation and organ hypo-perfusion^[13,14], leading to worsening of portal hypertension (*via* activation of neurohumoral pathways) and fluid retention^[15]. Development of BI is a common trigger of extra-hepatic organ failures, in particular acute kidney injury^[16], hepatic encephalopathy^[17], coagulopathy^[18], adrenal insufficiency^[19] and respiratory failure^[20].

CHANGING EPIDEMIOLOGY OF BACTERIAL INFECTION IN DECOMPENSATED CIRRHOSIS

In the past decades, there have been several improvements in the management of cirrhosis and its complications, such as hepatocellular carcinoma and portal hypertension. However, a significant proportion of patients with decompensated cirrhosis still need liver transplantation (LT), which represents the only effective therapeutic option.

In this setting, development of BI could significantly

impair the natural history of the liver transplant candidate^[21,22]. Preventive and therapeutic strategies for most of the complications of cirrhosis are well-defined; nevertheless, even if risk factors for the onset of BI in decompensated patients awaiting LT are well-known, they remain poor preventable.

The protean epidemiology of BI in cirrhosis depends on several factors, such as site of infection, setting of BI development, and local epidemiology.

Spontaneous bacterial peritonitis (SBP) and urinary tract infections are the most frequent BI in cirrhosis, followed by pneumonia, skin and soft tissue infections, bloodstream infections (BSI)^[12,23]. SBP is mainly due to bacterial translocation - especially gram-negative strains^[24], however epidemiology is rapidly changing. A multicenter study from Portugal^[25], evaluating patients with severe liver dysfunction (median Child-Pugh class C-10; MELD score 19) recently showed an increase in gram-positive bacteria (GPB, 42%) at diagnosis of SBP; notably, one out of three SBP episodes occurred during hospitalization. This has determined the adoption of new antibiotic strategies: Piano *et al*^[26] demonstrated that the combination of broad-spectrum antibiotics, meropenem plus daptomycin, was significantly more effective than conventional therapy (ceftazidime) in the treatment of nosocomial SBP (86.7% vs 25%; $P < 0.001$).

BSI represent another common cause of BI in cirrhosis^[12], mainly due to gram-positive strains^[27], because of the high number of invasive procedures and quinolone prophylaxis. However, there's an increasing prevalence of gram-negative bacteria (GNB) as the cause of BSI; Bartoletti *et al*^[28] showed in a multicenter observational study on 312 cirrhotic patients in Italy, an equal distribution between GNB and GPB (53% vs 47%) at diagnosis of BSI.

In the last decades, clinical practice in Hepatology has dramatically changed as a consequence of the implementation of the liver transplant programs. Cirrhotic patients are nowadays frequently admitted to the ICU and undergo many diagnostic and therapeutic invasive procedures. This is associated with a higher risk of secondary infections caused by nonclassical pathogens. Fernandez *et al*^[29] included 572 BI, 39% of which were nosocomial, reporting an increase in the rate of GPB infections associated with the increasing use of invasive procedures during hospitalization and in the ICU. More recently, Merli *et al*^[30], collected 173 episodes of BI requiring hospitalization or occurred during hospitalization in 424 patients with cirrhosis; BI episodes were further divided into three classes (community acquired, hospital acquired, health-care acquired). GNB were more frequent in community acquired and health-care acquired infections, while GPB in hospital-acquired ones. *Enterobacteriaceae* (44.3%) (particularly *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*) and *Enterococci* (*Enterococcus faecium* and *Enterococcus faecalis*) (19.7%), were the pathogens most frequently responsible for infection.

Table 1 Risk factors of bacterial infection in cirrhosis

Risk factors for bacterial infection in cirrhosis
Impairment of liver function
Child-Pugh score ^[36-38]
MELD score ≥ 15 ^[40]
Low serum albumin ^[39]
Alcohol related disease ^[45,51]
Total ascitic fluid protein concentration < 15 g/L ^[84]
ICU admission ^[39,85]
Variceal bleeding ^[41,86]
Blood transfusion requirements
Mean arterial pressure
Severity of bleeding
Malnutrition ^[40]
Invasive procedures ^[29]
ERCP in PSC patients or with incomplete drainage ^[87]
Hospitalization ^[29,40,43,44]

MELD: Model for end stage liver disease; ICU: Intensive care unit; ERCP: Endoscopic retrograde cholangiopancreatography; PSC: Primary sclerosing cholangitis.

