PREVENTION AND TREATMENT OF BACTERIAL INFECTIONS IN CIRRHOSIS

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AEEH Postgraduate Course,
Madrid, February 15 2017
Prevalence of infection in the ICU

PREVALENCE AT THE HOSPITAL

ICU PREVALENCE

25-35%

59%

Clinical impact of bacterial infections in cirrhosis


Infections increase mortality 4-fold

Mortality at 1 month

Before 2000

After 2000
Prevention of bacterial infections in cirrhosis
Antibiotic prophylaxis. Current indications in cirrhosis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Antibiotic and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Preserved liver function: norfloxacin 400 mg/12h PO for 7 days</td>
</tr>
<tr>
<td></td>
<td>Patients with advanced cirrhosis (at least 2 of the following: ascites, jaundice, hepatic encephalopathy and malnutrition): IV ceftriaxone 1 g/d during 7 days</td>
</tr>
</tbody>
</table>
| Primary prophylaxis of SBP in patients with low protein ascites (<15 g/L) | Norfloxacin 400 mg/d PO or ciprofloxacin 500 mg/d until liver transplantation or death in patients with advanced cirrhosis:  
- Child-Pugh score ≥9 points with serum bilirubin ≥3 mg/dl  
and/or  
- Renal dysfunction (serum creatinine ≥1.2 mg/dl, BUN ≥25 mg/dl and/or serum sodium ≤130 mEq/L) |
| Secondary prophylaxis of SBP                    | Norfloxacin 400 mg/d PO until liver transplantation, death, resolution of ascites or improvement in liver function to a compensated status |

Jalan, Fernandez. J Hepatol 2014
Antibiotic prophylaxis for the prevention of SBP in patients with cirrhosis and hemorrhage

Risk difference
-0.1 0.0 0.1 0.2 0.3 0.4

Soriano 92
Blaise 94
Pauwels 96
Hsieh 98
Total

0.0736, p=0.0060
Antibiotic prophylaxis in cirrhotic patients with hemorrhage. Effects on survival

Risk difference

-0.1 0.0 0.1 0.2 0.3 0.4

Rimola 85
Soriano 92
Blaise 94
Pauwels 96
Hsieh 98
Total

0.091, p=0.004

Bernard et al. Hepatology 1999
Bacterial infection and failure to control bleeding

Proven bacterial infection and failure to control bleeding


p<0.01
Antibiotic prophylaxis and rebleeding

Hou et al. Hepatology 2004

p < 0.01
Ceftriaxone vs. norfloxacin in the prevention of infections in UGB in advanced cirrhosis*

*At least two of the following: ascites, severe malnutrition, encephalopathy or bilirubin > 3 mg/dl

Fernández et al. Gastroenterology 2006
Secondary prophylaxis of SBP

- Norfloxacin (n=40)
- Placebo (n=40)

Probability of SBP

p=0.006

Gines et al. Hepatology 1990
Primary prophylaxis of SBP in patients with advanced cirrhosis*

*Ascitic fluid protein <15 g/L and serum creatinine ≥1.2 mg/dL or BUN ≥25 mg/dL or serum sodium ≤130 mEq/L or Child-Pugh score ≥ 9 points with serum bilirubin ≥ 3 mg/dL

Fernández et al. Gastroenterology 2007
Probability of type-1 HRS

Fernández et al. Gastroenterology 2007
Probability of short-term survival

Fernández et al. Gastroenterology 2007
Primary prophylaxis of SBP in cirrhotic patients with low protein ascites

PREVENTION OF SBP

1-YEAR PROBABILITY OF SURVIVAL

Terg et al. J Hepatol 2008
Impact on survival of primary prophylaxis with norfloxacin in Child-Pugh C

Moreau et al. AASLD 2016
Probability of bacterial infections in patients with ACLF and AD

P-value < 0.001

Fernandez et al. Submitted
Outline

✓ Current indications of antibiotic prophylaxis
✓ Drawbacks of antibiotic prophylaxis
✓ Potential alternatives
Definition of multiresistant (MDR) bacteria

✅ MDR: Strains resistant to $\geq 3$ of the main antibiotic families including $\beta$-lactams or to at least 1 agent in 3 or more families: difficult to treat bacteria.

✅ The most frequent are: extended-spectrum $\beta$-lactamase-producing *Enterobacteriaceae* (ESBL), *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, MRSA, VSE and VRE.

