Retrospective Study

Pathogen profile and drug resistance analysis of spontaneous peritonitis in cirrhotic patients

Yong-Tao Li, Cheng-Bo Yu, Jian-Rong Huang, Zheng-Ji Qin, Lan-Juan Li

Yong-Tao Li, Cheng-Bo Yu, Jian-Rong Huang, Lan-Juan Li, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

Zheng-Ji Qin, Medical Statistics Office of Public Health Department, Nantong University, Nantong 226000, Jiangsu Province, China

Author contributions: Li LJ designed the research; Li YT performed the research; Yu CB and Huang JR contributed to providing patient data; Li YT and Qin ZJ analyzed the data; Li YT and Li LJ wrote the paper.

Supported by Grants from the National Basic Research Program of China, 973 Program, No. 2013CB531401.

Institutional review board statement: The study was reviewed and approved by the medical ethics committee at The First Affiliated Hospital of Zhejiang University School of Medicine.

Informed consent statement: Patients were not required to give informed consent to the study as the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of the First Affiliated Hospital of Zhejiang University School of Medicine.

Conflict-of-interest statement: The authors declare no competing interests.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Abstract

AIM: To investigate the microbiological characteristics and drug resistance in liver cirrhosis patients with spontaneous peritonitis.

METHODS: We analyzed the data of patients with liver cirrhosis and abdominal infection at the First Affiliated Hospital of Zhejiang University between January 2011 and December 2013. Pathogens present in the ascites were identified, and their sensitivity to various antibiotics was determined.

RESULTS: We isolated 306 pathogenic bacteria from 288 cases: In 178 cases, the infection was caused by gram-negative strains (58.2%); in 85 cases, gram-positive strains (27.8%); in 9 cases, fungi (2.9%); and in 16 cases, more than one pathogen. The main pathogens were *Escherichia coli* (24.2%), *Klebsiella pneumoniae* (18.9%), *Enterococcus* spp. (11.1%), and *Staphylococcus aureus* (7.5%). Of the 306 isolated pathogens, 99 caused nosocomial infections and 207 caused community-acquired and...
other infections. The \textit{E. coli} and \textit{K. pneumoniae} strains produced more extended-spectrum β-lactamases in cases of nosocomial infections than non-nosocomial infections (62.5% vs 38%, \(P < 0.013\); 36.8% vs 12.8%, \(P < 0.034\), respectively). The sensitivity to individual antibiotics differed between nosocomial and non-nosocomial infections: Pipercillin/tazobactam was significantly more effective against non-nosocomial \textit{E. coli} infections (4% vs 20.8%, \(P < 0.021\)). Nitrofurantoin had stronger antibacterial activity against \textit{Enterococcus} species causing non-nosocomial infections (36.4% vs 86.3%, \(P < 0.009\)).

**CONCLUSION:** The majority of pathogens that cause abdominal infection in patients with liver cirrhosis are gram-negative, and drug resistance is significantly higher in nosocomial infections than in non-nosocomial infections.

**Key words:** Liver cirrhosis; Spontaneous peritonitis; Drug sensitive test; Drug resistance

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Monitoring drug resistance in cases of abdominal infection with liver cirrhosis is important for establishing appropriate antibiotic regimes, reducing the generation of drug-resistant bacteria and reducing the associated mortality. Therefore, this study addressed two primary issues regarding spontaneous peritonitis in cirrhotic patients in China: first, the pathogen profile and, second, drug resistance, and determined the differences between nosocomial infections and non-nosocomial infections. Based on these findings, clinicians can select the appropriate antibiotic treatment to control the emergence and development of pathogenic bacteria-resistant strains in intra-abdominal infections.

Li YT, Yu CB, Huang JR, Qin ZI, Li LJ. Pathogen profile and drug resistance analysis of spontaneous peritonitis in cirrhotic patients. \textit{World J Gastroenterol} 2015; 21(36): 10409-10417 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i36/10409.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i36.10409

**INTRODUCTION**

 Decompensated liver cirrhosis affects 25% to 47% of the population, and ascites is the most common complication; it is characterized by decreased immune function, which consequently leads to abdominal cavity, blood, lung, urinary tract and other infections that worsen with time and have a high fatality rate\(^{1-2}\). Studies have shown that decreased immunity combined with weak intestinal motility, increased intestinal permeability, reduced secretion of intestinal antimicrobial peptides and other factors are likely to lead to bacterial translocation in patients with decompensated cirrhosis\(^{3-5}\). Spontaneous bacterial peritonitis is a common infection; it causes further deterioration of liver function, multi-organ failure and sepsis, which are associated with poor prognosis and a low survival rate\(^{6-9}\). The mortality rate associated with multiple organ failure and septicopyemia caused by spontaneous bacterial peritonitis is still over 75%\(^{10-12}\). Therefore, antibiotic therapy for spontaneous peritonitis has become an important means of improving the survival rate in patients with cirrhosis.

Third-generation cephalosporins are mainly used for the treatment of spontaneous bacterial peritonitis; however, it was shown that cefotaxime, one of the most commonly used cephalosporins, had a lower success rate than expected\(^{13}\). This is probably attributable to the emergence of antibiotic-resistant pathogen strains. While earlier reports showed that 70% of the cases of spontaneous bacterial peritonitis were caused by gram-negative bacteria such \textit{Escherichia coli} (\textit{E. coli}) and \textit{Klebsiella pneumoniae}\(^{14}\), this bacterial profile has begun to change and the emergence of resistant bacterial species has been indicated. In recent years, the incidence of gram-positive abdominal infections in patients with decompensated cirrhosis has increased significantly; this phenomenon is attributed to the use of antibiotics that alter the intestinal flora such that it is conducive to the translocation of gram-positive bacteria\(^{15-17}\). Another study has attributed the increasing incidence of gram-positive bacterial peritonitis to increased resistance to quinolones, such as norfloxacin, which are also commonly used for the treatment of this infection\(^{18}\). Thus, it is important to study in detail the pathogen profiles in spontaneous bacterial peritonitis and resistance of the pathogens to currently used antibiotics. Based on this, clinicians can select the appropriate antibiotic treatment to control the emergence and development of pathogenic bacteria-resistant strains in intra-abdominal infections.

