

Opportunistic infections in end stage liver disease

Michele Bartoletti, Maddalena Giannella, Sara Tedeschi, Pierluigi Viale
 Infectious Diseases Unit, Department of Medical and Surgical Sciences, Sant'Orsola-Malpighi Hospital, University of Bologna, Italy

Abstract

Liver cirrhosis is the 10th most common cause of death in Western world and infection is associated with a high morbidity and mortality, and represents the leading cause of acute liver decompensation. Patients with end-stage liver disease exhibit an important impairment of immune system. This condition, called cirrhosis-associated immune dysfunction, summarizes both local and systemic immune system alterations in liver cirrhosis that play a pivotal role in determining both the high incidence of infections and the ominous infections related mortality in this population. Another concerning feature of infections in cirrhotic patients is the growing prevalence of multidrug-resistant or extensively drug-resistant pathogens, which are associated with higher mortality, increased length of in-hospital stay and higher healthcare related costs if compared with infection caused by susceptible strains. Finally, patient with liver cirrhosis have several unique pathophysiological characteristics including hypoalbuminemia and reduction binding to proteins; altered distribution; altered clearance of the antimicrobials that can affect the pharmacokinetic/pharmacodynamic of antimicrobials.

Introduction

Liver cirrhosis is the 10th most common cause of death in Western world.¹ Among the complications of the end-stage liver disease (ESLD), infection represents the leading cause of acute decompensation^{2,3} and is associated with a high mortality ranging from 12 to 52%.^{4,5}

Despite these patients are particularly prone to develop bacterial and fungal infections,⁶ the cirrhosis of the liver is not commonly considered a major immunodepressive condition. However, patients with ESLD exhibit an important impairment of immune system. This condition, called cirrhosis-associated immune dysfunction (CAID) summarizes both local and systemic immune system alterations in liver

cirrhosis that play a pivotal role in determining both the high incidence of infections and the ominous infections related mortality in this patient population.^{7,8} Overall mortality of infected cirrhotic patients is around 30% at 1 month and more than 50% at 12 months.⁸ The high mortality rate of infections in cirrhotic patients is related not only to the direct effects of infections but, above all, to their pivotal role in triggering the condition of acute-on-chronic liver failure (ACLF). For this reason, infection is considered an important prognostic marker in patients with ESLD.

Another concerning feature of infections in cirrhotic patients is the growing prevalence of multidrug-resistant (MDR) or extensively drug-resistant (XDR) pathogens, which are associated with higher mortality, increased length of in-hospital stay and higher healthcare related costs if compared with infection caused by susceptible strains.⁹⁻¹¹ In addition to these clinical features, the threat of MDR/XDR pathogens relies on their ability to rapidly spread to patients in absence of contact precautions. As a consequence, an important transmission of MDR gram-negative bacilli between patients is observed during outbreaks.¹²

In this setting a multifaceted approach is needed to face all the management challenges offered by patients with ESLD with infection. This include the knowledge of contemporary epidemiology, the development of prognostic tools and testing of novel therapeutic strategies.

Epidemiology

In light of the emerging threat of multidrug-resistant organisms (MDRO), mainly related the ominous spread of extended-spectrum beta-lactamase producing (ESBL) and carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem resistant non-fermenting bacilli in the last decade, an increasing number of epidemiological studies were recently published. To better understand the evolution of epidemiology of bacterial and fungal infections in this setting the most representative studies are summarized in the Table 1.¹³⁻²¹

The wide variability in term of site of infection and causative pathogens is mainly related to several factors. First, with exception of spontaneous bacterial peritonitis (SBP), there is no agreement for most of infection definitions and most studies did not adopted the widely agreed criteria for infection diagnosis used in non-cirrhotic population. Second, the epidemiology of infection is currently under constant evolution and may vary between centers. Third,

Correspondence: Michele Bartoletti, Infectious Diseases Unit, S. Orsola Malpighi Hospital, Via Massarenti 11, 40138 Bologna, Italy.
 Tel.: +39.051.2143199 - Fax: +39.051.343500.
 E-mail: michele.bartoletti4@unibo.it