Fernandez and Berg et al. J Hepatol 2016
Increasing prevalence of MDR bacteria over time

- 1998-2000: 10%
- 2005-2007: 18%
- 2010-2011: 23%

* p<0.05 vs. other periods

Prevalence of MDR bacteria according to the site of acquisition of infection

2005-2007

- Community-acquired: 4%
- Health care-associated: 14%
- Nosocomial: 35%

N=507
p=0.001

2010-2011

- Community-acquired: 20%
- Health care-associated: 20%
- Nosocomial: 39%

N=162
p=0.002

Fernandez et al. Hepatology 2012
<table>
<thead>
<tr>
<th>Risk factors for infections caused by MDR bacteria</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nosocomial infection</td>
<td>4.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>• <strong>Long-term norfloxacin prophylaxis</strong></td>
<td>2.69</td>
<td>0.004</td>
</tr>
<tr>
<td>• Use of beta-lactams (last 3 months)</td>
<td>2.39</td>
<td>0.02</td>
</tr>
<tr>
<td>• Infection by MDR bacteria (last 6 months)</td>
<td>2.45</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Fernández et al., Hepatology 2012**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nosocomial infection</td>
<td>2.54</td>
</tr>
<tr>
<td>• Previous use of cephalosporins</td>
<td>2.98</td>
</tr>
<tr>
<td>• Upper gastrointestinal bleeding</td>
<td>8.15</td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td>2.52</td>
</tr>
</tbody>
</table>

* 3rd generation cephalosporin-resistant bacteria in SBP

**Ariza et al., J Hepatol 2012**
Geographic distribution of antibiotic-resistant bacteria in cirrhosis

Fernandez and Berg et al. J Hepatol 2016
SBP prophylaxis and CDI

Prevalence of *Clostridium difficile* infection

- SBP prophylaxis
- No

P=0.01

Table 4. Univariate and multivariate logistic regression in the tertiary care sample with *Clostridium difficile* as the outcome

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>2.40</td>
<td>0.96–5.99</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender</td>
<td>0.73</td>
<td>0.35–1.51</td>
<td>0.71</td>
</tr>
<tr>
<td>CTP class</td>
<td>1.02</td>
<td>0.64–1.61</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>SBP prophylaxis</strong></td>
<td>5.42</td>
<td>2.14–13.73</td>
<td>0.0005</td>
</tr>
<tr>
<td>Inpatient antibiotic use</td>
<td>6.55</td>
<td>2.18–15.10</td>
<td>0.0005</td>
</tr>
<tr>
<td>Outpatient PPI use</td>
<td>23.78</td>
<td>5.66–99.8</td>
<td>0.0005</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient PPI use</td>
<td>37.6</td>
<td>6.22–227.6</td>
<td>0.0005</td>
</tr>
<tr>
<td>Inpatient antibiotic use</td>
<td>11.6</td>
<td>2.63–51.05</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Bajaj et al. Am J Gastroenterol 2010
Potential alternatives in the prevention of SBP in cirrhosis

RIFAXIMIN

COLONY-STIMULATING FACTORS

OBETICHOLIC ACID

New antibiotic strategies for bacterial infections in cirrhosis
Severe baseline circulatory dysfunction

Rapid deterioration of cardiovascular function and organ blood perfusion/higher organ damage

Kidneys
- Renal failure

Other organs and systems
- Liver: Jaundice, coagulopathy, encephalopathy
- Brain: Encephalopathy
- Adrenal glands: Relative adrenal insufficiency
- Gut: Increased translocation of viable bacteria and endotoxin

Excessive inflammatory response to SBP

Arroyo et al. Nat Rev Nephrol 2011
Impact of cirrhosis on the outcome of infected patients in the ICU

Mortality higher than that observed in the general population: 30-57% vs. 50-100%
Early antibiotic treatment

“The golden hour concept” in the cirrhotic population

In patients with cirrhosis and septic shock, inappropriate and delayed appropriate initial empiric antimicrobial therapy is associated with increased mortality.

Arabi et al. Hepatology 2012
MDR-XDR-PDR bacterial infections in cirrhosis

N=124 bacterial infections (51% resistant-strains)

Merli et al. Plos One 2015
Infections by MDR bacteria.
Resolution of infection and outcome

Resolution* (%)

<table>
<thead>
<tr>
<th>MDR bacteria</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>92%</td>
<td>70%</td>
</tr>
</tbody>
</table>

p<0.0001

Septic shock (%)

<table>
<thead>
<tr>
<th>MDR bacteria</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>26%</td>
</tr>
</tbody>
</table>

p<0.0001

* After modification of antibiotic therapy

Fernández et al., Hepatology 2012
Infections by MDR bacteria. Clinical outcome

Hospital mortality (%)

No: 12%  Yes: 25%

p=0.001

Fernández et al., Hepatology 2012
Nosocomial infections in cirrhosis. Failure of the guidelines based on the use of third-generation cephalosporins