The spreading of multidrug resistant (MDR) bacteria-related infection is alarming worldwide^[31,32]. In the past, patients with cirrhosis remained largely unaffected by this phenomenon because they were rarely admitted to the ICU. Nowadays, frequent hospitalizations, development of LT programs and antibiotic prophylaxis made cirrhosis at high risk of MDR infections^[33]. A multicenter study in Italy^[34] reported a 27% (83/395) prevalence of MDR infections, mainly due to GNB (extended-spectrum β lactamase *E. Coli* and Carbapenems resistant *K. Pneumoniae*). Another study from Greece^[35] reported 19% MDR infection rate amongst patients with SBP, being MDR bacteria associated with healthcare-acquired infections and with patients at higher MELD score (28 vs 19, $P = 0.012$). Also in the above-mentioned study by Merli *et al.*^[30], MDR infections occurred more frequently during hospitalization (56% in hospital acquired/healthcare-associated infections vs 22% in community acquired infections, $P = 0.008$).

RISK FACTORS FOR BACTERIAL INFECTION IN END STAGE LIVER DISEASE

Patients with end stage liver disease, listed for LT, have the highest risk for BI development. This might be due to frequent hospitalizations, severity of liver dysfunction and multiorgan failure (Table 1). Correlation between the development of BI and severity of liver disease has been widely demonstrated^[36]. In a Japanese group of patients with cirrhosis and hepatocellular carcinoma^[37], incidence of BI rose from 2.3% in Child-Pugh class A patients to 25.6% in Child-Pugh class C patients. In a further study^[38], even if patients with cirrhosis were younger and had less cardiopulmonary comorbidities than patients without cirrhosis, they had higher rates of septic shock at hospital admission, and equal mortality. Moreover, bacteremia and mortality increased with the severity of liver disease (5.6%, 20.5%, 33.3% and

0%, 8.5%, 38.9% in Child-Pugh classes A, B, and C, respectively; $P = 0.038$).

Furthermore, low serum albumin, ICU admission, and GI bleeding, are other independent predictors of BI development, according to Deschenes *et al.*^[39]. Merli *et al.*^[40] analyzing 54 BI episodes occurred in 50 patients, showed that, at multivariate analysis, a MELD score ≥ 15 (OR: 2.8, 95%CI: 1.3-6.1), history of previous infection within 12 mo (OR: 4.7, 95%CI: 2.2-10.6), and a diagnosis of malnutrition (OR: 4; 95%CI: 1.5-10) were independent predictors for infections and sepsis.

Variceal bleeding is another predictor of BI onset; Tandon *et al.*^[41], reviewing the available literature on patients admitted for GI bleeding without receiving antibiotic prophylaxis, showed that 242 out of 552 (44%) developed an episode of BI. Severity of GI bleeding, according to blood transfusion requirements (HR: 1.22; 95%CI: 1.01-1.47), mean arterial pressure (HR: 0.96; 95%CI: 0.93-0.99) were independent predictors for BI onset^[42]. In another Spanish study^[29], 126 patients underwent at least one invasive procedure, comprising variceal sclerotherapy or banding, surgical intervention, trans-jugular intrahepatic portosystemic shunt, having a higher probability of developing BI due to GPB.

Sinclair *et al.*^[43] showed that 43% of LT candidates required at least one hospitalization within 1 year; moreover, a significant proportion of hospitalized patients ($> 45\%$) required repetitive hospitalisations. Patients with cirrhosis have 4 to 5-fold higher probability to develop a BI episode during hospitalization than non cirrhotic population^[42,44].

The role of etiology of underlying liver disease as a risk factor for BI development is debated^[45]. Alcohol abuse is associated with increased intestinal permeability, dysbiosis and increased bacterial translocation^[46]. Furthermore, Legionella and Mycobacterium tuberculosis infections are significantly more prevalent in patients with alcohol abuse^[47,48]. In the setting of cirrhosis, several studies reported a higher rate of BI in patients with alcoholic etiology when compared with non-alcoholic^[49,50]. Sargenti *et al.*^[51] evaluating characteristics of 398 BI in 633 cirrhotics (363 alcoholic, 270 nonalcoholic), reported a similar occurrence of BI between groups, but pointed out that alcohol related disease was significantly associated with bacterial pneumonia and GPB.

IMPACT OF BACTERIAL INFECTIONS IN LIVER FUNCTION

Worsening of liver function is frequently observed in patients with infection, especially in those with sepsis, being itself a trigger for multiorgan failure, and development of Acute on Chronic Liver Failure (ACLF)^[52-54].

In the above-mentioned study by Merli *et al.*^[40], Child-Pugh and MELD scores worsened in 62% of patients after infection; moreover, onset of ascites, hepatic encephalopathy, hyponatremia, hepatorenal

syndrome, were more frequent in patients with infection as compared with those who were not infected.

