



BRIEF REPORT

# Spontaneous Fungal Ascites Infection in Patients with Cirrhosis: An Analysis of 10 Cases

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## ABSTRACT

**Introduction:** Spontaneous fungal ascites infection is a rare but devastating complication of cirrhosis. We aimed to analyse the clinical features, short-term mortality, and treatment of spontaneous fungal ascites infection in patients with cirrhosis.

**Methods:** We retrospectively studied ten patients with cirrhosis and spontaneous fungal ascites infections, and the clinical characteristics and outcomes were obtained.

**Result:** The patients' mean age was  $64 \pm 13$  years, and seven of the ten patients were men. Cirrhosis was primarily caused by infection with the hepatitis B virus. *Candida albicans* was the most frequently isolated fungus isolated from the ascites fluid. Three of the ten patients fulfilled the criteria of acute-on-chronic liver failure (ACLF) at baseline, and three of the remaining seven patients developed ACLF during hospitalisation. Of the ten patients, six had acute kidney injury (AKI), and six died within 28 days. Three patients did not receive anti-fungal treatment during hospitalisation because they died undiagnosed because of delays in the reporting of laboratory results.

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**Conclusion:** Patients with spontaneous fungal ascites infection had high incidence of AKI and 28-day mortality. Fungal cultures of ascitic fluid from patients with cirrhosis should be recommended to ensure optimal clinical management, especially in patients with severe liver disease and who received inadequate empirical antibacterial therapy. Hence, future studies should focus on the early diagnosis of fungal infection in patients with cirrhosis.

**Keywords:** Cirrhosis; Fungiascites; Spontaneous fungal peritonitis; Treatment

### Key Summary Points

#### Why carry out this study?

Spontaneous fungal ascites infection is a rare but devastating complication in patients with cirrhosis.

Few studies have been reported on this topic.

#### What was learned from the study?

Patients with spontaneous fungal ascites infection had high incidence of AKI and 28-day mortality.

Fungal cultures of ascitic fluid from patients with cirrhosis should be performed to ensure optimal clinical management, especially from those with critical liver disease and poorly administered empirical antimicrobial therapy.

The issue of delayed diagnosis is prominent and new technology for early pathogen detection is necessary.

for this article go to <https://doi.org/10.6084/m9.figshare.14054375>.

## INTRODUCTION

Patients with cirrhosis are at risk of developing various types of infection and have a fourfold higher risk of mortality [1]. Ascites infection is a common complication in patients with cirrhosis. According to the type of pathogen, patients with cirrhosis may develop two types of spontaneous peritonitis: spontaneous bacterial peritonitis (SBP) and spontaneous fungal peritonitis (SFP). SBP is the most common type of infection and has been clearly described in international guidelines [2, 3]. SFP is a rare, less-recognised complication of cirrhosis, with an incidence of less than 5% [4]. Furthermore, fungiascites is another form of spontaneous fungal ascites infection in patients with liver cirrhosis, which is characterised by a positive fungal ascitic fluid culture, but with an ascites neutrophil cell count less than 250 cells/mm<sup>3</sup>.

Fungal infections often occur in hospitalised patients with cirrhosis and critical liver disorders, especially those with acute-on-chronic liver failure (ACLF) [5, 6]. Patients with end-stage liver disease, such as invasive pulmonary aspergillosis, who developed common fungal infections are at higher risk of short-term mortality (73.4–100%) [7–10]. For patients with refractory ascites, the ascitic fluid contains agents with a low immune activity, providing a good environment for pathogen growth, including bacterial and fungus [11]. This can result in ascitic fluid infection and other related complications, especially acute kidney injury (AKI) as well as progression of ACLF in decompensated patients with cirrhosis. Bucsecs et al. reported that 14 patients with cirrhosis and spontaneous fungal ascites infection had a poor prognosis [12]. Only a few studies have investigated patients with SFP, and there are no established guidelines regarding the management of fungal infections in patients with cirrhosis. Thus, this study aimed to observe the clinical features and prognosis of spontaneous fungal ascites infection in ten patients.