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similarly to the previous point, different study site may be characterized by different level of commitment in the management of cirrhotic patients. Thus, tertiary sites with dedicated liver unit and access to a transplantation program may exhibit a population with more advanced stage of liver disease if compared with urban hospitals. Despite inhomogeneity, these studies clearly show that the rate of MDRO has increased dramatically and the improvement of the management of liver cirrhosis may have changed also the characteristics of infection site. In fact, in the studies published in the 90' and in the first years of the 21th Century the diagnosis of SBP was prevalent (24-56% of cases). Conversely latter studies report a lower prevalence of SBP (8-18%, excluding one paper that included bacterial ascites in the definition of SBP and reported 42% of such infections) and higher rate of bloodstream infection (6-28%) and pneumonia (7-38%).

Few studies reported to date differences in the kind of infection and in the causative pathogens in patients with alcoholic liver disease (ALD) and patients with other causes of liver cirrhosis. Previous studies on bloodstream infections (BSI) including mainly patients with alcoholic cirrhosis report a higher prevalence of gram-positive

cocci (GPC) among the different etiologies of BSI. However most of these studies are old or characterized by a single-center design.^{22,23} In addition, infection in alcoholic cirrhosis seems to be characterized by higher frequency of ACLF, however conflicting results on the outcome are reported.^{3,24}

Risk factors for multidrug-resistant pathogens

To date few studies evaluated risk factors for MDRO in the setting of cirrhosis (Table 2).^{4,9,25-29}

Most of the reported studies focused on SBP whereas only 2 studies included all various sources of infection. The most reported risk factors for MDR were antibiotic exposure (antibiotic prophylaxis, use of third generation cephalosporines, fluoroquinolones or beta-lactams) and exposure to healthcare environment (*i.e.* hospital acquired or healthcare associated infections, previous hospital admission).

Prognosis

As mentioned before the high mortality rate of infections in cirrhotic patients is related not only to the direct effects of infections but, above all, to their pivotal role in triggering the condition of acute-on-chronic liver failure (ACLF). In a prospective multicenter study (CANONIC study), bacterial infection was found to be the precipitating event of ACLF in 32% of cases.³⁰ A further analysis of the CANONIC study revealed that BSI, pneumonia and SBP are more likely to be associated with ACLF. In addition, in patients with grade I and II ACLF, the presence of bacterial or fungal infection was associated with a worse outcome.³¹ Similarly, in a single-center study enrolling patients with ACLF, bacterial infection was a predictor of 30-day mortality.³² Despite these findings, a better understanding of the interaction between bacterial infection and ACLF is needed. In fact, the specific role of different kind of infections in determining ACLF and its risk factors are not clearly established.

Infection is considered an important prognostic marker in patients with ESLD. In a large multicenter cohort of patients with biopsy-proven compensated viral cir-

rhosis, the occurrence of a bacterial infection impaired survival both in HCV-infected (5-year survival: 60.2% vs 90.4%, $P < 0.001$) and HBV-infected patients (5-year survival: 69.2% vs 97.6%, $P < 0.001$), representing the third cause of death (14.1%) after liver failure and liver cancer. Similarly, in a single-center study enrolling 501 patients, bacterial infection was independently associated to mortality. The authors concluded that bacterial infection represents a different stage of the disease, which affect survival, even after recovery from an infectious episode.¹³

Antimicrobial pharmacokinetic/pharmacodynamic issues in liver cirrhosis

Ensuring a prompt and appropriate empirical antimicrobial treatment for infections in liver cirrhosis is essential in liver cirrhosis.^{33,34}

The concept of appropriateness for empirical and targeted antimicrobial treatment relies on a right antimicrobial coverage associated with an appropriate exposure consistent with the drugs' pharmacokinetic-pharmacodynamic (PK/PD) features. PK

Table 1. Summary of epidemiological studies on patients with liver cirrhosis. Only studies including all different source of infection are reported.