Prognosis of BI significantly correlates with the severity of liver disease and with the severity of extra-hepatic organ involvement^[54,55]. A systematic review^[21] considering 11987 patients with an episode of BI from 178 different studies, reported 1-, 3-, and 12-mo mortality of 30.3%, 44%, and 63%, respectively, and almost half of patients surviving at 1 mo died within a year. Renal failure, stage of cirrhosis (according to Child-Pugh score), age and severe sepsis were the factors independently associated with death. Several studies confirmed the critical role of renal failure in patients with cirrhosis and BI^[56,57]. Mortality increased with the occurrence and severity of acute kidney injury and with the outcome of renal failure (15% 90-d mortality after complete recovery, 40% after partial renal recovery, and 80% in patients without renal recovery or progression). According to the study by Cazzaniga *et al.*^[58], systemic inflammation and fulfillment of SIRS criteria, are other factors significantly associated with mortality, since in-hospital mortality of these decompensated patients with MELD score > 18 rose from 12% to 43%. Dionigi *et al.*^[22] retrospectively evaluated prognosis of patients who were hospitalized in a tertiary center in the United Kingdom; they demonstrated that in-hospital mortality rate was higher in those patients who had infection at admission and/or developed infection during hospitalization (HR: 5.02; 95%CI: 2.75–9.16; $P < 0.001$).

IMPACT OF BACTERIAL INFECTION IN THE LIVER TRANSPLANT CANDIDATE

The onset of BI usually determines a further worsening of liver function and multiorgan failure, with high probability of death or drop-out from the WL^[59,60]. Reddy *et al.*^[61] prospectively evaluated the outcome of 136 patients after an episode of BI developed while awaiting LT: 42% were delisted or died, 35% underwent transplantation, and only 24% achieved transplant-free survival within 6 mo. As expected, those who remained in the waiting list had a lower MELD score compared to those who either received a transplant or died/delisted; furthermore, those patients who underwent LT after BI recovery had a significant higher survival than those without LT (95% vs 5%; $P < 0.001$). At univariate analysis, the number of organ failures was the main factor that predicted death or delisting, whereas MELD score did not differentiate between those who were ultimately transplanted vs those who were delisted. Mounzer *et al.*^[62] showed that, 38% of patients who had experienced an episode of SBP before waiting list admission, were subsequently removed from the list or died.

Regarding patients who fully recovered from an episode of BI, the study by Sun *et al.*^[63] showed that recipients with pre-transplant BI ($n = 32$) within 12 mo before LT had a higher MELD score (median 25 vs 22, $P < 0.05$) at transplant, higher time of post-LT intubation

(3 d vs 2 d, $P = 0.05$), and longer post-transplant hospitalization (29 d vs 20 d, $P = 0.05$). However, post-transplant mortality was not different between groups (9.4% vs 2.9%) and was not associated with pre-LT infection. Lin *et al.*^[64] retrospectively analyzed the outcome of 34 living donor LT candidates who had experienced an episode of BI within 4 wk prior surgery, which was effectively treated (e.g., disappearance of symptoms and signs suggestive of sepsis, normalization or improvement of laboratory and/or imaging findings after antibiotic therapy). The post-operative outcome was compared with 20 patients with pre-LT ACLF without infection. The only difference between groups was the longer total hospital stay (89.0 d vs 65.5 d, $P = 0.024$), whereas post-LT ICU stay, one-year survival, and post-LT infection rates were similar between groups. Few data are available on the possibility to offer a standardized MELD exception after recovery from infection^[65-67]. A possible scenario is the onset of recurrent episodes of cholangitis in PSC candidates; in a study by Goldberg *et al.*^[68], 300 patients who received MELD exception points for an increased risk of waitlist mortality, had a lower proportion of death/drop out (20.0% vs 1.3% $P < 0.001$); however, this non-standardized exception has not been further confirmed.

Several studies recently investigated the outcome of patients who underwent LT under “controlled” infection. In an Italian study^[69], 84 patients were considered eligible for LT after disappearance of symptoms and signs suggestive of severe sepsis/septic shock. The overall post-LT 90-d mortality, septic shock, and sepsis as cause of death were not significantly different between infected and not-infected LT recipients; however, patients with previous infection had in the post-operative course higher rates of infections (40% vs 36%, $P = 0.003$) and post-transplant MDR strains (26% vs 13%, $P = 0.005$). Artru *et al.*^[70] recently demonstrated that ACLF grade 3 patients were transplanted in France after they had recovered from an episode of BI according to a subjective criterion of “controlled sepsis” for at least 24 h within transplant; the authors demonstrated an excellent 1-year post-LT survival (83.8%), not different than that observed in patients with no ACLF or with lower stages of ALCF.

MDR bacteria colonization represents another important issue in the setting of WL, because of the risk of spreading of BI in the post-operative course and/or after the introduction of immunosuppression. Giannella *et al.*^[71] prospectively evaluate the role of carbapenems resistant *K. Pneumoniae* (CR-KP) colonization (e.g., presence of MDR bacteria in the rectal swab in absence of symptoms and signs of active infection) in 237 patients awaiting LT, of whom 11 (4.6%) were positive at the time of LT. Hospital admission, higher MELD at LT, prior antibiotic exposure, post-operative complications, and ICU length of stay were the factors associated with the CR-KP active infection after LT. In addition, the same group, performing a multicenter prospective

study on CR-KP carriers^[72], not only in the setting of LT, demonstrated that the number of additional colonization sites was an independent risk factor for invasive infection.