## DIGITAL FEATURES

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## METHODS

We retrospectively studied ten patients with cirrhosis and spontaneous fungal ascites infections who were hospitalised during 2013–2017 in Nanfang Hospital, Shanghai Public Health Clinical Centre, Xiangya Hospital, and Ditan Hospital. Diagnostic paracentesis was performed, and ascitic fluid was inoculated in the blood culture bottles at the bedside of patients with cirrhosis. The demographic data, results of routine laboratory tests, findings of microbiological analyses, and treatment regimens were recorded. The fungus was isolated from ascitic fluid cultures. Identification and susceptibility tests of the isolated fungus were performed using the Vitek 2 automated system (bioMérieux, Craaponne, France). Drug sensitivity testing was performed according to the guidelines of the Clinical and Laboratory Standard Institute [13]. The antimicrobial susceptibility test results were available within 48–72 h after the ascitic fluid culture indicated positive results.

Cirrhosis was diagnosed on the basis of the patients' clinical manifestations, radiological findings, and/or histological findings. The criteria for diagnosing SFP were as follows: ascites neutrophil cell count greater than 250 cells/mm<sup>3</sup> and isolation of fungi in ascitic fluid cultures. Fungi ascites was defined as an ascites neutrophil cell count less than 250 cells/mm<sup>3</sup> and isolation of fungi from the ascitic fluid. AKI and ACLF were defined according to the criteria established by the International Club of Ascites (ICA) [14] and the European Association for the Study of Liver Failure (EASL-CLIF) [15], respectively. Patients with fungal ascites infection were diagnosed with sepsis if they fulfilled at least two of the following criteria: body temperature less than 36 °C or greater than 38 °C, heart rate greater than 90 beats per minute, respiratory rate greater than 20/min, white blood cells less than 4000/μL or greater than 12,000/μL, or immature neutrophils greater than 10%. Evaluations regarding the clinical efficiency of antibiotic therapy were entrusted to the attending physicians and were based on the clinical, laboratory, and microbiological analysis results [16].

Quantitative variables are expressed as mean ± standard deviation or median (interquartile range), whereas categorical variables are expressed as percentages. IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses.

The study received ethics approval from the ethics committee of all the participating medical centres (Nanfang Hospital, Shanghai Public Health Clinical Centre, Xiangya Hospital and Beijing Ditan Hospital). The ethics committees waived the informed consent because the data were de-identified and individual patient's data were not published. The study was performed in accordance with the declaration of Helsinki 1964 and its later amendments.

## RESULTS

### Patients' Characteristics

We retrospectively studied ten patients with cirrhosis and spontaneous fungal ascites infections from four hospitals. The baseline characteristics of the ten patients are presented in Table 1. Hepatitis B virus (8/10) was the primary agent causing cirrhosis. The patients' mean age was 64 ± 13 years, and seven of the ten patients were men. Eight patients were admitted because of a larger volume of ascites, whereas two had new-onset ascites during hospitalisation. The median time interval between ascites diagnosis and paracentesis was 2.5 days (range 1.8–4.2). *Candida albicans* was the most commonly isolated fungus in this study. The mean model for end-stage liver disease (MELD) score among the ten patients was 22 ± 8. Three patients (30%) who fulfilled the EASL-CLIF criteria were diagnosed with ACLF. Two patients were diagnosed with sepsis at the time of ascites paracentesis. Of the ten patients, six patients developed AKI. For seven patients with acute decompensation who did not fulfil the EASL-CLIF criteria for diagnosing ACLF, three were developed ACLF during hospitalisation. Six patients died within 28 days. In this study, four (40%) patients with cirrhosis were diagnosed with fungi ascites, whereas six (60%) were diagnosed with SFP. The

**Table 1** Baseline characteristics of the patients

	Patients included ( <i>n</i> = 10)
Male, <i>n</i> (%)	7 (70)
Age (years), mean (SD)	64 (13)
Etiology of cirrhosis, <i>n</i> (%)	
HBV	6 (60)
HBV plus alcohol	1 (10)
Schistosomiasis	2 (20)
PBC	1 (10)
Exposed to antibacterial agents, <i>n</i> (%)	8 (80)
SFP, <i>n</i> (%)	6 (60)
ACLF diagnosis when paracentesis, <i>n</i> (%)	
Non-ACLF	7 (70)
ACLF-1	2 (20)
ACLF-2	1(10)
Child–Pugh score, mean (SD)	11 (2)
MELD score, mean (SD)	22 (8)
SIRS, <i>n</i> (%)	2 (20)
Ascites WBC count, median (IQR)	751 (104–8740)
Ascites PMN count, median (IQR)	400 (66–7208)
Type of strain isolated, <i>n</i> (%)	
<i>Candida albicans</i>	8 (80)
<i>Candida glabrata</i>	1 (10)
<i>Trichosporon</i>	1 (10)