Author/year/ geographic area (ref)	Population	Most representative source of infection, %				Etiology (prevalence of MDRO), %		
		SBP	UTI	LRTI	Primary BSI	Gram- negative	Gram- positive	Fungi
Studies published in the 90'								
Caly/1993/Brazil (14)	All cirrhotics	31	25	25	NR	72 (NR)	28	NR
Toledo/1994/Spain (15)	All cirrhotics	44	26	10	5	65 (61 <i>E.coli</i>)	39	NR
Studies published from 2000 to 2015								
Borzio/2001/Italy (16)	All cirrhotics	23	41	17	21	46	49	4
Rosa/2000/Brazil (17)	All cirrhotics	54	7	18	NR	NR	NR	NR
Fernandez/2002/Spain (18)	All cirrhotics	24	19	13	5	45	47	NR
Fernandez/2012/Spain (4) /first series	All cirrhotics	56	43	20	13	44 (MRSA 3% of all infections)	46 (ESBL 9% of all infections)	NR
Fernandez/2012/Spain (4)/ second series	All cirrhotics	20	25	13	13	MRSA 7% of all infections	ESBL 7% of all infections	NR
Studies published from 2015 to 2017								
Merli/2015/Italy (9)	All cirrhotics	8	61	12	6	47	47	NR
Park/2015/Korea (19)	Alcoholic liver disease	9	4	38	4	35 (MRSA 86%)	63 (ESBL in 42% of Enterobacteriaceae)	2
Dionigi/2017/England (13)	All cirrhotics	42	19	9	28	58 (MRSA 18%)	41 (ESBL 20% of GNB)	NR
Salerno/2017/ (21) Italy and England	All cirrhotics	18	43	7	17	58 (MRSA 51%)	47 (44% ESBL production, 9% CR-GNB)	3
Piano/2017/Italy (21)	All cirrhotic	33	23	14	13	46	47	7

MDRO multidrug-resistant organisms; SBP spontaneous bacterial peritonitis; UTI urinary tract infection; LRTI low respiratory tract infection; BSI bloodstream infection; MRSA methicillin resistant *Staphylococcus aureus*; ESBL extended-spectrum beta-lactamase; CRE carbapenem-resistant Enterobacteriaceae; NR not reported

variability is a major contributor to therapeutic failure: therefore to guarantee a correct exposure to antibiotics, timely administration of the right dose at the right schedule, according to the pathophysiological and immunological status of the patient, is required.³⁵

Patient with liver cirrhosis have several unique pathophysiological characteristics that can alter the PK/PD behavior and the *in vivo* activity of antimicrobial agents. These characteristics include: i) hypoalbuminemia and reduction binding to proteins; ii) altered distribution; iii) altered clearance of the antimicrobial.³⁶

The reduction of antimicrobial protein binding is a consequence of decreased albumin production and accumulation of antibiotic binding inhibitors (such as bilirubin or α -acid glycoprotein) in patients with liver cirrhosis.³⁷ Depending on the degree of antibiotic protein binding, patients with liver cirrhosis may have, both in plasma and tissues, a higher fraction of unbound drug. This is the microbiologically active drug, but also the fraction that is cleared more rapidly through renal or hepatic pathways. Hence, patients with hypoalbuminemia have a higher proportion of drug *escaping* from the bloodstream and distributing into tissues, translating to increased distribution volume (Vd) and reduced or sometimes sub-therapeutic bloodstream concentrations required to treat severe infection.^{37,38}

In patients with advanced liver cirrhosis, splanchnic congestion and fluid retention due to hypoalbuminemia and reduced renal blood flow can further increase the Vd

for relatively hydrophilic antibiotics, such as beta-lactams, aminoglycosides, and vancomycin. As a result, most of the patients with ACLF presents with edema, ascites and third space expansion resulting in inadequate blood levels of these antibiotics.^{38,39} Therefore, larger loading and daily doses and are often required for hydrophilic antibiotics to achieve therapeutic blood levels.

