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# When to use antibiotics in the cirrhotic patient? The evidence base

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**Abstract**

Bacterial infections are very common in advanced cirrhosis and are a leading cause of death of these patients. Early and appropriate empirical antibiotic treatment of infection is essential in determining patient's outcome. A strategy of careful restriction of prophylactic antibiotics to the high-risk populations could contribute to the reduction of multidrug resistant bacteria. This article reviews and reports the current knowledge in the use of antibiotics in the cirrhotic patient.

**Keywords** Cirrhosis, antibiotics, bacterial infection

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## Introduction

Bacterial infections are commoner in patients with cirrhosis than in the general population, and those with decompensated cirrhosis are more susceptible to infection than those with a compensated lesion [1,2]. The absence of clinical signs of infection in the cirrhotic patient is frequent [3], and the limited diagnostic capacity of C-reactive protein and systemic inflammatory response syndrome criteria in the cirrhotic population often delay the diagnosis of bacterial infection. The application of preventive measures against infection is therefore of utmost importance in cirrhotic patients. When they are in the hospital environment essential measures include appropriate hand hygiene of nursing and medical staff, use of chlorhexidine solution for skin preparation, full-barrier precautions during the insertion of central venous catheters, and the use of the subclavian vein as the preferred site for insertion of the catheter, with the removal of any unnecessary central lines or urinary catheter [4]. Failing to ensure good care of central and peripheral intravenous lines, as well as urinary catheters increases the risk of infection [5]. Furthermore, antibiotic prophylaxis is necessary in patients with cirrhosis who have gastrointestinal bleeding, as well as in invasive procedures such as transjugular intrahepatic portosystemic shunt [6].

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## Treatment of bacterial infections

The commonest infection in cirrhotic patients is spontaneous bacterial peritonitis (SBP), followed by urinary tract infection, pneumonia, bacteremia following a therapeutic procedure, cellulitis, and spontaneous bacteremia [1]. Culture positive infections are reported in 50-70% of cases. The causative organisms of community acquired infection are Gram-negative bacilli (GNB), especially *Escherichia coli* (*E. coli*), in about 60%, Gram-positive cocci (GPC) in about 30-35% and mixed in 5-10%. The figures are reversed for nosocomial infections; 60% GPC and 30-35% GNB, due to previous antibiotic exposure. With *E. coli* being the commonest in community, the next most frequently isolated bacteria are *Staphylococcus aureus* (*S. aureus*), *Enterococcus faecalis*, and *Streptococcus pneumoniae* (*S. pneumoniae*). In the case of SBP, less-virulent strains of *E. coli* may be causative as liver function deteriorates, suggesting that in advanced cirrhosis, bacteria do not need to develop strategies to confound host defences and invade the host [7]. Fungal infections (*Candida spp.*) are responsible for up to 15% of severe sepsis in patients with cirrhosis [8].

Cirrhotic patients with severe sepsis and septic shock require emergency care during the early stage of sepsis (especially the first 6 h). Early and appropriate initiation of antibiotics correlates with higher survival rate. A retrospective study by Kumar *et al* suggested that each hour of delay decreased survival by 7.6% [9]. Choosing adequate empiric antimicrobial treatment will therefore improve the prognosis of patients [10].

Microbiological samples should be taken as early as possible when infection is suspected, before starting empiric antibiotic therapy and empiric antimicrobial therapy will need to be adapted to local epidemiology, prevalence of antibiotic resistance and results of bacterial cultures. Empiric antibiotic treatments for classical community-acquired bacterial infec-

**Table 1** Empirical antibiotic therapy for community-acquired bacterial infections in cirrhosis

| Type of infection | Organism | Antibiotics |
|---|---|---|
| Spontaneous bacterial peritonitis (SBP) | *Escherichia coli*<br>*Streptococcus viridans*<br>*Enterobacter spp.* | Cefotaxime (2g/6 h or 2g/12 h IV)<br>or amoxicillin/clavulanic acid (1-0.2 g/8 h then 0.5-0.125g/8 h PO)<br>or ofloxacin (400 mg/12 h PO)<br>or ciprofloxacin (200 mg/12 h IV then 500 mg/12 h PO) |
| Urinary tract infections | *Escherichia coli*<br>*Klebsiella pneumoniae*<br>*Enterococcus spp.* | Ciprofloxacin (500 mg/12 h PO)<br>or cotrimoxazole (160-800 mg/12 h PO)<br>or amoxicillin/clavulanic acid(1-0.2 g/8 h IV) |
| Pneumonia | *Streptococcus pneumoniae*<br>*Staphylococcus aureus*<br>*Escherichia coli* | Amoxicillin/clavulanic acid (1-0.2 g/8 h IV) and macrolide<br>or moxifloxacin (400 mg/24 h PO) |
| Soft tissue infections | *Staphylococcus aureus*<br>*Streptococcus pyogenes*<br>*Klebsiella pneumoniae*<br>*Escherichia coli*<br>*Pseudomonas aeruginosa* | Ceftazidime (2 g/8 h IV + oxacillin 2 g/6 h IV) |

tions are shown in Table 1. The relevant causative bacteria as well as empiric antibiotic treatments for classical community-acquired bacterial infections in cirrhosis are as follows:
In SBP where the commonest organisms are *E. coli*, *Streptococcus viridans* and *Enterobacter spp*., preferred antibiotic regimens are cefotaxime (2 g/6 h or 2 g/12 h IV) or amoxicillin/clavulanic acid (1-0.2 g /8 h then 0.5-0.125 g/8 h PO) or ofloxacin (400 mg/12 h PO) [11-14]. Courses should not last less than 5-7 days. Intravenous albumin administration reduces the incidence of renal impairment (from 33% to 10%) and improves hospital survival (from 71% to 90%) in patients with SBP [11].