*HBV* hepatitis B virus, *PBC* primary biliary cirrhosis, *SFP* spontaneous fungi peritonitis, *ACLF* acute-on chronic liver failure, *MELD* model for end-stage liver disease, *SIRS* systemic inflammatory response syndrome, *WBC* white blood cell, *PMN* absolute polymorphonuclear leukocyte

clinical characteristics and outcomes of fungiascites and SFP are shown in Table 2.

### Antifungal Treatment

The drug sensitivity results were not available in four patients since the test was not performed. Meanwhile, results of the remaining six patients showed that the fungus was susceptible to

antifungal drugs (5-fluorocytosine, amphotericin B, fluconazole, itraconazole, and voriconazole) (Table 3). Three (30%) of the patients with spontaneous fungal infections did not receive antifungal treatment during hospitalisation because they died undiagnosed because of delays in the reporting of laboratory results (Table 3). Eight of the ten patients received empirical antibiotic treatment prior to the administration of antifungal treatment. Of

**Table 2** Clinical characteristics between SFP and fungiascites groups

	Fungiascites ( <i>N</i> = 4)	SFP ( <i>N</i> = 6)
Age (years), mean (SD)	65 (18)	63 (10)
Male, <i>n</i> (%)	4 (100)	3 (50)
Clinical symptoms, <i>n</i> (%)		
Abdominal pain	2(50)	1 (16.7)
Fever	–	3(50.0)
Insensitive to diuretics	2 (50)	2 (33.3)
New-onset/worsening HE	–	1(16.7)
Concomitant infection, <i>n</i> (%)		
Pneumonia, <i>n</i> (%)	1 (25)	2 (33.3)
Bacteraemia (positive blood culture), <i>n</i> (%)	–	1 (16.7)
Urinary tract infection, <i>n</i> (%)	–	–
Skin and soft tissue infection, <i>n</i> (%)	–	–
Ascites white blood cell ( $\times 10^6$ /L), median (IQR)	88 (16–406)	7420 (855–10,129)
Ascites neutrophil ( $\times 10^6$ /L), median (IQR)	12 (2–120)	4642 (382–9489)
Ascites total protein (g/L), mean (SD)	19.9 (6.5)	22.6 (7.2)
Laboratory measurements		
Bilirubin ( $\mu\text{mol/L}$ ), median (IQR)	121.5 (53.3–408.5)	41.0 (29.1–151.7)
INR, median (IQR)	1.8 (1.3–2.2)	1.5 (1.3–1.8)
Serum creatinine ( $\mu\text{mol/L}$ ), median (IQR)	153.9 (96.2–366.3)	116.3 (63.5–355.5)
Leukocytes ( $\times 10^9$ /L), median (IQR)	10.9 (7.5–16.9)	9.9 (5.3–18.7)
C-reactive protein (mg/L), median (IQR)	43.4 (26.7–60.0)	76.7 (66.9–119.3)
Serum sodium (mmol/L), mean (SD)	122.7 (20.1)	133.1 (8.5)
Albumin (g/L)	25.7 (5.2)	26.5 (7.1)
ACLF, <i>n</i> (%)	1 (25)	2 (33.3)
AKI, <i>n</i> (%)	3 (75)	3 (50)
Sepsis diagnosis, <i>n</i> (%)	1 (25)	1 (16.7)
Child–Pugh score, mean (SD)	12 (1)	10 (2)
MELD score, mean (SD)	26 (7)	20 (9)
Hospital stay (days), median (IQR)	13 (3–23)	19 (10–56)
28-day mortality, <i>n</i> (%)	3 (75)	3 (50)