On the other hand, increased Vd may also prolong the drug elimination irrespective of the clearance rates.³⁷ In some patients with liver cirrhosis, antibiotics half-life is increased, paradoxically causing drug accumulation and potential for toxicity.⁴⁰

Finally, the PK of antibiotics can be affected by liver-disease related changes in renal function that are very common in this population. Renal failure in liver cirrhosis is mainly due to a reduced renal perfusion secondary to a vasodilatation in the splanchnic circulation without a compensation of cardiac output.⁴¹ Although clearance of creatinine is widely accepted as a viable method for renal function assessment, several studies demonstrate that measured creatinine clearance from timed urine collection may overestimate the glomerular filtration rate in LC even in patients without hepatorenal syndrome.⁴²

Unfortunately, antibiotic PK/PD is rarely studied in patients with liver dysfunction, especially in patients with advanced cirrhosis and ascites (*i.e.* Child-Pugh Class C). This kind of patients are commonly excluded from phase 1, phase 2 and phase 3 studies. Consequently, there is currently lit-

tle or no scientific basis for antibiotic doses currently administered to treat life-threatening infections in patients with advanced cirrhosis. Given the unpredictable drug exposure, therapeutic drug monitoring (TDM) might play a pivotal role for individualizing doses, both in lowering exposure-dependent toxicity and in ensuring an optimal drug exposure, especially for the treatment of serious infections or MDR pathogens.

Beta-lactams are commonly used and represent the first-line therapy of most infection in patients with liver cirrhosis.⁴³ Beta-lactams are time-dependent drugs which ensure the best effectiveness with a prolonged time of exposure above the pathogen minimal inhibitory concentration (T>MIC).⁴⁴ Previous studies in general population indicate that continuous or extended infusion of beta-lactams is associated to better drug exposure and higher T>MIC and consequently better outcome for severe infection.⁴⁵

According with the aforementioned pathophysiological characteristics, the cirrhotic patient seems an important setting to test continuous infusion of beta-lactams for treating severe infections.

Conclusions

Bacterial and fungal infection is common in the natural history of liver cirrhosis and seems to have an impact on prognosis. Several aspects of infections deserve further investigation, such as the interaction

Table 2 Risk factors for multidrug-resistant pathogens in patients with liver cirrhosis and infection.

Author/Year/Geographic Area (Ref)	Kind of infections	Prevalence and kind of MDRO	Risk factors
Merli/2015/Italy (9)	All bacterial infections	51%	Antibiotic prophylaxis; HA or HCA infections
Kim/2013/Korea (25)	Community-onset SBP	32% of FQ resistant E.coli	FQ use (30dd); Previous SBP episode; Third-generation cephalosporin resistance
Fernandez/2012/Spain (4)/ first series	All bacterial infections		Nosocomial origin of infection; Long-term norfloxacin prophylaxis; Recent infection by multi-resistant bacteria; Recent use of b-lactams
Chaulk/2013/Canada (26)	SBP	19% third-generation cephalosporin resistance	Nosocomial acquisition of infection
Song/2009/Korea (27)	SBP	7% ESBL-Enterobacteriaceae	Nosocomial acquisition; Previous SBP episode
Alexopolu/2012/Greece (28)	SBP	24%	MELD score; HCA; Quinolone prophylaxis
Ariza/2012/Spain (29)	HA and HCA SBP	42% third generation cephalosporine resistance of HA SBP	Diabetes mellitus; Upper GI bleeding; Hospital acquired; Previous 3 rd Gen Cephalosporine use

MDRO, multidrug-resistant organisms; HA hospital associated; HCA healthcare associated; FQ fluoroquinolone; SBP spontaneous bacterial peritonitis; ESBL extended-spectrum beta-lactamase; MELD Model for End-Stage Liver Disease; GI gastrointestinal

between infection and ACLF. Additional studies are needed to assess novel therapeutic strategies like continuous infusion of beta-lactams on the outcome of infection in this setting.

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