Risk factors for the emergence of multidrug-resistant organisms in liver cirrhosis

Figueiredo LM; Rafael MA; Alexandrino G; Martins A; Oliveira A; Carvalho R; Santos L; Horta D; Lourenço L; Reis J; Costa M

Hospital Professor Doutor Fernando Fonseca
Introduction

Infections in patients with liver cirrhosis (LC) are common.

Infections are present at admission or develop during hospitalization in 25–35% of patients (4–5 fold higher compared with general population)

Jalan R et al Bacterial infections in cirrhosis Journal of Hepatology 2014; Piano S et al Infections complicating cirrhosis Liver International. 2018
Introduction

Multidrug resistant organisms (MDROs) are bacteria resistant to 3 or more of the main antibiotic families.

ESBL: extended spectrum beta lactamase producing Enterobacteriaceae
MRSA: methicillin resistant Staphylococcus aureus
VSR/VRE: vancomycin-susceptible/resistant enterococci

Introduction

Liver cirrhosis is the 10th most common cause of death in the Western world.

Overall mortality of infected cirrhotic patients is around 30% at 1 month and more than 50% at 12 months.

Bartoletti M, et al. Opportunistic infections in end stage liver disease. Infectious Disease Reports 2017; Marcus M et al. Bacterial infection-triggered acute-on-chronic liver failure is associated with increased mortality. L International. 2017
Introduction

Research on risk factors of bacterial infections in cirrhosis.

- Impairment of liver function
  - Child-Pugh score [26,30]
  - MELD score $\geq 15$ [31]
  - Low serum albumin [32]
- Alcohol related disease [4,6,12]
- Total ascitic fluid protein concentration $< 15$ g/L [34]
- ICU admission [9,65]
- Variceal bleeding [41,16]
- Blood transfusion requirements
- Mean arterial pressure
- Severity of bleeding
- Malnutrition [42]
- Invasive procedures [38]
- ERCP in PSC patients or with incomplete drainage [37]
- Hospitalization [29,40,43,44]

Ferrarese A et al Management of bacterial infection in the liver transplant candidate World J Hepatol 2018

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of cirrhosis / biomarkers</td>
<td></td>
</tr>
<tr>
<td>Bilirubin $&gt; 3.2$ mg/dl</td>
<td>Guarnier et al. Gastroenterology 1999</td>
</tr>
<tr>
<td>PLT $&lt; 98000$/mmc</td>
<td>Andreu et al. Gastroenterology 1993</td>
</tr>
<tr>
<td>Protein levels in ascitic fluid $&lt; 1.5$ g/l</td>
<td>Fernandez et al. Gastroenterology 2007</td>
</tr>
<tr>
<td>MELD $&gt; 19$</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes $\leq 900$/mmc</td>
<td></td>
</tr>
</tbody>
</table>

Medications
- Use of PPI
- Long term exposure to antibiotics
  - Nahon et al. Gut 2015

Precipitating events
- Acute variceal haemorrhage
- Previous infection
  - Bernard et al. Hepatology 1999
  - Fernandez et al. Gastroenterology 2007

Viale P, Decompensated cirrhosis Infections in cirrhotic patient viale The International Liver congress 2017 EASL Postgraduated course

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Luisa Martins Figueiredo

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Aim

Identify risk factors for the occurrence of MDROs in patients with LC.

Methods

- Prospective study from October 2017 to March 2018
- Consecutively hospitalized patients with decompensated LC with infection
- Blood, urine and ascitic fluid cultures were analysed
- Statistical significance: $p$-value <0.0500
# Patients Analysis

52 episodes of infection | 22 patients

<table>
<thead>
<tr>
<th>GENDER</th>
<th>AGE</th>
<th>CHILD-TURCOTTE-PUGH SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83%</td>
<td></td>
</tr>
</tbody>
</table>

### Gender Distribution

- **Female Patients**: 17%
- **Male Patients**: 83%

### Age

- **Average**: 63.5
- **Minimum**: 30.0
- **Maximum**: 88.0
- **Std. deviation**: 14.4
Patients Analysis

Risk factors for the emergence of multidrug-resistant organisms in liver cirrhosis

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Patients Analysis

52 episodes of infection | 18 MDROs

<table>
<thead>
<tr>
<th>GENDER</th>
<th>AGE</th>
<th>CHILD-TURCOTTE-PUGH SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average: 63.9</td>
<td>Minimum: 30.0</td>
</tr>
<tr>
<td>17%</td>
<td>Female Patients</td>
<td></td>
</tr>
<tr>
<td>83%</td>
<td>Male Patients</td>
<td></td>
</tr>
</tbody>
</table>

[Graph showing infection episodes and MDROs]

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Patients Analysis

Number of isolated microorganisms identified

- **MDROs identified:** Klebsiella ESBL, E. faecium, E. Faecalis, MRSA, KPC, Clostridium difficile, Staphylococcus haemolyticus methicillin resistant

- **Klebsiella ESBL** was the most frequently isolated MDRO – 44.4%
## Results

MDROs were significantly associated with:

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>ANTIBIOTICS &lt;90 DAYS</th>
<th>HOSPITALIZATION &gt;48H / HOSPITAL DISCHARGE &lt;30 DAYS</th>
<th>PROTON PUMP INHIBITORS</th>
<th>MORTALITY 3M</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRO #18</td>
<td>94.4%</td>
<td>100%</td>
<td>72.2%</td>
<td>71.4%</td>
</tr>
<tr>
<td>NON MDRO #19</td>
<td>47.4%</td>
<td>68.4%</td>
<td>36.8%</td>
<td>35.7%</td>
</tr>
<tr>
<td>P-VALUE</td>
<td>0.0033</td>
<td>0.0082</td>
<td>0.0312</td>
<td>0.0316</td>
</tr>
</tbody>
</table>

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Results

There was no MDROs relevant statistical association with:

<table>
<thead>
<tr>
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<th>MDRO #18</th>
<th>NON MDRO #19</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLADDER CATHETER</td>
<td>61.1%</td>
<td>42.1%</td>
<td>0.2599</td>
</tr>
<tr>
<td>CENTRAL VENOUS CATHETER</td>
<td>38.9%</td>
<td>26.3%</td>
<td>0.4283</td>
</tr>
<tr>
<td>DIABETES MELLITUS</td>
<td>38.9%</td>
<td>31.6%</td>
<td>0.6526</td>
</tr>
<tr>
<td>HEPATO-CELLULAR CARCINOMA</td>
<td>33.3%</td>
<td>31.6%</td>
<td>0.9124</td>
</tr>
<tr>
<td>MORTALITY 1M</td>
<td>27.8%</td>
<td>26.3%</td>
<td>0.9230</td>
</tr>
</tbody>
</table>
Conclusion

- MDROs are a current reality that can alter the paradigm of treatment and prevention of infection in LC.

- The indiscriminate use of antibiotics and PPIs increases the risk of MDROs infections, suggesting that the prescription of these drugs should be restricted to formal indication.

- Hospitalization for more than 48 hours or hospital discharge for less than 30 days have been shown to influence the onset of MDROs, suggesting that hospitalizations in LC patients should be limited to the minimum number of days required.
References


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Bartoletti M, Giannella M, Tedeschi S, Viale P Opportunistic infections in end stage liver disease Opportunistic infections Infectious Disease Reports 2017; volume 9:7621

EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosisq European Association for the Study of the Liver Journal of Hepatology 2018

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