SFP spontaneous fungal peritonitis, ACLF acute-on-chronic liver failure, AKI acute kidney injury, HE hepatic encephalopathy, MELD model for end-stage liver disease, IQR interquartile range

Table 3 Antifungal treatment of the 10 cases

Patient ID	Diagnosis	Ascites culture result	MELD score	Concomitant infection	Antibiotic exposure before antifungal treatment (duration, days)	Interval time between paracentesis and start of antifungal treatment (days)	Antifungal treatment (duration, days)	Drug sensitivity MIC (mg/ml), sensitivity	Dosage of antifungal treatment (g)	Clinical efficiency of treatment	28-day mortality
1	Fungascites	<i>Candida albicans</i>	29	Pneumonia	3rd-generation cephalosporin (10); carbapenem (7)	–	None	5-Fluorocytosine (< 4, S); amphotericin B (< 0.5, S); fluconazole (< 1, S); itraconazole (< 0.125, S); voriconazole (0.15, S)	–	–	Dead
2	SFP	<i>Candida albicans</i>	36	No	Beta-lactamase-resistant penicillin (4); carbapenem (6)	6	Voriconazole (5)	5-Fluorocytosine (< 4, S); amphotericin B (0.5, S); fluconazole (< 1, S); itraconazole (< 0.125, S); voriconazole (< 1, S)	0.4	No response	Dead
3	SFP	<i>Candida albicans</i>	19	No	–	0	Fluconazole (6)	–	0.4 g loading dose, followed by a maintenance dose of 0.2 g daily	No response	Dead
4	SFP	<i>Candida albicans</i>	15	Pneumonia	Carbapenem (8)	0	Voriconazole (7)	–	0.2	Response	Survived
5	SFP	<i>Candida albicans</i>	19	Bacteraemia	Carbapenem (8)	3	Fluconazole (16)	5-Fluorocytosine (< 4, S); amphotericin B (< 0.5, S); fluconazole (< 1, S); itraconazole (< 0.125, S); voriconazole (< 0.062, S)	0.4	Response	Survived

**Table 3** continued

Patient ID	Diagnosis	Ascites culture result	MELD score	Concomitant infection	Antibiotic exposure before antifungal treatment (duration, days)	Interval time between paracentesis and start of antifungal treatment (days)	Antifungal treatment (duration, days)	Drug sensitivity MIC (mg/ml), sensitivity	Dosage of antifungal treatment (g)	Clinical efficiency of treatment	28-day mortality
6	SFP	<i>Candida albicans</i>	10	Pneumonia	Carbapenem (4); glycopeptides (13)	0	Fluconazole (15)	5-Fluorocytosine (< 4, S); amphotericin B (< 0.5, S); fluconazole (< 1, S); itraconazole (< 0.125, S); voriconazole (< 0.062, S)	0.4	Response	Survived
7	Fungiascites	<i>Candida albicans</i>	34	No	Carbapenem (1)	-	None	-	-	-	Dead
8	Fungiascites	<i>Candida glabrata</i>	19	No	-	7	Fluconazole (14)	5-Fluorocytosine (< 4, S); amphotericin B (< 0.5, S); fluconazole (4, I); itraconazole (0.25, I); voriconazole (0.25, S)	0.2	Response	Survived
9	Fungiascites	<i>Trichosporon</i>	23	No	3rd-generation cephalosporin (6); glycopeptides (4); carbapenem (7);	-	None	-	-	-	Dead
10	SFP	<i>Candida albicans</i>	19	No	3rd-generation cephalosporin (4); carbapenem (9)	7	Caspofungin (9)	5-Fluorocytosine (< 4, S); amphotericin B (< 0.5, S); fluconazole (< 1, S); itraconazole (< 0.125, S); voriconazole (< 0.062, S)	0.15	Response	Dead

SFP spontaneous fungal peritonitis, MIC minimum inhibitory concentration, MELD model for end-stage liver disease, intermediate (I), sensitivity (S)

the patients treated with antifungal agents, three received empirical antifungal treatment on the day of the paracentesis procedure. The remaining four patients received antifungal treatment after the ascites culture result was returned. The most frequent antifungal agent used was fluconazole, followed by voriconazole. The dosages of antifungal agents administered to patients are presented in Table 3. Approximately, 71.4% (5 of 7) of the patients responded to antifungal therapy, and four of these patients survived through 28 days. The median duration of antifungal treatment was 9 days (range 5–16 days).