In conclusion, BI significantly modify the natural history of patients with cirrhosis listed for LT. Severe BI in a sick and frail patient can produce a multiorgan failure comprising further deterioration of liver function. Even if this can increase priority in the WL, this gain in priority should be used only after adequate control of infection. To date, standardized definition of “controlled infection” is lacking. As for other patients with severe ACLF in the WL^[73,74], prioritization rules in the respect of distributive justice, definition of the ideal timing for LT and definition of delisting criteria have to be refined in the next future.

MEDICAL PROPHYLAXIS OF BACTERIAL INFECTION

Antibiotic prophylaxis in patients with decompensated cirrhosis is standard of care in patients with recent gastrointestinal bleeding^[75], and in those with high risk of SBP (e.g., Child-Pugh > 9, serum bilirubin > 3 mg/dL and impaired renal function), or in secondary prophylaxis for SBP^[24].

Antibiotic prophylaxis after upper GI bleeding reduces the incidence of in-hospital infections, re-bleeding rate within 7 d (7% vs 34%), and 28-d mortality (13% vs 35%, $P = 0.04$).

However, some concerns about long-term prophylaxis has been recently raised, since it's been associated with high prevalence of MDR BI, before and after LT. Tandon *et al.*^[76] evaluating 110 episodes of BI (30% hospital acquired), reported 47% of antibiotic resistance and a significant association between previous exposure to systemic antibiotics and antibiotic-resistance. Infections due to MDR bacteria are associated with an increased risk of septic shock, acute kidney injury, and death, in the post-transplant setting^[44]. Furthermore, antibiotic use has been identified as the strongest predictor of invasive post-transplant fungal infection, associated with a 60% mortality^[77].

Even if several studies suggested the need to stratify patients who need antibiotic prophylaxis, both after variceal bleeding and after an episode of SBP, no robust data are available to date^[12,23,78,79].

Patients with cirrhosis admitted to ICU could be at higher risk of BI. Recently, a metaanalysis on prognosis of cirrhotics admitted to ICU showed that acute kidney injury and sepsis as indications to ICU admission were the only factors significantly associated with mortality^[80]. Another retrospective study^[81] on 42 patients who underwent LT from the ICU, showed that pre-LT intubation was a factor significantly associated with post-LT pneumonia ($P = 0.02$).

On the contrary, patients who recover liver function while in the WL (e.g., after viral eradication/suppres-

sion), history of BI would not be a sufficient factor for administering long-term antibiotic prophylaxis. In addition, the spreading of MDR bacteria will reduce the potential role of antibiotic mono-prophylaxis with quinolones or cephalosporines.

Given the crucial role played by dysbiosis in BI in patients with cirrhosis, several studies assessed the role of intestinal decontamination. Grat *et al.*^[82] evaluated the fecal microflora in 40 LT candidates, showing that abundance of several species (e.g., *Bifidobacterium* and *Enterococcus*) significantly correlated with the severity of liver disease. In systematic review and metanalysis, Safdar *et al.*^[83] compared parenteral (e.g., cephalosporins/quinolones), topically applied or non-absorbable antibiotic strategies (polymyxin, gentamicin, and nystatin) for intestinal decontamination. The Authors found an association between selective decontamination and reduction of GNB infections ($P = 0.001$), however studies were underpowered and heterogeneous.

CONCLUSION

BI represent a turning point in the natural history of cirrhosis, being the first cause of development of ACLF, and significantly affecting the outcome of patients listed for LT. These patients are at the highest risk of infection, because of frequent hospitalizations and contacts with healthcare facilities, immune dysregulation, end-stage liver disease. SBP, pneumonia and bloodstream infection represent the commonest sites of BI. In such cases, early institution of empirical antibiotic therapy is mandatory, to reduce infection-related mortality. However, empirical antibiotic therapy should take into account the changing epidemiology of infections, related both to an increase of gram positive strains and to MDR bacteria.

In the setting of LT, patients should be considered suitable for transplant after resolution of infection. However, according to recent studies, selected patients with “controlled infection” should be considered for transplant, since this condition does not impair the post-transplant outcome^[69,70]. Antibiotic prophylaxis is the standard of care in cirrhotic patients with gastrointestinal bleeding or with previous episodes of SBP. However, it should be considered also in other settings with a high prevalence of BI, as in patients listed for LT, admitted to ICU and requiring intubation, because of a higher risk of post-LT pneumonia.

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