Efficacy predictors of third-generation cephalosporins in treating spontaneous bacterial peritonitis

Long-Chuan Zhu, MDa,* Wei Wu, MMeDb, Bo Zou, MMeDa, Da-Kai Gan, MMeDa, Xue Lin, MBBSa, Wei Zhou, MBBSa, Mo-Long Xiong, MBBSa

Abstract

Objective: Third-generation cephalosporins (3rd GCs) have recently become controversial as the first-line strategy for empirical spontaneous bacterial peritonitis (SBP) treatment. This study aimed to identify SBP treatment efficacy predictors of 3rd GCs.

Methods: In this retrospective cohort study, 279 cirrhosis patients with SBP who received 3rd GC monotherapy for initial empirical treatment from 2013 to 2019 were included. Nonresponse was defined as a decreased ascites polymorphonuclear (PMN) count < 25% from baseline after 48 hours of antibacterial treatment. Multivariate regression analysis was used to identify efficacy predictors of 3rd GCs in treating SBP. Kaplan–Meier analysis was used to evaluate survival data.

Results: The nonresponder group included 120 patients with no response, and the responder group included 159 patients with responses. The response rate to 3rd GCs was 57.0% among all patients. The common pathogens were Escherichia coli (40.6%), Staphylococcus (15.6%), Klebsiella pneumonia (12.5%), and Streptococcus (12.5%) in 32 ascites culture isolates. Nosocomial SBP (NSBP) (odds ratio [OR]: 2.371, 95% confidence interval [CI]: 1.323–4.249, P = .004), pneumonia (OR: 11.561, 95% CI: 1.876–71.257, P = .004), recurrent SBP (OR: 3.386, 95% CI: 1.804–6.357, P < .001), platelet count (≥113.5 × 10⁹/L) (OR: 3.515, 95% CI: 1.973–6.263, P < .001), and ascites PMN count (≤0.760 × 10⁹/L) (OR: 9.467, 95% CI: 2.553–9.663, P < .001) were independent predictors of nonresponse to 3rd GCs against SBP. Survival plot analysis at 30 days showed worse survival for the nonresponders (P = .003).

Conclusion: NSBP, pneumonia, recurrent SBP, increased platelet count, and lower ascites PMN count were independent predictors of nonresponse to 3rd GC in treating SBP. Nonresponse to initial antibiotic treatment was associated with worse survival.

Abbreviations: 3rdGC = third-generation cephalosporin, CASBP = community-acquired SBP, CI = confidence interval, GNB = gram-negative bacteria, GPB = gram-positive bacteria, MDR = multidrug-resistant, OR = odds ratio, PMN = polymorphonuclear, PPI = proton pump inhibitor, ROC = receiver operating characteristic, SBP = spontaneous bacterial peritonitis.

Keywords: efficacy, predictor, spontaneous bacterial peritonitis, third-generation cephalosporin

1. Introduction

Spontaneous bacterial peritonitis (SBP) is a common complication of cirrhosis, with an incidence of ≈14.6%[1] and a 30-day mortality as high as 24.1% to 26.1%.[2,3] Antibiotics are the main means to treat SBP, among which third-generation cephalosporins (3rd GCs) are classic first-line drugs for initial empirical treatment.[4]

In recent years, with the gradual spread of bacterial drug resistance, negative reports about SBP treatment with 3rd GCs have been increasing. Research shows that the drug resistance rates of pathogens of community-acquired SBP (CASBP) and nosocomial SBP (NSBP) to 3rd GCs are as high as 33.8% and 54.3%, respectively.[5] In NSBP cases, the proportion of pathogens that are multidrug-resistant (MDR) bacteria can be as high as 22% to 73%,[6] the composition of SBP pathogens has also changed, with the proportion of gram-positive bacteria (GPB) increasing. In Asia, Europe, North America, South America, and Africa, the highest proportions of GPB have reached 53%, 68.3%, 73.9%, 63.6%, and 73.2%, respectively.[7] The response rate of SBP to empirical treatment with 3rd GCs is only 56.3% to 59%.[8,9] Given this situation, some scholars have recommended that drugs that can cover vancomycin-resistant enterococci, methicillin-resistant staphylococci, and gram-negative bacteria (GNB) producing extended-spectrum β-lactamases should be selected as the first choice for empirical treatment of SBP instead of 3rd GCs.[10]

Different conclusions regarding the effects of 3rd GCs have been reached. Badawy et al.[11] found that the response rate of SBP to cefotaxime could be as high as 81% and, therefore,
concluded that cefotaxime was still a reliable choice for the first-line treatment of SBP. Sunjaya et al. found that the drug resistance rate of SBP pathogens against 3rd GCs was only 10% and concluded that 3rd GCs were effective for empirical treatment of CASBP and healthcare-related SBP patients without liver cancer. Solà et al. thought that 3rd GCs were a good first choice for treatment of CASBP. These results indicated that 3rd GCs can still be used as the first choice for some SBP cases.