Although some studies have examined the pathogen profiles and drug resistance in spontaneous peritonitis\(^{19,20}\), there is definitely a need for new and comprehensive data on the same. Therefore, in this study, we retrospectively surveyed and analyzed the types of pathogens and their drug resistance in the ascites culture samples of 288 patients who had cirrhosis with abdominal infection at our hospital between January 2011 and December 2013.

**MATERIALS AND METHODS**

**Clinical data**

The medical ethics committee at The First Affiliated Hospital of Zhejiang University School of Medicine approved the protocol for the retrospective study before the clinical data were collected. All cirrhotic patients at our hospital between January 2011 and
December 2013 were retrospectively analyzed. Each case history was registered using a unified registration form: the information included gender; age; duration of hospitalization; medical history; clinical manifestations; hospitalization course; disease prognosis; and the results of abdominal ultrasonography, abdominal paracentesis, routine ascites test, ascites culture, liver function test, kidney function test, blood coagulation test, and routine blood examination. If the ascites culture results obtained following abdominocentesis at 48 h after admission was positive, this was considered to indicate a nosocomial infection. If a patient repeatedly tested positive for the same pathogen in the ascites culture examination, only the first result was recorded. The criteria for the diagnosis of spontaneous bacterial peritonitis were positive ascites culture for bacteria and neutrophil count in the ascites sample greater than 250/mm$^3$.[21]

Materials
The Bactec blood culture system produced by Becton Dickinson (Mountain View, CA, United States) and antibacterial agents, antimicrobial gradient strips and media produced by Oxoid (Basingstoke, United Kingdom) were used. The antibacterial agents included piperacillin/ tazobactam, ampicillin/sublactam, gentamicin, amikacin, imipenem, meropenem, ciprofloxacin, levofloxacin, moxifloxacin, cefotaxime, ceftriaxone, cefoperazone/ sublactam, ceftazidine, aztreonam, aztreonam/ceftriaxone, piperacillin/tazobactam, cephalosporins, and glycopeptides, which were used at high concentrations (120 μg). The test strips of vancomycin used were purchased from AB BIODISK (Solna, Sweden).

Susceptibility testing
The Kirby-Bauer (KB) method was used for drug sensitivity testing on Müller-Hinton agar. The results of the drug sensitivity tests were assessed according to the standards of the US Clinical and Laboratory Standards Institute (CLSI) in 2011. Methicillin-resistant Staphylococcus aureus (S. aureus, MRSA) strains and methicillin-resistant coagulase-negative staphylococci (MRNS) were identified using the standard method for susceptibility testing of antimicrobial drugs recommended by the National Committee for Clinical Laboratory Standards (NCCLS) in 2003, except that oxacillin was replaced by cefoxitin. S. aureus ATCC25923, E. coli ATCC25922 and Pseudomonas aeruginosa ATCC27853 were used as quality-control strains. Paper screening for extended-spectrum β-lactamases (ESBLs) and the enzyme inhibitor enhanced paper confirmatory method recommended by the US CLSI were used to examine ESBL production in E. coli and K. pneumoniae.

Statistical analysis
The variables were counting variables, and the description of the count data is described by a ratio or the rate of the data. The $t$ test was used to analyze measurement data, and the $\chi^2$ test was used to analyze count data. $P < 0.05$ was considered to indicate statistical significance. SPSS 17.0 was used for all the statistical analyses.

RESULTS

Clinical characteristics
The clinical data of 6086 patients with liver cirrhosis were gathered over the three-year study period. Of these patients, 506 had abdominal infections, excluding secondary abdominal infections (ascites fluid neutrophil count was $\geq$ 250/mm$^3$, a positive ascites fluid culture, and evidence of an intra-abdominal source of infection, demonstrated by surgery, autopsy, or abdominal CT).[22] According to the results of the ascites neutrophil count and bacterial culture. Spontaneous bacterial peritonitis was identified in 288 cases (198 male and 90 female patients; age range, 23-79 years; mean age, 55 ± 12.6 years), and 306 pathogens were isolated. Most patients had advanced liver cirrhosis (68.9%, Child C; 28.6%, Child B; and 2.5%, Child A); the mean Child score was 10.5. A few patients (less than 10%) had received preventive quinolone treatment. Among the 288 patients, 208 had abdominal pain and fever; 22 had septic shock and 42 had multiple organ dysfunction syndrome. Fifty-one of the patients died at the end of the treatment. In 137 cases, the WBC count was $\geq 10.0 \times 10^9$ in 45 cases, the WBC count was $\leq 4.0 \times 10^9$.