In urinary tract infections with *E. coli*, *Klebsiella pneumoniae* and *Enterococcus spp*. being the commonest causative organisms, suggested regimens are ciprofloxacin (500 mg/12 h PO) or cotrimoxazole (160-800 mg/12 h PO) or amoxicillin/clavulanic acid (1-0.2 g/8 h PO) [15]. Patients with complicated cystitis must be treated for at least 5 days, and in case of pyelonephritis, antibiotic therapy should be prolonged for 10-14 days.

In pneumonia the commonest causative organisms are *S. pneumoniae*, *S. aureus*, and *E. coli*. The suggested regimens are amoxicillin/clavulanic acid 1-0.2 g/8 h IV) and macrolide or moxifloxacin (400 mg/24 h PO) [16]. Patients with community-acquired pneumonia must be treated for a minimum of 5 days.

In soft tissue infections with *S. aureus*, *Streptococcus pyogenes*, *Klebsiella pneumonia*e, *E. coli* and *Pseudomonas aeruginosa* most frequently being the infecting organisms, the most appropriate regimen is ceftazidime (2 g/8 h IV) plus oxacillin (2 g/6 h IV) [17]. Soft tissue infections must be treated for a minimum of 10 days. In all cases, the duration of antibiotic therapy depends on response to treatment and resolution of infection.

With microbial infections being so common and severe in patients with liver cirrhosis, it is important to target high-risk patients, such as those with acute gastrointestinal bleeding and SBP. In such instances infection is frequently caused by translocation of GNB of intestinal origin. Prevention is by selective intestinal decontamination, and is best based on long-term maintenance of a fluoroquinolone.

Bacterial infections are particularly common in patients with acute gastrointestinal bleeding, when treated by endoscopic banding or sclerotherapy. A meta-analysis of trials in patients with variceal bleeding has shown that antibiotic prophylaxis reduced the incidence of severe infections (SBP and/or septicemia) and decreased mortality [18]. Mortality due to variceal hemorrhage is decreased from 43% to 15% over a 20-year period and antibiotic prophylaxis is independently associated with improved survival [19]. Oral norfloxacin (800 mg/day for 7 days) is commonly used [20], although in a randomized controlled trial IV ceftriaxone (1 g/day for 7 days) was more effective than oral norfloxacin with respect to the prevention of severe infections in patients with advanced cirrhosis (characterized by at least two of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dL) and variceal hemorrhage [21].

In cirrhotic patients with low protein ascites (<1.5g/dL) but no prior SBP (primary prophylaxis), oral norfloxacin (400 mg/day) is recommended when Child-Pugh score is ≥9 points or if serum bilirubin level is ≥3 mg/dL or renal function is impaired (serum creatinine level ≥1.2 mg/dL, blood urea nitrogen level ≥25 mg/dL, or serum sodium level ≤130 mEq/L). This has been shown to reduce the probability of

SBP and hepatorenal syndrome and improved the 3-month survival [22]. Likewise, oral ciprofloxacin (500 mg/day) will reduce the 1-year mortality rate in patients with ascitic protein levels <1.5 g/dL without prior SBP episode [23].

In those patients who have had one previous episode of SBP, the cumulative recurrence rate at 1 year is 70%. Oral norfloxacin is recommended for secondary prophylaxis since it decreases the recurrence rate of SBP from 70% to 20% [24]. Alternative antibiotics include ciprofloxacin (750 mg once weekly, orally) or co-trimoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim daily, orally), but evidence is not as strong as with norfloxacin [25].

However, there is no consensus regarding how long prophylactic oral antibiotic therapy should be continued to prevent SBP or its recurrence. Not surprisingly, prolonged antibiotic treatment is associated with the emergence of resistant organisms and alternative approaches are needed. Interestingly the preliminary results of a large double-blind randomized controlled trial has shown that pentoxifylline administered orally (1200 mg/day) significantly decreases the risk of bacterial infection in patients with advanced cirrhosis [26].

Hepatic encephalopathy with the increasing evidence for infection or the inflammatory responses in the progression and severity is another clinical situation in which antibiotics are indicated. Although neomycin has been used for many years in the treatment of hepatic encephalopathy, a randomized trial of 39 patients comparing neomycin at a dose of 6 g/day to placebo showed no difference in outcomes between the two treatment groups [27]. Furthermore, neomycin is associated with ototoxicity and nephrotoxicity, limiting long-term use. Other antibiotics, such as metronidazole, oral vancomycin, and rifaximin have been found to be effective in clinical trials and are better tolerated than neomycin [28]. A meta-analysis of five controlled trials of rifaximin showed it had a similar efficacy as nonabsordable disaccharides for acute and chronic hepatic encephalopathy, but was found to be better tolerated [29]. Later placebo-controlled trials showed that rifaximin improved quality of life [30], and performance on a simulated driving test in patients with minimal hepatic encephalopathy [31]. Rifaximin remains currently a second-line treatment for hepatic encephalopathy, due to the major cost difference between rifaximin and lactulose, and because of the possible emergence of resistant strains and drug interactions [32]. Thus, they are most suitable for patients who cannot tolerate or are resistant to disaccharides.

## Conclusions

Despite extensive research in the field of antibiotic regimens in cirrhotic patients there are many unanswered questions, especially with regard to treatment duration. A policy of careful restriction of prophylactic antibiotics to the high-risk populations could reduce the spread of multidrug resistant bacteria.

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