In fact, the effectiveness of 3rd GCs in treating SBP is not only related to the species and drug resistance of the pathogenic bacteria but also associated with the general condition, underlying diseases, and severity of illness of the patient. Therefore, we aim to identify some efficacy predictors of 3rd GCs in treating SBP with the goal of helping clinicians rationally choose antibiotics.

2. Methods

2.1. Subjects

This was a retrospective, single-center cohort study. The research center was a grade III level A public hospital in China. From January 2013 to December 2019, a total of 290 cirrhosis patients with SBP who received 3rd GC monotherapy for initial empirical treatment in The Ninth Hospital of Nanchang were enrolled consecutively. Among 290 patients, 11 were excluded for the following reasons: 2 suffered from tuberculosis, 3 suffered from acquired immunodeficiency syndrome, 1 had fungal ascites, and 5 had missing data. Finally, 279 patients were included in the study. The study protocol was approved by the Ethics Committee of The Ninth Hospital of Nanchang (approval No. [2017] Lun JiaN Shenzhi No. 031). All the data were gathered anonymously, and the requirement for informed consent was exempted by the ethics committee.

2.2. Diagnosis and definition

Cirrhosis was diagnosed based on imaging evidence, clinical manifestations, and laboratory tests. SBP was diagnosed based on an ascites polymorphonuclear (PMN) count ≥ 0.25 × 10^9/L in the absence of an intra-abdominal source of infection, and with at least one sign of infection (e.g., abdominal pain and/or tenderness, fever, unexplained encephalopathy, worsening of liver and/or renal function, altered white blood cell count, and gastrointestinal bleeding).[4] Nonresponse was defined as an ascites PMN count decrease < 25% from baseline after 48 hours of treatment, whereas a decrease in the ascites PMN count ≥25% from baseline represented a response.[4] Nosocomial infection was defined as an infection occurring >48 hours after hospitalization, and earlier onset was considered community-acquired infection.[10] Broad-spectrum antibiotic exposure was defined as having received broad-spectrum antibiotic treatment within 3 months before the onset of SBP. Pneumonia was diagnosed simultaneously with SBP and initially treated with the same antibiotic as for SBP. The use of a proton pump inhibitor (PPI) was defined as the use of any PPI for at least 1 week within 1 month before the onset of SBP. The use of propranolol was defined as the administration of propranolol for at least 2 weeks before the onset of SBP.

2.3. Data collection

General data, medical history characteristics, clinical manifestations, laboratory test results, and survival data were collected. Among them, the clinical manifestations and laboratory test results were the values on the day of SBP diagnosis before antibiotic use. Candidate efficacy predictors of 3rd GCs in treating SBP were chosen based on previous research[12,13] and our clinical judgment. The Child–Pugh score[14] and Model for End-Stage Liver Disease score[15] were calculated with reference to the literature. The ascites cell count was determined by automated flow cytometry.

2.4. Statistical analysis

Student t test or the rank sum test was used to examine continuous variables, and the χ² test or Fisher exact test was adopted to examine categorical variables. Binary multiple regression (forward conditional method) was used for multivariate analysis. A receiver operating characteristic (ROC) curve was drawn to evaluate the prediction accuracy of the predictors, and the best cutoff value of a predictor was defined according to the maximum Youden index. The Kaplan–Meier method and log-rank test were used to evaluate survival data. P < .05 was considered statistically significant.

SPSS 26.0 (SPSS, Inc, Chicago, IL) was used for data analysis. As this study was exploratory in design, the sample size and power of the test were not estimated formally.

3. Results

3.1. General data

After initial treatment with 3rd GCs, 120 patients with no response were included in the nonresponder group, and 159 patients with response were included in the responder group. Among all 279 patients, only 57.0% presented a response to initial empirical treatment with 3rd GCs. The study population had an age range of 25 to 80 years, 81.4% of the patients were male, and most (70.6%) patients had hepatitis B as the cause of cirrhosis. No significant differences in general data were found between the nonresponder group and the responder group (P > .05). Details are shown in Table 1.