Isolation and characterization of pathogens
A total of 306 pathogens were isolated from the 288 cases: 178 patients were positive for gram-negative bacteria (58.2%), 85 for gram-positive bacteria (27.8%), 9 for fungi (2.9%), and 16 for more than one pathogen. The main pathogens identified were E. coli (74 strains, 24.2%), K. pneumoniae (58 strains, 18.9%), glucose non-fermenting bacteria (including Acinetobacter baumannii and P. aeruginosa) (6.2%), Enterococcus species (11.1%), coagulase-negative staphylococci (CNS, 5.6%), S. aureus (7.5%), and Streptococcus pneumoniae (3.6%). Among the 306 isolated pathogens, 207 strains caused community-acquired and other hospital-acquired infections in 206 patients (67.6%). Among the 206 patients, 82 had hospital-acquired infections, in whom 99 strains were identified (32.4%). A. baumannii, P. aeruginosa and fungal pathogens caused a significantly higher number of nosocomial than non-nosocomial infections (Table 1). Six MRSA strains were detected [detection rate, 26.1% (6/23)], and five MRNS strains were detected [29.4% (5/17)]. Fungal infections mainly occurred in patients with nosocomial infections.
**Drug tolerance of the isolated pathogens**

**Gram-negative bacteria:** Imipenem, meropenem, piperacillin/tazobactam, and amikacin showed good antibacterial activity against *E. coli* and *K. pneumoniae* in cases of abdominal infection (sensitivity rate, $\geq 86.2\%$). Piperacillin/tazobactam was significantly more effective against non-nosocomial *E. coli* infections; gentamicin, cefoperazone/sulbactam, ceftriaxone, and ampicillin/sulbactam were more effective against non-nosocomial infections caused by *K. pneumoniae*. The sensitivity rates of *P. aeruginosa* and *Acinetobacter* spp. were generally low; however, *Acinetobacter* spp. showed greater drug tolerance than *P. aeruginosa* (Table 2). Thirty-four *E. coli* strains that produced ESBLs were detected [detection rate, 45.9\% (34/74)], and 12 *K. pneumoniae* strains that produced ESBL were detected [detection rate, 20.7\% (12/58)]. ESBL was produced in more cases of nosocomial infections than in non-nosocomial infections, and the sensitivity of individual antibiotics differed between nosocomial and non-nosocomial infections: Ampicillin/sulbactam and ceftriaxone were significantly more effective against non-nosocomial *K. pneumoniae* infections (23.1\% vs 57.9\%, $P < 0.009$; 28.2\% vs 63.4\%, $P < 0.011$) (Tables 3 and 4).

**Gram-positive bacteria:** The antimicrobial activity of vancomycin, nitrofurantoin and rifampin against *Staphylococcus* spp. in abdominal infections was strong, with a sensitivity rate of $\geq 87\%$. The antimicrobial activity of gentamicin, clindamycin and moxifloxacin was also strong, with a sensitivity rate of $\geq 60.9\%$. *Enterococcus* spp. had drug resistance to a variety of antibacterial agents, but vancomycin, clindamycin and gentamicin had strong antibacterial activity against *Enterococcus* spp., with a sensitivity rate of $\geq 70.6\%$. Furthermore, nitrofurantoin had stronger antibacterial activity against *Enterococcus* spp. that caused non-nosocomial infections. Vancomycin, rifampin, moxifloxacin and nitrofurantoin had good antibacterial activity against *S. pneumoniae*, with a sensitivity rate of $\geq 71.9\%$. The sensitivity of individual antibiotics differed between nosocomial and non-nosocomial infections: ofloxacin, levofloxacin,

### Table 1 Distribution of the major pathogens in the ascites samples of 288 patients with spontaneous bacterial peritonitis between 2011 and 2013 ($n$ (%) )

| Pathogen | Total ($n = 306$) | Non-nosocomial infection ($n = 207$) | Nosocomial infection ($n = 99$) | $P$ value ($\chi^2$ test) |
|----------|------------------|------------------------------------|-------------------------------|---------------------------|
| Gram-negative bacteria | 178 (58.2) | 113 (54.6) | 65 (65.7) | 0.06 |
| *Escherichia coli* | 74 (24.2) | 50 (24.1) | 24 (24.2) | 0.98 |
| *Klebsiella pneumoniae* | 58 (18.9) | 39 (18.8) | 19 (19.1) | 0.94 |
| *Acinetobacter* spp. | 10 (3.3) | 2 (0.9) | 8 (8.1) | 0.001 |
| *Pseudomonas aeruginosa* | 9 (2.9) | 2 (0.9) | 7 (7.1) | 0.003 |
| Enterobacter cloacae | 17 (5.6) | 12 (5.8) | 5 (5.1) | 0.79 |
| *Aerogenes* spp. | 10 (3.3) | 8 (3.9) | 2 (2.0) | 0.39 |
| Gram-positive bacteria | 85 (27.8) | 58 (28.0) | 27 (27.3) | 0.89 |
| *Enterococcus* | 34 (11.1) | 22 (10.6) | 12 (12.1) | 0.69 |
| *Staphylococcus aureus* | 23 (7.5) | 16 (7.7) | 7 (7.1) | 0.83 |
| Coagulase-negative staphylococci | 17 (5.6) | 12 (5.8) | 5 (5.1) | 0.79 |
| *Streptococcus pneumoniae* | 11 (3.6) | 8 (3.9) | 3 (3.0) | 0.71 |
| *Fungi* | 9 (2.9) | 2 (0.9) | 7 (7.1) | 0.004 |

$P < 0.05$ was considered statistically significant.