Resolution without treatment modification (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>CA</th>
<th>Nosocomial</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>78%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UTI</td>
<td>90%</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S. bacteremia</td>
<td>67%</td>
<td>18%</td>
<td>0.05</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>82%</td>
<td>50%</td>
<td>ns</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>67%</td>
<td>44%</td>
<td>ns</td>
</tr>
<tr>
<td>Other</td>
<td>91%</td>
<td>65%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Fernández et al., Hepatology 2012
Healthcare-associated infections in cirrhosis. Efficacy of third-generation cephalosporins

Resolution without treatment modification (%)

- Community-acquired: 83%, p=0.05
- Health care-associated: 73%

<table>
<thead>
<tr>
<th>Condition</th>
<th>CA</th>
<th>HCA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>78%</td>
<td>71%</td>
<td>ns</td>
</tr>
<tr>
<td>UTI</td>
<td>90%</td>
<td>59%</td>
<td>0.02</td>
</tr>
<tr>
<td>S. bacteremia</td>
<td>67%</td>
<td>60%</td>
<td>ns</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>82%</td>
<td>81%</td>
<td>ns</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>68%</td>
<td>33%</td>
<td>ns</td>
</tr>
<tr>
<td>Other</td>
<td>91%</td>
<td>91%</td>
<td>ns</td>
</tr>
</tbody>
</table>

Fernández et al., Hepatology 2012
Problems and solutions in the history of SBP and other infections in cirrhosis

- Low efficacy of treatment
- High rate of recurrence
- High prevalence of HRS
- High prevalence of MDR bacteria

Solution

3rd-generation cephalosporins
Antibiotic prophylaxis
Albumin infusion
Preventive measures & modification of antibiotic guidelines

Fernández and Gustot, J Hepatol 2012
Proposed algorithm for the empirical treatment of spontaneous infections in cirrhosis

Spontaneous bacterial infection (SBP, SBE or SB)

- Community-acquired infection
- Health-care associated infection
- Nosocomial infection

Presence of ≥ 2 risk factors for multiresistant bacteria* or severe sepsis or shock?

- NO: Third-generation cephalosporins
- YES: Carbapenem + glycopeptide**

Acevedo et al., Hepatol Int 2012
# Recommended empirical antibiotic therapy

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Community-acquired infections</th>
<th>Nosocomial infections*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, SBE and spontaneous bacteremia</td>
<td>Cefotaxime or ceftiraxone or amoxicillin/clavulanic acid</td>
<td>Piperacillin/tazobactam^ or meropenem^ ± glycopeptide^</td>
</tr>
<tr>
<td>Urinary infections</td>
<td><strong>Uncomplicated:</strong> ciprofloxacin or cotrimoxazole</td>
<td><strong>Uncomplicated:</strong> nitrofurantoin or fosfomycin</td>
</tr>
<tr>
<td></td>
<td>If sepsis: cefotaxime or ceftiraxone or amoxicillin/clavulanic acid</td>
<td>If sepsis: piperacillin/tazobactam^ or meropenem^ ± glycopeptide^</td>
</tr>
<tr>
<td>Pneumonia**</td>
<td>Amoxicillin/clavulanic acid or ceftiraxone + macrolide or levofloxacin or moxifloxacin</td>
<td>Piperacillin/tazobactam^ or meropenem/ceftazidime + ciprofloxacin ± glycopeptide^ should be added in patients with risk factors for MRSA^</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Amoxicillin/clavulanic acid or ceftiraxone + oxacillin</td>
<td>Meropenem/ceftazidime^ + oxacillin or glycopeptides^</td>
</tr>
</tbody>
</table>

SBP, spontaneous bacterial peritonitis; SBE, spontaneous bacterial empyema; MRSA, methicillin-resistant *Staphylococcus aureus*.

Dosages of antibiotics have not been formally investigated or defined in cirrhotic population and it is advisable to follow standard recommended dosages.

*Recommended empirical treatment also for health-care associate (HCA) urinary infections and pneumonia. Empirical antibiotic treatment of HCA spontaneous infections and cellulitis will be decided on the basis of the severity of infection (patients with severe sepsis should receive the schedule proposed for nosocomial infections) and on the local prevalence of multiresistant bacteria in HCA infections.

\^In areas with a low prevalence of multiresistant bacteria.

\^To cover extended-spectrum \(\beta\)-lactamase (ESBL)-producing *Enterobacteriaceae*.

\^IV vancomycin or teicoplanin in areas with a high prevalence MRSA and vancomycin-susceptible enterococci (VSE). Glycopeptides must be replaced by IV linezolid in areas with a high prevalence of vancomycin-resistant enterococci (VRE).

\^Liver disease is considered as severe comorbidity for community-acquired pneumonia in guidelines.

\^Antibiotics active against *Pseudomonas aeruginosa*.