The 3rd GCs used for initial treatment of CASBP cases (n = 175) and NSBP cases (n = 104) included cefazidime (30.9% vs 26.9%), ceftriaxone (9.7% vs 17.3%), cefotaxime (36.6% vs 35.6%), and cefoperazone (22.9% vs 20.2%), and difference in the constituent ratio of 3rd GCs was not significant (χ² = 3.572, P = .312). The response rate of CASBP cases to 3rd GCs (64.6%, 113/175) was higher than that of NSBP cases (44.2%, 46/104), and the difference was significant (χ² = 11.001, P = .001).

3.2. Medical history characteristics, clinical manifestations, and laboratory tests

Platelet counts and the proportions of broad-spectrum antibiotic exposure, NSBP, pneumonia, and recurrent SBP in the nonresponder group were higher than those in the responder group (P < .05), whereas serum alanine aminotransferase, aspartate aminotransferase, ascites nucleated leukocyte counts, and ascites PMN counts were lower in the nonresponder group (P < .05). No significant differences in other features were noted between the 2 groups (P > .05). Details are shown in Tables 2 and 3.

The response rates of patients with broad-spectrum antibiotic exposure, pneumonia, and recurrent SBP to 3rd GCs were 40.0% (18/45), 16.7% (2/12), and 33.3% (27/81), respectively, as shown in Table 2.

At the best cutoff values of ≥ 113.5 × 10^9/L, ≤33.5 u/L, ≤1.135 × 10^9/L, and ≤ 0.760 × 10^9/L, platelet count, alanine aminotransferase, aspartate aminotransferase, ascites nucleated leukocyte count, and ascites PMN count had 0.550, 0.667, 0.528, and 0.453 sensitivity, 0.723, 0.500, 0.733, and 0.867 specificity, and Youden index values of 0.273, 0.167, 0.262, and 0.319 for predicting no response to 3rd GCs, respectively; the areas under the ROC curve were 0.656, 0.575, 0.615, and 0.670, all P < .05, respectively (Fig. 1).

3.3. Multivariate analysis

The candidate predictors with significant differences in univariate analysis were further examined in the multivariate analysis.
The results showed that 5 indicators, including NSBP (odds ratio [OR]: 2.371, 95% confidence interval [CI]: 1.323–4.249, \( P = .004 \)), pneumonia (OR: 11.561, 95% CI: 1.876–71.257, \( P = .008 \)), recurrent SBP (OR: 3.386, 95% CI: 1.804–6.357, \( P < .001 \)), platelet count (≥113.5 × 10⁹/L) (OR: 3.515, 95% CI: 1.973–6.263, \( P < .001 \)), and ascites PMN count (≤0.760 × 10⁹/L) (OR: 4.967, 95% CI: 2.553–9.663, \( P < .001 \)) were independent predictors for no response to 3rd GCs against SBP. Details are shown in Table 4.

### 3.4. Microbiological profile

Ascites and blood cultures were conducted in all patients. Of the 279 cases of SBP, 32 (11.5%) had positive ascites cultures. GNB were isolated from 19 cultures (59.4%), and 13 cultures (40.6%) grew GPB. The main organisms found included 13 *Escherichia coli* strains (40.6%), 5 *Staphylococcus* strains (15.6%), 4 *Klebsiella pneumoniae* strains (12.5%), and 4 *Streptococcus* strains (12.5%). The microbiological patterns of ascites cultures in CASBP and NSBP are shown in Table 5. Additionally, 73.3% (11/15) of 3rd GC-resistant strains were found in the nonresponder group and 11.8% (2/17) in the responder group; the coincidence rate of the drug sensitivity test and antibiotic effectiveness was 81.3% (26/32) in positive ascites culture cases.

Only 3 cases of SBP had positive blood cultures, the organisms of which were all *E. coli* strains and consistent with ascites cultures: 2 were 3rd GC-sensitive and 1 was extended-spectrum β-lactamases positive.