### Table 2 Drug resistance rate of major gram-negative bacteria to commonly used antibacterial agents

| Antibacterial agents | *Escherichia coli* ($n = 74$) | *Klebsiella pneumoniae* ($n = 58$) | *Acinetobacter* spp. ($n = 10$) | *Pseudomonas aeruginosa* ($n = 9$) |
|---------------------|-------------------------------|---------------------------------|-------------------------------|-------------------------------|
| **Strains** | **Drug resistance rate (%)** | **Strains** | **Drug resistance rate (%)** | **Strains** | **Drug resistance rate (%)** |
| Ampicillin/sulbactam | 30 | 40.5 | 23 | 39.7 | 8 | 80 | 7 | 77.8 |
| Piperacillin/tazobactam | 7 | 9.4 | 8 | 13.8 | 6 | 60 | 3 | 33.3 |
| Ceftriaxone | 18 | 24.3 | 20 | 34.5 | 8 | 80 | 9 | 100 |
| Cefotaxime | 31 | 41.9 | 15 | 25.9 | 7 | 70 | 3 | 33.3 |
| Cefoperazone/sulbactam | 12 | 16.2 | 17 | 29.3 | 4 | 40 | 3 | 33.3 |
| Cefazidime | 33 | 44.6 | 17 | 29.3 | 7 | 70 | 3 | 33.3 |
| Amikacin | 5 | 6.8 | 3 | 5.1 | 2 | 20 | 1 | 11.1 |
| Gentamicin | 37 | 50 | 12 | 20.7 | 6 | 60 | 2 | 22.2 |
| Ciprofloxacin | 37 | 50 | 16 | 27.6 | 7 | 70 | 3 | 33.3 |
| Aztreonam | 26 | 35.1 | 13 | 22.4 | 6 | 60 | 4 | 44.4 |
| Imipenem | 1 | 1.3 | 7 | 12.1 | 6 | 60 | 3 | 33.3 |
| Meropenem | 2 | 2.7 | 4 | 6.9 | 7 | 70 | 2 | 22.2 |
moxifloxacin and clindamycin were more effective against *S. aureus* strains that caused non-nosocomial infections. Nitrofurantoin had stronger antibacterial activity against *Enterococcus* spp. that caused non-nosocomial infections (36.4% vs 86.3%, P < 0.009) (Tables 5-7).

**DISCUSSION**

In this study, we isolated 306 pathogens from ascites culture samples of 288 hospitalized patients with liver cirrhosis and abdominal infection over a period of 3 years: gram-negative bacteria formed the majority of the pathogens (58.2%), and mainly included *E. coli*, *K. pneumoniae*, *A. baumannii*, *A. hydrophila*, *P. aeruginosa*, *Burkholderia cepacia* and other glucose non-fermenting bacteria. Other studies have also shown that gram-negative bacteria formed the majority of pathogens in patients with liver cirrhosis complicated with spontaneous bacterial peritonitis. However, the findings from these studies, including the present study, are in contrast to the more recent trends, which have shown an increase in the number of infections caused by gram-positive bacteria. For example, Alexopoulou et al. showed that 55% of the spontaneous bacterial peritonitis cases in cirrhotic patients were caused by gram-positive cocci. Furthermore, Piroth et al. showed that gram-positive cocci formed the majority of pathogenic bacteria in cases of spontaneous bacterial peritonitis and ascites; the authors supposed that this was related to the use of prophylactic antibiotics in patients with liver cirrhosis (which altered the intestinal flora), the use of invasive procedures and other factors. Our data showed that the use of prophylactic antibiotics was not too high in our group of patients with liver cirrhosis, which probably explains why more gram-negative than gram-positive bacteria were isolated.

Of the 306 isolated pathogens, 99 were responsible for hospital-acquired infections (32.4%); this finding was similar to that of Ariza et al., who found that 40.9% of cases of spontaneous bacterial peritonitis were nosocomial infections. Our patient population comprised a high number of cases with advanced

| Table 3  Comparison of the drug resistance of *Escherichia coli* to commonly used antibacterial agents between nosocomial and non-nosocomial spontaneous bacterial peritonitis n (%) |
|-----------------------------------------------|
| Antibacterial agents                  | Non-nosocomial infections (n = 50) | Nosocomial infections (n = 24) | P value (χ² test) |
|-----------------------------------------------|
| ESBL test                                  | 19 (38.0)                          | 15 (62.5)                      | 0.013            |
| Ampicillin/sulbactam                       | 11 (28.0)                          | 12 (66.7)                      | 0.093            |
| Piperacillin/tazobactam                    | 2 (4.0)                            | 5 (20.8)                       | 0.021            |
| Ceftriaxone                                | 7 (14.0)                           | 11 (45.8)                      | < 0.001          |
| Cefepime                                   | 17 (34.0)                          | 14 (58.3)                      | 0.04             |
| Cefoperazone/sulbactam                     | 4 (8.0)                            | 8 (33.3)                       | 0.006            |
| Cefazidime                                 | 16 (32.0)                          | 17 (70.8)                      | 0.002            |
| Amikacin                                   | 2 (4.0)                            | 3 (12.5)                       | 0.173            |
| Gentamicin                                 | 17 (34.0)                          | 20 (83.3)                      | < 0.001          |
| Ciprofloxacin                              | 18 (36.0)                          | 19 (79.1)                      | 0.001            |
| Aztreonam                                  | 11 (22.0)                          | 15 (62.5)                      | 0.001            |
| Imipenem                                   | 1 (2.0)                            | 0 (0)                          | 0.485            |
| Meropenem                                  | 0 (0)                              | 2 (8.3)                        | 0.039            |

ESBL test: Extended-spectrum β-lactamase test. P < 0.05 was considered statistically significant.