## DISCUSSION

We retrospectively described the spontaneous fungal ascites infection that developed in ten patients with liver cirrhosis, and *Candida albicans* was the most frequent aetiologic agent. Patients with cirrhosis and spontaneous fungal infection had non-negligible AKI and 28-day mortality rates, which may be related to the delayed diagnosis of ascites fungal infection.

SBP is a common complication in patients with cirrhosis and ascites. A previous study reported that the incidence of SBP ranged from 10% to 30% [17]. Currently, multidrug-resistant bacterial infection in patients with end-stage liver disease has become a global threat, leading to empirical antibiotic treatment failure [16]. However, spontaneous fungal ascites infection rarely occurs, with a rate of less than 5%, but causes severe complications in patients with cirrhosis. Recent descriptions of disturbed intestinal fungome argue that translocation of these microorganisms may be associated with infection and progression as is seen with bacterial translocation in patients with cirrhosis [18, 19]. This study showed that patients with spontaneous fungal ascites infection had a high incidence of AKI and 28-day mortality rate, which is in line with the results of a previous study [20]. In this study, three of four fungiascites patients (75%) did not receive any antifungal treatment, indicating that the potential impact of fungal infection may be underestimated in routine clinical setting, since

these patients had poor outcomes. In the clinical practice, the indication for initiating empirical antimicrobial treatment is ascites neutrophil greater than 250 cells/mm<sup>3</sup>. Nevertheless, current guidelines do not indicate the recommended treatment for fungiascites [4]. Hence, this study suggests that the threshold of ascites neutrophil counts to initiate antifungal treatment should be low, particularly in those with severely advanced liver disease.

Patients with critical liver disorders have higher risk of developing infection, including fungal infection. In current clinical practice, liver transplantation is the only treatment method for end-stage liver disease. Active fungal infection is a contraindication for transplantation. For patients with SBP, the inpatient mortality decreased over past decades (19.1% to 16.1%) because of the effective use of empirical antibiotics treatment. Our results show that spontaneous fungal ascites infection that occurred in patients with cirrhosis had non-negligible complications, especially AKI and progression to ACLF. We speculated that this may attribute to the improper use of empirical antibiotics which targeted bacteria and the delay diagnosis of fungal infection. Hence, early diagnosis of fungal infection is urgently needed. However, the diagnosis of spontaneous fungal ascites infection depends on the results of traditional ascites culture and usually takes a few days (3–5 days), thus leading to delays in the initiation of therapy in patients with cirrhosis. Recently, metagenomics next-generation sequencing (mNGS) has proved to be a promising approach for the diagnosis of infectious diseases covering a wide range of pathogens, including bacteria, fungi, and viruses [21], and the results of mNGS can be obtained within 48 h. Thus, early identification of high-risk patients who are prone to fungal infection and early diagnosis are the key steps in improving the patient's clinical outcomes. Conducting ascites mNGS in patients with cirrhosis may lead to their timely treatment.

With regard to the treatment of spontaneous fungal ascites infection, neither EASL nor Chinese guidelines provide recommendations on the management of ascites in patients with cirrhosis [4, 22]. Different antifungal agents



were used in this study: voriconazole, fluconazole, and caspofungin. The differences in the antifungal regimen may relate to the severity of liver and renal function and the clinical experience. A previous study showed that ascites infections are the most common triggering factors of AKI and strongly affect the outcome of patients with cirrhosis and ascites [23]. In this study, AKI was more prevalent in patients who developed spontaneous fungal ascites infection. For patients with SBP, current guidelines recommend that the transfusion of human serum albumin (HSA) significantly reduces the incidence of AKI [24]. However, the dosage of HSA for patients with SFP and fungiascites remains unclear. Therefore, the treatment of SFP and fungiascites, including antifungal agents and dosage of HSA, needs to be explored further in future studies.

This study has several limitations. First, it is a retrospective study, which possibly includes information bias. Second, although our study reported high AKI incidence and 28-day mortality rate, the difference in these outcomes between patients with SFP and those with fungiascites could not be clearly demonstrated because of the small sample size. Hence, related studies with a larger sample size should be conducted to further evaluate the outcomes of patients with fungal ascites infection. Finally, the microbiological findings may be representative of primary or secondary fungal infections since the blood cultures were not performed in all patients with cirrhosis.