### 3.5. Survival data

A total of 55 of 279 (19.7%) patients died 30 days after SBP onset. The 30-day mortality rate was higher in the nonresponder...
Table 3

| Laboratory tests. |
|-------------------|
| Candidate predictors | Nonresponder (n = 120) | Responder (n = 159) | Statistics | P       |
| Blood test         |                       |                       |            |         |
| WBC (×10^9/L), median (IQR) | 6.1 (4.4–8.2) | 6.2 (4.2–8.7) | Z = -0.263 | .793    |
| NEU%, median (IQR) | 72.9 (64.6–79.6) | 75.1 (65.3–81.1) | Z = -1.254 | .210    |
| HGB (g/L), (mean ± SD) | 106.3 ± 24.5 | 104.2 ± 20.4 | t = -0.746 | .456    |
| PLT (×10^9/L), median (IQR) | 110.0 (71.0–157.8) | 71.0 (49.0–123.0) | Z = -4.468 | <.001   |
| ALT (μL), median (IQR) | 34.0 (20.3–81.8) | 51.0 (29.0–94.0) | Z = -2.147 | .032    |
| AST (μL), median (IQR) | 65.5 (36.0–129.5) | 84.0 (48.0–134.0) | Z = -1.828 | .068    |
| TBL (μmol/L), median (IQR) | 55.7 (23.1–80.1) | 55.6 (35.5–97.9) | Z = -0.844 | .399    |
| ALB (g/L), (mean ± SD) | 28.6 ± 5.3 | 27.9 ± 5.2 | t = -1.072 | .284    |
| BUN (mmol/L), median (IQR) | 5.2 (3.4–7.3) | 5.5 (4.0–7.9) | Z = -0.857 | .391    |
| Cr (μmol/L), median (IQR) | 72.0 (50.0–90.0) | 72.0 (50.0–95.0) | Z = -0.458 | .647    |
| Na (mmol/L), median (IQR) | 136.3 (131.9–139.1) | 136.4 (132.1–138.7) | Z = -0.154 | .877    |
| Bicarbonate (mmol/L), median (IQR) | 21.2 (21.0–23.8) | 21.7 (20.6–25.0) | Z = -0.722 | .470    |
| PT (s), median (IQR) | 17.1 (15.1–23.7) | 19.1 (16.3–22.5) | Z = -1.632 | .103    |
| INR, median (IQR) | 1.4 (1.2–2.1) | 1.6 (1.3–2.0) | Z = -1.901 | .057    |
| Ascites examination |                       |                       |            |         |
| NL count (×10^9/L), median (IQR) | 0.810 (0.623–1.258) | 1.200 (0.640–2.590) | Z = -3.298 | .001    |
| PMN count (×10^9/L), median (IQR) | 0.333 (0.268–0.559) | 0.648 (0.325–1.619) | Z = -4.816 | <.001   |
| Percentage of PMN count (%) | 50.7 (54.2–64.9) | 57.0 (43.0–75.0) | Z = -1.867 | .062    |
| SAAG (g/L), median (IQR) | 18.9 ± 5.7 | 20.0 ± 4.9 | t = -1.692 | .092    |

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, Cr = creatinine, HGB = hemoglobin, INR = international normalized ratio, IQR = interquartile range, Na = sodium, NEU% = neutrophil percentage, NL = nucleated leukocyte, PLT = platelet, PMN = polymorphonuclear, PT = prothrombin time, SAAG = serum-ascites albumin gradient, SD = standard deviation, TB = total bilirubin, WBC = white blood cell.

4. Discussion

This study found that NSBP was an independent predictor for treatment failure of SBP by 3rd GCs, and only 44.2% of NSBP cases responded to 3rd GCs. Related studies have confirmed that NSBP is more often caused by pathogenic bacteria that are resistant to 3rd GCs and have a high risk of death,[16,17] which is the main reason why 3rd GCs have poor efficacy against some NSBP cases. Significantly, in the subgroup analysis of Fiore et al.[18] the data after 2008 and the data in China showed that the drug resistance risk of pathogens in CASBP was not lower than that of NSBP, suggesting that 3rd GCs might not be effective to treat CASBP in certain areas. In this study, the response rate of CASBP cases to 3rd GCs was only 64.6%, which may be an early warning for the 3rd GC therapy in CASBP.

Pneumonia was an independent predictor for poor efficacy of 3rd GCs in treating SBP in this study, and patients with pneumonia had a very low response rate to 3rd GCs (16.7%). The study of Niu et al.[19] found that surgical infection is a risk factor for the death of hospitalized SBP patients, suggesting that pneumonia will increase the difficulty of SBP treatment. For patients with infection at 2 sites at the same time, their bacterial load is heavy, so it may be difficult to achieve an effective antibacterial concentration with a conventional dose of 3rd GC. Second, the pathogenic bacteria may be plural bacteria, which cannot be completely covered by the 3rd GC.