| Table 4  Comparison of the drug resistance of *Klebsiella pneumoniae* to commonly used antibacterial agents between nosocomial and non-nosocomial spontaneous bacterial peritonitis n (%) |
|-----------------------------------------------|
| Antibacterial agents                  | Non-nosocomial infections (n = 39) | Nosocomial infections (n = 19) | P value (χ² test) |
|-----------------------------------------------|
| ESBL test                                  | 5 (12.8)                           | 7 (36.8)                       | 0.034            |
| Ampicillin/sulbactam                       | 11 (28.2)                          | 12 (63.1)                      | 0.011            |
| Piperacillin/tazobactam                    | 3 (7.7)                            | 5 (26.3)                       | 0.054            |
| Ceftriaxone                                | 9 (23.1)                           | 11 (57.9)                      | 0.009            |
| Cefepime                                   | 8 (20.1)                           | 7 (36.8)                       | 0.183            |
| Cefoperazone/sulbactam                     | 8 (20.1)                           | 9 (47.4)                       | 0.035            |
| Cefazidime                                 | 10 (25.6)                          | 7 (36.8)                       | 0.098            |
| Amikacin                                   | 2 (5.1)                            | 1 (5.3)                        | 0.983            |
| Gentamicin                                 | 5 (12.8)                           | 7 (36.8)                       | 0.034            |
| Ciprofloxacin                              | 10 (25.6)                          | 6 (31.6)                       | 0.635            |
| Aztreonam                                  | 8 (20.1)                           | 5 (26.3)                       | 0.619            |
| Imipenem                                   | 4 (10.3)                           | 3 (15.8)                       | 0.544            |
| Meropenem                                  | 2 (5.10)                           | 2 (10.5)                       | 0.446            |

ESBL test: Extended-spectrum β-lactamase test. P < 0.05 was considered statistically significant.
cirrhosis (70.9% with Child C type). They had severe fever, abdominal pain and other symptoms of peritonitis.

In our study, the most predominant pathogen was *E. coli* (24.2%), followed by *K. pneumoniae* (18.9%) and then enterococci (11.1%). Moreover, the percentages of MRSA and MRCNS were 26.1% and 29.4% respectively. These findings are similar to some recent and older studies on the pathogen profile of spontaneous bacterial peritonitis. Furthermore, fungal pathogens caused 2.9% of the infections, which was similar to a previous report. It is therefore

### Table 5 Drug resistance rate of the major gram-positive bacteria against commonly used antibacterial agents

| Antibacterial agents | Enterococcus (n = 34) | Staphylococcus aureus (n = 23) | Coagulase-negative staphylococci (n = 17) | Streptococcus pneumoniae (n = 11) |
|----------------------|-----------------------|-------------------------------|------------------------------------------|----------------------------------|
| Strains              | Drug resistance rate (%) | Strains                       | Drug resistance rate (%)                  | Strains                          | Drug resistance rate (%)                  |
| Penicillin           | 26 (76.5)             | 21 (91.3)                     | 15 (88.2)                                | 10 (90.9)                        |
| Oxacillin            | 23 (67.6)             | 12 (52.2)                     | 13 (76.5)                                | 7 (63.3)                         |
| Erythromycin         | 19 (55.9)             | 14 (60.9)                     | 12 (70.6)                                | 8 (72.7)                         |
| Cefazolin            | 25 (73.5)             | 13 (56.5)                     | 10 (58.8)                                | 7 (65.3)                         |
| Nitrofurantoin       | 18 (52.9)             | 2 (8.7)                       | 1 (5.9)                                  | 2 (18.1)                         |
| Rifampicin           | 5 (14.7)              | 3 (13.0)                      | 2 (11.8)                                 | 1 (9.1)                          |
| Clindamycin          | 8 (23.5)              | 6 (26.1)                      | 6 (35.3)                                 | 4 (36.4)                         |
| Levofloxacin         | 28 (82.4)             | 10 (43.4)                     | 7 (41.2)                                 | 4 (36.4)                         |
| Ciprofloxacin        | 26 (76.5)             | 11 (47.8)                     | 8 (47.1)                                 | 6 (54.5)                         |
| Gentamicin           | 10 (29.4)             | 3 (13.0)                      | 4 (23.5)                                 | 2 (18.1)                         |
| Moxifloxacin         | 14 (41.1)             | 9 (39.1)                      | 5 (29.4)                                 | 2 (18.1)                         |
| Vancomycin           | 2 (5.9)               | 0 (0)                         | 0 (0)                                    | 0 (0)                            |

### Table 6 Comparison of the drug resistance of *Enterococcus* species to commonly used antibacterial agents between nosocomial and non-nosocomial spontaneous bacterial peritonitis n (%)

| Antibacterial agents | Non-nosocomial infections (n = 22) | Nosocomial infections (n = 12) | P value (χ² test) |
|----------------------|-------------------------------------|-------------------------------|------------------|
| Penicillin           | 16 (72.7)                           | 10 (83.3)                     | 0.486            |
| Oxacillin            | 14 (63.6)                           | 9 (75.0)                      | 0.498            |
| Erythromycin         | 10 (45.5)                           | 9 (75.0)                      | 0.097            |
| Cefazolin            | 14 (63.6)                           | 11 (91.7)                     | 0.077            |
| Nitrofurantoin       | 8 (36.4)                            | 10 (85.3)                     | 0.009            |
| Rifampicin           | 3 (13.6)                            | 2 (16.7)                      | 0.812            |
| Clindamycin          | 5 (22.7)                            | 3 (25.0)                      | 0.881            |
| Levofloxacin         | 18 (81.8)                           | 10 (83.3)                     | 0.912            |
| Ciprofloxacin        | 18 (81.8)                           | 8 (66.7)                      | 0.320            |
| Gentamicin           | 4 (18.2)                            | 6 (50.0)                      | 0.052            |
| Moxifloxacin         | 7 (31.8)                            | 7 (58.3)                      | 0.133            |
| Vancomycin           | 1 (4.5)                             | 1 (8.3)                       | 0.645            |

P < 0.05 was considered statistically significant.