\^Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage.
Impact of new empirical antibiotic strategies

**NOSOCOMIAL SBP**
Cefepime vs meropenem+daptomycin

**HCA INFECTIONS**
B-lactams vs Imipenem+GPC

**RESOLUTION RATE:**
Cefepime: 25%
Meropenem+daptomycin: 87%

Algorithm of empirical antibiotic treatment in ICU

1. Risk factors of MDR bacteria: a) previous colonization; b) Antibiotic treatment > 5 days in the last 3 months; c) Hospitalization > 5 days in the last 3 months, and d) Nursing-home

2. High-risk infection: pneumonia, peritonitis (high bacterial load) or with high-risk of severe complications (meningitis).

3. CRP levels correlate with bacterial load

4. Plus azitromicin 500 mg/day, 3 days in pneumonia or change to fluoroquinolones

5. Daptomycin in infections with high-risk of bacteremia (catheter, IE). Linezolid in pneumonia, cellulitis or CNS infection. Vancomycin instead of daptomycin or linezolid if GFR >60 mL/min, no other nephrotoxic drug and no use in the previous month

6. If previous treatment with carbapenem (6 weeks) start with piperacillin-tazobactam or ceftazidime + tigecyclin

7. Consider to add depending on local epidemiology, recent antibiotic treatments and source of infection

8. Add an echinocandin if 2 or more of the following criteria: a/ colonization by Candida spp (candiduria or rectal swab) and antibiotic treatment or steroids, b/ parenteral nutrition, c/ Gastro-duodenal surgery or necrohemorragic pancreatitis, d/ renal replacement therapy

Fernandez et al, Hepatogy 2015
Doses and patterns of IV administration of the main antibiotics in severe sepsis or shock

<table>
<thead>
<tr>
<th></th>
<th>Initial dose</th>
<th>Doses and way of administration in the first 48 h</th>
<th>“de-escalation” at 72h</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefotaxime</td>
<td>2 g</td>
<td>6-8 g / d in continuous infusion</td>
<td>1-2 g / 8 h</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>2 g</td>
<td>6 g / d in continuous infusion</td>
<td>1-2 g / 8 h</td>
</tr>
<tr>
<td>meropenem</td>
<td>2 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>2 g</td>
<td>1 g / 12 h</td>
<td>1 g / 12-24 h</td>
</tr>
<tr>
<td>piperacillin</td>
<td>4-0,5 g</td>
<td>16 g / d in continuous infusion</td>
<td>4,5 g / 6-8 h</td>
</tr>
<tr>
<td>(tazobactam)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>levofloxacin</td>
<td>1000 mg</td>
<td>500 mg / 12 h</td>
<td>500 mg / 24 h</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>600 mg</td>
<td>400 mg / 8 h</td>
<td>400 mg / 8-12 h</td>
</tr>
<tr>
<td>fosfomycin</td>
<td>4 g</td>
<td>200-300 mg / kg / d in continuous infusion</td>
<td>2 g / 6 h</td>
</tr>
<tr>
<td>tigecycline</td>
<td>200 mg</td>
<td>100 mg / 12 h</td>
<td>50-100 mg / 12 h</td>
</tr>
<tr>
<td>metronidazole</td>
<td>1000-1500 mg</td>
<td>500 mg / 6 h</td>
<td>500 mg / 6-8 h</td>
</tr>
</tbody>
</table>

1. The first dose is independent of the renal function

Fernandez et al, Hepatology 2015
Re-evaluation of treatment at 48-72 h

Positive cultures

- Adjust antibiotic treatment to the results of the cultures: monotherapy if possible

Negative or no cultures

<table>
<thead>
<tr>
<th>Good evolution</th>
<th>Bad evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>(decrease in CRP levels)</td>
<td>(increase in CRP levels)</td>
</tr>
<tr>
<td>Maintain treatment for 5 days if no source of infection and for 7 days in the rest</td>
<td>New samples, change of catheters, image techniques, new antibiotic schedules</td>
</tr>
</tbody>
</table>

Fernandez et al, Hepatology 2015
Key points and conclusions

✓ Antibiotic prophylaxis must be restricted to high-risk groups to decrease the likelihood of emergence of antibiotic resistance.

✓ New RCT are needed to assess potential alternatives to classical antibiotics, mainly rifaximin, obeticholic acid and G-CSF
Key points and conclusions

- MDR bacteria are frequently isolated in nosocomial and to a lesser extend HCA infections in cirrhosis.
- They are associated with poorer prognosis and higher mortality rate.
- Third-generation cephalosporins continue to be the gold-standard antibiotic treatment of many of the infections acquired in the community.
Key points and conclusions

✅ Empirical treatment of nosocomial and possibly some health care-associated infections should be adapted to the local epidemiological pattern of antibiotic resistance.

✅ Patients with severe sepsis or shock should receive broad spectrum antibiotic regimens, with optimized IV administration (high doses/continuous infusion).

✅ Empirical antibiotic regimen should be rapidly narrowed and shortened to decrease the risk of emergence of antibiotic resistance.