In this study, recurrent SBP was an independent predictor for poor efficacy of 3rd GC against SBP, and only 33.3% of recurrent SBP cases responded to 3rd GC. Conversely, Kim et al.[20] found that more than 90% of SBP patients with initial onset responded to cefotaxime for initial empirical treatment. Because secondary prophylaxis and recurrent hospitalization are associated with broad-spectrum antibiotic exposure, patients suffering from SBP recurrently are more likely to experience drug-resistant bacterial infection; meanwhile, recurrent infection attacks will also cause the body’s immune function and liver function to worsen, which will ultimately lead to poor efficacy of 3rd GC.

An increased platelet count could predict poor efficacy of 3rd GC in SBP patients with pneumonia.

Figure 1. Receiver operating characteristic curve of the platelet count, alanine aminotransferase, ascsites nucleated leukocyte count, and ascsites polymononuclear count in predicting the efficacy of third-generation cephalosporins against spontaneous bacterial peritonitis.

group (27.5%, 33/120) than in the responder group (13.8%, 22/159), χ² = 8.067, P = .005. Survival plot analysis at 30 days (Fig. 2) also showed worse survival for the nonresponder group and better survival for the responder group (χ² = 8.648, P = .003).

The most common cause of death was septic shock in both the nonresponder group (18/33, 54.5%) and the responder group (8/22, 36.4%), and the cause of death did not differ between groups (P = .797). Details are shown in Table 6.

4. Discussion

This study found that NSBP was an independent predictor for treatment failure of SBP by 3rd GCs, and only 44.2% of NSBP
A lower ascites PMN count in this study could predict poor effectiveness of 3rd GCs and that nonresponders to 3rd GCs, which might be because increased platelets represent serious infection and gram-positive bacterial infection.

In this study, the response rate of SBP patients to 3rd GCs was 57.0%, which is similar to some reports (56.3%–59%) but obviously lower than the results of Badawy et al (81%).

Different pathogen spectra and severities of patients may be responsible for this inconsistency. The common pathogens of SBP in the present study were E. coli, Staphylococcus, K pneumoniae, and Streptococcus, which is similar to the findings of a previous study in China. The proportion of MDR bacteria in this study was at a high level (46.9%), possibly because the study population included more NSBP and previous broad-spectrum antibiotic exposure cases. There were more 3rd GC-resistant and MDR strains in NSBP cases than in CASBP cases in this study, which is consistent with the current general knowledge. However, this difference was not significant, which may be associated with the small sample size. Generally, the positive rate of ascites culture is limited, and it will take ≥3 days after the onset of SBP for the ascites culture to be available. As a result, some effective and quick-acting factors in this study are also indispensable in guiding antibiotic treatment, although our results showed that the positive rate of ascites culture is limited, and it will take ≥3 days after the onset of SBP for the ascites culture to be available. As a result, some effective and quick-acting factors in this study are also indispensable in guiding antibiotic treatment, although our results showed that the positive rate of ascites culture is limited, and it will take ≥3 days after the onset of SBP for the ascites culture to be available.
treat SBP patients with severe conditions, such as hyperpyrexia, septic shock, or acute respiratory distress syndrome in our hospital, the study population lacks these patients, which can lead to selection bias. Approximately 20% of patients in this study have liver cancer. Cancerous ascites can also lead to an increased ascites cell count, and the peritoneal culture positivity rate is at a low level in this study, which may result in false-positive diagnoses of infection. This condition may affect the identification of infection and the study results.

5. Conclusion

This study showed that the response rate of SBP patients to 3rd GCs was 57.0%. Nonresponse to initial antibiotic treatment was associated with worse survival.

Acknowledgments

We thank all the individuals and groups who provided help in conducting this study.

Author contributions

Conceptualization: Zhu Long-Chuan.
Data curation: Zhu Long-Chuan, Wu Wei.
Formal analysis: Zhu Long-Chuan, Wu Wei.
Investigation: Zhu Long-Chuan, Wu Wei, Zou Bo, Gan Da-Kai, Lin Xue, Zhou Wei, Xiong Mo-Long.
Methodology: Zhu Long-Chuan, Wu Wei, Zou Bo, Gan Da-Kai, Lin Xue, Zhou Wei, Xiong Mo-Long.
Project administration: Zhu Long-Chuan.
Resources: Zhu Long-Chuan.
Supervision: Zhu Long-Chuan.
Writing—original draft: Zhu Long-Chuan.
Writing—review & editing: Zhu Long-Chuan, Wu Wei, Zou Bo, Gan Da-Kai, Lin Xue, Zhou Wei, Xiong Mo-Long.
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