### Table 7 Comparison of the drug resistance of *Staphylococcus aureus* to commonly used antibacterial agents between nosocomial and non-nosocomial spontaneous bacterial peritonitis n (%)

| Antibacterial agents | Non-nosocomial infections (n = 16) | Nosocomial infections (n = 7) | P value (χ² test) |
|----------------------|-------------------------------------|-------------------------------|------------------|
| Penicillin           | 15 (93.8)                           | 6 (85.7)                      | 0.529            |
| Oxacillin            | 6 (37.5)                            | 6 (85.7)                      | 0.033            |
| Erythromycin         | 9 (56.3)                            | 5 (71.4)                      | 0.493            |
| Cefazolin            | 8 (50.0)                            | 5 (71.4)                      | 0.240            |
| Nitrofurantoin       | 2 (12.5)                            | 0 (0)                         | 0.328            |
| Rifampicin           | 2 (12.5)                            | 1 (4.3)                       | 0.907            |
| Clindamycin          | 2 (12.5)                            | 4 (57.1)                      | 0.025            |
| Levofloxacin         | 4 (25.0)                            | 6 (85.7)                      | 0.007            |
| Ciprofloxacin        | 5 (31.3)                            | 6 (85.7)                      | 0.016            |
| Gentamicin           | 2 (12.5)                            | 1 (4.3)                       | 0.907            |
| Moxifloxacin         | 3 (18.6)                            | 6 (85.7)                      | 0.002            |
| Vancomycin           | 0 (0)                               | 0 (0)                         | NS               |

P < 0.05 was considered statistically significant; NS: Not significant.
important to start anti-fungal treatment as soon as fungal species are discovered in the ascites culture of cirrhotic patients with peritonitis.

Our data showed that resistance of the major gram-negative as well as gram-positive bacteria to third-generation cephalosporins was higher in nosocomial infections than in non-nosocomial infections, which is in agreement with Song et al\(^\text{[29]}\)'s findings and a recent study by Sheikhhahaei et al\(^\text{[20]}\). Imipenem, meropenem, piperacillin/tazobactam, and amikacin had good antibacterial activity against *E. coli* and *K. pneumoniae* in abdominal infections (sensitivity rate, ≥ 86.2%). However, *E. coli* and *K. pneumoniae* showed high resistance against gentamicin, ampicillin and cephalosporins; this is in keeping with the recent trend observed by Park et al\(^\text{[19]}\). Therefore, the findings indicate that preference should be given to the first group of antibiotics when treating cirrhotic patients with peritonitis caused by *E. coli* and *K. pneumoniae* strains. Furthermore, piperacillin/tazobactam showed significantly stronger activity against non-nosocomial infections caused by *E. coli*, and gentamicin, cefoperazone/sulbactam, ceftriaxone, and ampicillin/sulbactam showed stronger activity against non-nosocomial infections caused by *K. pneumoniae*.

The sensitivity of *P. aeruginosa* and *Acinetobacter* spp. to the antibiotic agents was low, but *Acinetobacter* spp. had stronger drug tolerance than *P. aeruginosa*. The drug resistance of gram-negative bacteria against quinolone antibiotics was higher than that of gram-positive bacteria, particularly in cases of nosocomial infections, which is consistent with the results of previous studies\(^\text{[20]}\).

The detection rate of ESBL-producing *E. coli* was higher than that of ESBL-producing *K. pneumoniae* (45.9% vs 20.7%). Moreover, ESBL production was higher in cases of nosocomial infections than in cases of non-nosocomial infections. Previous studies have also shown that ESBL production was higher in cirrhotic patients with nosocomial infection than in those with non-nosocomial infection; ESBL production improves bacterial resistance and consequently results in increased mortality\(^\text{[10,30]}\). Our results showed a significant difference in the meropenem resistance of *E. coli* between nosocomial and non-nosocomial infections; this was probably related to the widespread use of carbapenems. The aminoglycoside and β-lactamase inhibitor complex had higher activity against ESBL-producing *E. coli* and *K. pneumoniae* strains. Although glucose non-fermenting bacteria have higher sensitivity to commonly used antibiotics, the detection rate of non-fermenting bacteria in clinical specimens has been increasing every year. This trend is probably related to the use of mechanical ventilator-assisted ventilation, atomization devices, cardiopulmonary bypass, various types of catheters, and the long-term use of high doses of cephalosporins, carbapenems and other antibacterial drugs; thus, non-fermenting bacteria are important pathogens in nosocomial infection\(^\text{[31,32]}\). Therefore, patients with cirrhosis who are likely to have abdominal infection should be treated with the enzyme complex comprising aminoglycoside and β-lactamase inhibitors and diene hydrocarbon enzyme antibacterials that have strong activity against gram-negative bacteria. Aminoglycoside antibiotics have high renal toxicity and weak activity against a number of drug-resistant strains, so they are not usually preferred for the treatment of cirrhosis.