## CONCLUSION

Patients with cirrhosis and spontaneous fungal ascites infection had poor outcomes. Hence, fungal cultures of ascitic fluid from patients with cirrhosis should be performed to ensure optimal clinical management, especially from those with critical liver disease and poorly administered empirical antimicrobial therapy. Future studies should focus on the early diagnosis of fungal infection and optimise antifungal treatment in patients with cirrhosis.

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**Compliance with Ethics Guidelines.** The study received ethics approval from the ethics committee of all the participating medical

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**Data Availability.** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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## REFERENCES

- Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology*. 2010;139(1246–1256):1251–6.
- Runyon BA. Management of adult patients with ascites due to cirrhosis. *Hepatology*. 2004;39:841–56.
- 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.
- 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.
- Koulenti D, Garnacho-Montero J, Blot S. Approach to invasive pulmonary aspergillosis in critically ill patients. *Curr Opin Infect Dis*. 2014;27:174–83.
- Bienvenu AL, Walter T, Boulez F, et al. Acute liver failure may lead to lethal pulmonary aspergillosis. *J Clin Gastroenterol*. 2010;44:593–4.
- Wu Z, Ling Z, Shao F, Sheng J, Li L. Invasive pulmonary aspergillosis in patients with acute-on-chronic liver failure. *J Int Med Res*. 2012;40:1958–65.
- Chen J, Yang Q, Huang J, Li L. Risk factors for invasive pulmonary aspergillosis and hospital mortality in acute-on-chronic liver failure patients: a retrospective-cohort study. *Int J Med Sci*. 2013;10:1625–31.
- Gustot T, Maillart E, Bocci M, et al. Invasive aspergillosis in patients with severe alcoholic hepatitis. *J Hepatol*. 2014;60:267–74.
- Gao J, Zhang Q, Wu Y, et al. Improving survival of acute-on-chronic liver failure patients complicated with invasive pulmonary aspergillosis. *Sci Rep*. 2018;8:876.
- Albillos A, Lario M, Alvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol*. 2014;61:1385–96.
- Bucsics T, Schwabl P, Mandorfer M, Peck-Radosavljevic M. Prognosis of cirrhotic patients with fungiascites and spontaneous fungal peritonitis (SFP). *J Hepatol*. 2016;64:1452–4.
- Jones RN, Glick T, Sader HS, et al. Educational antimicrobial susceptibility testing as a critical component of microbiology laboratory proficiency programs: American Proficiency Institute results for 2007–2011. *Diagn Microbiol Infect Dis*. 2013;75:357–60.
- Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol*. 2015;62:968–74.
- Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144(1426–1437):1431–7.
- Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with

- cirrhosis worldwide. *Gastroenterology*. 2019;156:1368–80.
17. Dever JB, Sheikh MY. Review article: spontaneous bacterial peritonitis—bacteriology, diagnosis, treatment, risk factors and prevention. *Aliment Pharmacol Ther*. 2015;41:1116–31.
  18. Bajaj JS, Khoruts A. Microbiota changes and intestinal microbiota transplantation in liver diseases and cirrhosis. *J Hepatol*. 2020;72:1003–27.
  19. Jiang L, Starkel P, Fan JG, et al. The gut mycobiome: a novel player in chronic liver diseases. *J Gastroenterol*. 2021;56:1–11.
  20. Huang CH, Pang LT, Xu LC, et al. Risk factors, clinical features, and short-term prognosis of spontaneous fungal peritonitis in cirrhosis: a matched case-control study. *World J Clin Cases*. 2019;7:2438–49.
  21. Forbes JD, Knox NC, Ronholm J, Pagotto F, Reimer A. Metagenomics: the next culture-independent game changer. *Front Microbiol*. 2017;8:1069.
  22. Xu X, Duan Z, Ding H, et al. Chinese guidelines on the management of ascites and its related complications in cirrhosis. *Hepatol Int*. 2019;13:1–21.
  23. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19:329–38.
  24. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341:403–9.