[1] Caly WR, Strauss E. A prospective study of bacterial infections in patients with cirrhosis. J Hepatol. 1993;18:333–8.
[2] Hung TH, Tsai CC, Hsieh YH, et al. The long-term mortality of spontaneous bacterial peritonitis in cirrhotic patients: a 3-year nationwide cohort study. Turk J Gastroenterol. 2015;26:159–62.
[3] Iliaz R, Ozpolat T, Baran B, et al. Predicting mortality in patients with spontaneous bacterial peritonitis using routine inflammatory and biochemical markers. Eur J Gastroenterol Hepatol. 2018;30:786–91.
[4] European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–60.
[5] Fiore M, Gentile I, Marzolo AE, et al. Are third-generation cephalosporins still the empirical antibiotic treatment of community-acquired spontaneous bacterial peritonitis? A systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2018;30:329–36.
[6] Fiore M, Marzolo AE, Gentile I, et al. Nosocomial spontaneous bacterial peritonitis antibiotic treatment in the era of multi-drug resistance pathogens: a systematic review. World J Gastroenterol. 2017;23:4654–60.
[7] Fiore M, Marzolo AE, Gentile I, et al. Current concepts and future strategies in the antimicrobial therapy of emerging Gram-positive spontaneous bacterial peritonitis. World J Hepatol. 2017;9:1166–75.
[8] Angeloni S, Leboffe C, Parente A, et al. Efficacy of current guidelines for the treatment of spontaneous bacterial peritonitis in the clinical practice. World J Gastroenterol. 2008;14:2757–62.
[9] Piano S, Fasolato S, Salinas F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: results of a randomized, controlled clinical trial. Hepatology. 2016;63:1299–309.
[10] Fiore M. Letter: the emergence of multi-drug resistant spontaneous bacterial peritonitis: a new challenge for the hepatologist? Aliment Pharmacol Ther. 2016;43:944–5.
[11] Badawy AA, Zaher TI, Sharaf SM, et al. Effect of alternative antibiotics in treatment of cefotaxime resistant spontaneous bacterial peritonitis. World J Gastroenterol. 2013;19:1271–7.
[12] Sunjaya DB, Lennon RJ, Shah VH, et al. Prevalence and predictors of third-generation cephalosporin resistance in the empirical treatment of spontaneous bacterial peritonitis. Mayo Clin Proc. 2019;94:1499–508.
[13] Solà E, Solé C, Ginès P. Management of uninfected and infected ascites in cirrhosis. Liver Int. 2016;36:109–15.
[14] Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transsection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646–9.
[15] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–70.
[16] Jain M, Sanglodkar U, Venkataraman J. Risk factors predicting nosocomial, healthcare-associated and community-acquired infection in spontaneous bacterial peritonitis and survival outcome. Clin Exp Hepatol. 2019;5:133–9.
[17] Chauilk J, Carbonneau M, Qamar H, et al. Third-generation cephalosporin-resistant spontaneous bacterial peritonitis: a single-centre experience and summary of existing studies. Can J Gastroenterol Hepatol. 2014;28:83–8.
[18] Niu B, Kim B, Limketkai BN, et al. Mortality from spontaneous bacterial peritonitis among hospitalized patients in the USA. Dig Dis Sci. 2018;63:1327–33.
[19] Kim SU, Chon YE, Lee CK, et al. Spontaneous bacterial peritonitis in patients with hepatitis B virus-related liver cirrhosis: community-acquired versus nosocomial. Yonsei Med J. 2012;53:328–36.
[20] Mishra D, Das AK, Chagappain RH, et al. Thrombocytosis as a predictor of serious bacterial infection in febrile infants. J Nepal Health Res Counc. 2019;16:401–4.
[21] Johannson D, Shannon O, Rasmussen M. Platelet and neutrophil responses to Gram positive pathogens in patients with bacteremic infection. PLoS One. 2011;6:e26928.
[22] Arzua X, Lora-Tamayo J, Castellote J, et al. Polymorphonuclear counts in ascitic fluid and microorganisms producing spontaneous bacterial peritonitis: an under-recognized relationship. Scand J Gastroenterol. 2013;48:1213–21.
[23] Fiucia C, Salcedo M, Clemente G, et al. In vivo neutrophil dysfunction in cirrhotic patients with advanced liver disease. J Infect Dis. 2000;182:526–33.
[24] Shi L, Wu D, Wei L, et al. Nosocomial and community-acquired spontaneous bacterial peritonitis in patients with liver cirrhosis in China: comparative microbiology and therapeutic implications. Sci Rep. 2017;7:46025.