The antimicrobial activity of vancomycin, nitrofurantoin and rifampin against *Staphylococcus* spp. in abdominal infections was strong (sensitivity rate, ≥ 87%). Furthermore, the susceptibility of *Staphylococcus* spp. to gentamicin, clindamycin and moxifloxacin was also strong (sensitivity rate, ≥ 60.9%). *Enterococcus* was resistant to a variety of antibacterial agents, but showed high sensitivity to vancomycin, rifampin, clindamycin and gentamicin (sensitivity rate, ≥ 70.6%). Furthermore, nitrofurantoin showed stronger activity against *Enterococcus* spp. in non-nosocomial infections than in nosocomial infections. Vancomycin, rifampin, moxifloxacin and nitrofurantoin had strong antibacterial activity against *S. pneumoniae* (sensitivity rate, ≥ 71.9%); oxofloxacin, levofloxacin, moxifloxacin and clindamycin had greater activity against *S. aureus* strains in non-nosocomial infections. Thus, when there is evidence of *Staphylococcus* spp. in abdominal infections, glycopeptide antibiotics should be the preferred medication.

Cirrhosis with secondary bacterial infection in patients is an important cause of liver function deterioration and other complications, thus early diagnosis and prompt treatment are important\(^\text{[2,33]}\). This study is a retrospective analysis, so there are some selection biases and limitations due to the limited sample size. Nonetheless, the findings are important and they lay the foundation for future improvements in the culture, sensitivity tests and the antibiotic regime for spontaneous bacterial peritonitis in cirrhotic patients.

**COMMENTS**

**Background**

Spontaneous bacterial peritonitis (SBP) is a common and severe complication in cirrhotic patients with ascites. Monitoring drug resistance in cases of abdominal infection with liver cirrhosis is important for establishing the appropriate antibiotic regimes, reducing the generation of drug-resistant bacteria and reducing the associated mortality.

**Research frontiers**

Changes in the epidemiology of the causative bacteria in SBP and bacteraemics and in their susceptibility to antibiotics have been associated with low treatment efficacy of traditional therapy in nosocomial infections.

**Innovations and breakthroughs**

This study addressed two primary issues regarding spontaneous peritonitis in cirrhotic patients in China: first, the pathogen profile and, second, drug resistance. The majority of pathogenic bacteria that cause abdominal infection in liver cirrhosis are gram-negative, and drug resistance is significantly higher in
nosocomial infections than in non-nosocomial infections.

**Applications**

Based on this study, clinicians can select the appropriate antibiotic treatment to control the emergence and development of pathogenic bacteria-resistant strains in intra-abdominal infections.

**Terminology**

Extended Spectrum β-Lactamases, are usually produced by Escherichia coli, Klebsiella pneumoniae, and Acinetobacter baumannii, and can hydrolyze penicillin antibiotics, cephalosporins, and single ring β-lactam-amide antibiotics. MRSA: Methicillin-resistant *Staphylococcus aureus*.

**Peer-review**

This is a very interesting study, and is important mainly because it describes and analyses the etiological agents and drug resistance which are responsible for SBP.

**REFERENCES**

1. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, Rodés J. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; 35: 140-148 [PMID: 11786970]

2. Fernández J, Acevedo J, Castro M, García O, de Lope CR, Roca D, Pavesi M, Sola E, Moreira L, Silva A, Seva-Pereira T, Corradi F, Mensa J, Ginès P, Arroyo V. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012; 55: 1551-1561 [PMID: 22183941 DOI: 10.1002/hep.25532]

3. Scarpellini E, Valenza V, Gabrielli M, Lauritano EC, Perotti G, Merra G, Dal Lago A, Ogetti V, Ainora ME, Santoro MR, Ghirlanda G, Gasbarrini A. Intestinal permeability in cirrhotic patients with and without spontaneous bacterial peritonitis: is the ring closed? *Am J Gastroenterol* 2010; 105: 323-327 [PMID: 19844200 DOI: 10.1038/ajg.2009.558]

4. Teltchlik Z, Wiest R, Beisner J, Nuding S, Hofmann C, Schoelmerich J, Bevis CL, Stange EF, Wehkamp J. Intestinal bacterial translocation in rats with cirrhosis is related to compromised Paneth cell antimicrobial host defense. *Hepatology* 2012; 55: 1154-1163 [PMID: 22095436 DOI: 10.1002/hep.24789]

5. Steffen EK, Berg RD, Deitch EA. Comparison of translocation rates of various indigenous bacteria from the gastrointestinal tract to the mesenteric lymph node. *J Infect Dis* 1988; 157: 1032-1038 [PMID: 3283254]

6. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gunst T, Saliba E, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013; 144: 1426-1437, 1426-137, [PMID: 23474284 DOI: 10.1053/j.gastro.2013.02.042]

7. Arvaniti V, D’Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Immune dysfunction and infections in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011; 9: 727-738 [PMID: 21397731 DOI: 10.1016/j.cgh.2011.02.031]

8. Arabi YM, Dara SI, Memish Z, Al Abdullah A, Tamim HM, Al-Shrawi N, Parrillo JE, Dodek P, Lapinsky S, Feinstein D, Wood G, Dial S, Zanotti S, Kumar A. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. *Hepatology* 2012; 56: 2305-2315 [PMID: 22753144 DOI: 10.1002/hep.25931]

9. Angeloni S, Leboffe C, Parente A, Venditti M, Giordano A, Merli M, Riggio O. Efficacy of current guidelines for the treatment of spontaneous bacterial peritonitis in the clinical practice. *World J Gastroenterol* 2008; 14: 2757-2762 [PMID: 18461661]

10. García-Tsao G. Spontaneous bacterial peritonitis: a historical perspective. *J Hepatol* 2004; 41: 522-527 [PMID: 15464231]

11. Campillo B, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. *Clin Infect Dis* 2002; 35: 1-10 [PMID: 12060868]

12. Reuken PA, Pletz MW, Baier M, Pfister W, Stallmach A, Bruns T. Emergence of spontaneous bacterial peritonitis due to enterococci - risk factors and outcome in a 12-year retrospective study. *Aliment Pharmacol Ther* 2012; 35: 1199-1208 [PMID: 22449290 DOI: 10.1111/j.1365-2036.2012.05076.x]

