Opportunistic infections in end stage liver disease

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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 (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. 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.

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. Despite these patients are particularly prone to develop bacterial and fungal infections, 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 population. Overall mortality of infected cirrhotic patients in around 30% at 1 month and more than 50% at 12 months. 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.

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Introduction

Liver cirrhosis is the 10th most common cause of death in Western world. Among the complications of the end-stage liver disease (ESLD), infection represents the leading cause of acute decompensation and is associated with a high mortality ranging from 12 to 52%. Despite these patients are particularly prone to develop bacterial and fungal infections, 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. Overall mortality of infected cirrhotic patients in around 30% at 1 month and more than 50% at 12 months. 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.

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Key words: liver cirrhosis; bacterial infection; multidrug-resistant pathogens.

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Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Accepted for publication: 29 January 2018.

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Contributions: MB, ST, MG, review of the literature; MB, ST, draft of the manuscript; MG, PV, Revision and final approval.

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Licensee PAGEPress, Italy
Infectious Disease Reports 2018; 10:7621
doi:10.4081/idr.2018.7621

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Infectious Disease Reports 2017; volume 9:7621
coccii (GPC) among the different etiologies of BSIs. 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.1,24

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).

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

<table>
<thead>
<tr>
<th>Author/year/ geographic area (ref)</th>
<th>Population</th>
<th>Most representative source of infection, %</th>
<th>Etiology (prevalence of MDRO), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SBP</td>
<td>UTI</td>
</tr>
<tr>
<td>Studies published in the 90's</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caly/1993/Brazil (14)</td>
<td>All cirrhotics</td>
<td>31</td>
<td>25</td>
</tr>
<tr>
<td>Toledo/1994/Spain (15)</td>
<td>All cirrhotics</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>Studies published from 2000 to 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borzio/2001/Italy (16)</td>
<td>All cirrhotics</td>
<td>23</td>
<td>41</td>
</tr>
<tr>
<td>Rosa/2000/Brazil (17)</td>
<td>All cirrhotics</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>Fernandez/2002/Spain (18)</td>
<td>All cirrhotics</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>Fernandez/2012/Spain (4)</td>
<td>All cirrhotics</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>Fernandez/2012/Spain (4)/first series</td>
<td>All cirrhotics</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Fernandez/2012/Spain (4)/second series</td>
<td>All cirrhotics</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Studies published from 2015 to 2017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merli/2015/Italy (9)</td>
<td>All cirrhotics</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Park/2015/Korea (19)</td>
<td>Alcoholic liver disease</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Dionigi/2017/England (14)</td>
<td>All cirrhotics</td>
<td>42</td>
<td>19</td>
</tr>
<tr>
<td>Salerno/2017/Italy and England (21)</td>
<td>All cirrhotics</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>Piano/2017/Italy (21)</td>
<td>All cirrhotics</td>
<td>33</td>
<td>23</td>
</tr>
</tbody>
</table>

MDRO multidrug resistant organisms; SBP spontaneous bacterial peritonitis; UTI urinary tract infection; LRTI lower 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.33

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.39,40 Therefore, larger loading and daily doses 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 little 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-depending 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

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

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

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.

References