13. Guggenbichler JP, Allerberger FJ, Dierich M. Influence of cephalosporines III generation with varying biliary excretion on fecal flora and emergence of resistant bacteria during and after cessation of therapy. *Padiatr PAdol* 1986; 21: 335-342 [PMID: 3562044]

14. Cholongitas E, Papatheodoridis GV, Lahanas A, Xanthaki A, Kontou-Kastelanou C, Archimandritis AJ. Increasing frequency of Gram-positive bacteria in spontaneous bacterial peritonitis. *Liver Int* 2005; 25: 57-61 [PMID: 15609390]

15. Park MK, Lee JH, Byun YH, Lee H, Gwak GY, Choi MS, Koh KC, Paik SW, Yoo BC, Rhee JC. [Changes in the profiles of causative agents and antibiotic resistance rate for spontaneous bacterial peritonitis: an analysis of cultured microorganisms in recent 12 years]. *Korean J Hepatol* 2007; 13: 370-377 [PMID: 17896553]

16. Sheikhzahabi S, Abdollahi A, Hafezi-Nojad N, Zare E. Patterns of antimicrobial resistance in the causative organisms of spontaneous bacterial peritonitis: a single centre, six-year experience of 1981 samples. *Int J Hepatol* 2014; 2014: 917856 [PMID: 24778884 DOI: 10.1155/2014/917856]

17. Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, Landeira C, Romero G, Dominguez N, Muñoz A, Levi D, Miñuez C, Abeasis R. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. *J Hepatol* 2008; 49: 774-779 [PMID: 18316137 DOI: 10.1016/j.jhep.2008.01.024]

18. Wu SS, Lin OS, Chen YY, Hwang KL, Soon MS, Keeffe EB. Ascitic fluid carcinoembryonic antigen and alkaline phosphatase levels for the differentiation of primary from secondary bacterial peritonitis with intestinal perforation. *J Hepatol* 2001; 34: 215-221 [PMID: 11281549]

19. Segzin Göksu S, Bilal S, Coşkun HŞ. Hepatitis B reactivation related to everolimus. *World J Hepatol* 2013; 5: 43-45 [PMID: 23383366 DOI: 10.4245/wjh.v5.i1.16]

20. Alexopoulos N, Papadopoulos N, Elipopoulos DG, Alexaki A, Tsiriga A, Toutouzas M, Pectasides D. Increasing frequency of gram-positive cocci and gram-negative multidrug-resistant bacteria in spontaneous bacterial peritonitis. *Liver Int* 2013; 33: 975-981 [PMID: 23522099 DOI: 10.1111/lit.12152]

21. Piroth L, Pechinot A, Di Martino V, Hansmann Y, Putat P, Patry I, Hadou J, Jaulhac B, Chirouze C, Rabaud C, Lozniewski A, Neuwirth C, Chavanan P, Minello A. Evolving epidemiology and antimicrobial resistance in spontaneous bacterial peritonitis: a two-year observational study. *BMC Infect Dis* 2014; 14: 287 [PMID: 24884471 DOI: 10.1186/1471-2334-14-287]

22. Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, Ariza X, Xiol X. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial
spontaneous bacterial peritonitis. *J Hepatol* 2012; **56**: 825-832 [PMID: 22173153 DOI: 10.1016/j.jhep.2011.11.010]

27 **Hwang SY**, Yu SJ, Lee JH, Kim JS, Yoon JW, Kim YJ, Yoon JH, Kim EC, Lee HS. Spontaneous fungal peritonitis: a severe complication in patients with advanced liver cirrhosis. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 259-264 [PMID: 23996048 DOI: 10.1007/s10096-013-1953-2]

28 **Song JY**, Jung SJ, Park CW, Sohn JW, Kim WJ, Kim MJ, Cheong HJ. Prognostic significance of infection acquisition sites in spontaneous bacterial peritonitis: nosocomial versus community acquired. *J Korean Med Sci* 2006; **21**: 666-671 [PMID: 16891810]

29 European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; **53**: 397-417 [PMID: 20633946 DOI: 10.1016/j.jhep.2010.05.004]

30 **Cheong HS**, Kang CI, Lee JA, Moon SY, Joung MK, Chung DR, Koh KC, Lee NY, Song JH, Peck KR. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clin Infect Dis* 2009; **48**: 1230-1236 [PMID: 19302016 DOI: 10.1086/597585]

31 **Ghassemi S**, Garcia-Tsao G. Prevention and treatment of infections in patients with cirrhosis. *Best Pract Res Clin Gastroenterol* 2007; **21**: 77-93 [PMID: 17223498]

32 **Tandon P**, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012; **10**: 1291-1298 [PMID: 22902776 DOI: 10.1016/j.cgh.2012.08.017]

33 **Heo J**, Seo YS, Yim HJ, Hahn T, Park SH, Ahn SH, Park JY, Park JY, Kim MY, Park SK, Cho M, Um SH, Han KH, Kim HS, Baik SK, Kim BI, Cho SH. Clinical features and prognosis of spontaneous bacterial peritonitis in korean patients with liver cirrhosis: a multicenter retrospective study. *Gut Liver* 2009; **3**: 197-204 [PMID: 20431746 DOI: 10.5009/gnl.2009.3.3.197]

**P- Reviewer**: de F Higuera-de la Tijera M  **S- Editor**: Yu J  **L- Editor**: Webster JR  **E- Editor**: Zhang DN
