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Original article

Clinical and microbiological characteristics of bacterial infections in patients with cirrhosis. A prospective cohort study from Argentina and Uruguay

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Abbreviations: ACLF, acute-on-chronic liver failure; HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; INR, international normalized ratio; MELD, model for end-stage liver disease; MDRO, multidrug-resistant-organism; qSOFA, quick sequential organ failure assessment; SB, spontaneous bacteremia; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infections

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ABSTRACT

Introduction and Objectives: there is insufficient data regarding bacterial infections in patients with cirrhosis to support recommendations for empiric antibiotic treatments, particularly in Latin America. This study aimed to evaluate bacterial infection's clinical impact and microbiological characteristics, intending to serve as a platform to revise current practices.

Materials and Methods: multicenter prospective cohort study of patients with cirrhosis and bacterial infections from Argentina and Uruguay. Patient and infection-related information were collected, focusing on microbiology, antibiotic susceptibility patterns, and outcomes.

Results: 472 patients were included. Spontaneous bacterial infections and urinary tract infections (UTIs) were registered in 187 (39.6%) and 116 (24.6%) patients, respectively, representing the most common infections. Of the 256 culture-positive infections, 103 (40.2%) were caused by multidrug-resistant organisms (reaching 50% for UTI), and 181 (70.7%) received adequate initial antibiotic treatment. The coverage of cefepime and ceftriaxone was over 70% for the empirical treatment of community-acquired spontaneous infections, but ceftazidime's coverage was only 40%. For all UTI cases and for healthcare-associated or nosocomial spontaneous bacterial infections, the lower-spectrum antibiotics that covered at least 70% of the isolations were imipenem and meropenem. During hospitalization, a second bacterial infection was diagnosed in 9.8% of patients, 23.9% required at least one organ support, and 19.5% died.

Conclusions: short-term mortality of bacterial infections in patients with cirrhosis is very high, and a high percentage were caused by multidrug-resistant organisms, particularly in UTIs. The information provided might serve to adapt recommendations, particularly related to empirical antibiotic treatment in Argentina and Uruguay. The study was registered in Clinical Trials (NCT03919032).

1. Introduction

Bacterial infections are among the most frequent and severe complications in patients with cirrhosis, being the leading cause of death in this population [1–3]. They are particularly frequent in patients with acutely decompensated cirrhosis and acute-on-chronic liver failure (ACLF), either as a trigger of these events or during their course [4,5].

Several studies describe the clinical characteristics of patients with cirrhosis complicated with bacterial infections. As expected, significant geographical variability exists. For instance, in India, patients are reported to be more severely compromised with higher MELD-sodium score and ACLF rates at the time of the infection and show lower recovery rates from sepsis in comparison with Europe and America [6]. The most frequent infection is spontaneous bacterial peritonitis (SBP) around the world. Urinary tract infection (UTI) ranks second in Europe, but in America is as frequent as SBP, accounting for almost 60% of infections. Pneumonia is the third most common infection, except in Asia, where it ranks second after SBP [7].

Empiric antibiotics should be started in patients with bacterial infection as soon as possible. They are recommended to cover around 80% of the expected pathogens in stable patients and 90% in critically ill individuals [8,9]. This recommendation is challenged by the fact that infections by multidrug-resistant organisms (MDROs) and extensively drug-resistant organisms [10] are frequent in patients with cirrhosis and their incidence is increasing at worrying rates [11–13]. Empiric antibiotic regimens underestimating the burden of MDROs might contribute to sepsis-related mortality [14,15]. Therefore, it is important to understand the expected microorganisms of the most frequent infections in a given population and region and their antibiotic susceptibility patterns.

A large worldwide prospective observational study performed by *Piano* et al. reported a global prevalence of infections caused by multidrug-resistant and extensively drug-resistant organisms of 35% and 8%, respectively, but with important geographical differences. In America, the United States has a prevalence lower than 20%, but a higher prevalence has been reported in countries such as Brazil and Chile (30–50%), and an intermediate position was described for Argentina (20–30%) [7,16]. Data from Uruguay has yet to be available. Thus, the absence of granular data regarding the microbiological characteristics of infections results in a lack of supported recommendations for empiric antibiotic prescription in the region.

Considering the above, the present study was designed to evaluate the clinical and microbiological characteristics of bacterial infections and antibiotic usage patterns in patients with cirrhosis from Argentina and Uruguay. This may allow a better understanding of this important health problem and the revision of current practices.

2. Materials and Methods

2.1. Study design

This was a multicenter prospective cohort study of patients with cirrhosis and bacterial infections in 28 centers from Argentina (n = 26) and Uruguay (n = 2). The study was coordinated by the Liver Unit of Hospital Italiano de Buenos Aires with the collaboration of the infectious disease department. The study was registered in Clinical Trials (NCT03919032). All investigators were trained by the coordinating center in patient selection, data collection and management, and general issues regarding the study methodology.

2.2. Study population

Patients were eligible for the study if they were older than 17 years, had cirrhosis, and were admitted due to a confirmed bacterial infection or developed an infection at any time during hospitalization for another reason. Bacterial infections were defined according to the following criteria [7]: *Spontaneous bacterial peritonitis*: Polymorphonuclear cell count ≥ 250/mm3 in ascitic fluid, with no evidence of intra-abdominal, surgical, or medical infectious source (with negative or positive cultures). *Urinary tract infection*: the patient had at least 1 of the following signs or symptoms (fever ≥ 38C, urgency, and/or increased urination frequency , dysuria, or suprapubic tenderness) and a positive urine culture or at least 2 of the following signs or symptoms (fever ≥ 38C, urgency , and or increased urination frequency, dysuria, or suprapubic tenderness) and more than 10 leukocytes/mL in a urine sample. *Pneumonia*: a chest x-ray and/or a computed tomography revealing a new or progressive infiltrate, consolidation, cavitation, or pleural effusion and at least one of the following: the new appearance of purulent sputum,

change in sputum characteristics, positive blood cultures or isolation of an etiologic agent from a sample obtained by transtracheal aspirate, bronchial brushing, or biopsy. *Spontaneous bacteremia*: positive blood cultures with no apparent cause of bacteremia, excluding contaminating microorganisms. *Other infections* such as skin and soft tissue, cholangitis/cholecystitis, secondary peritonitis, etc. were diagnosed according to the usual criteria.

Exclusion criteria were a history of solid organ or hematopoietic stem cell transplantation; or the patient's refusal to consent. The study period lasted from September 1st, 2018 until December 31st, 2020. The admission date to the cohort (the day follow-up started) was defined by the day of the infection diagnosis. Patients were followed up until discharge, referral to another center, in-hospital death, or liver transplantation. Each patient could only contribute once to this cohort, providing data from the first infection episode developed during the study period.

2.3. Data collection and main variables definitions

After inclusion, the patients were treated according to the criteria of each participating center, following the usual practices for managing patients with cirrhosis and bacterial infections. Information regarding demographic characteristics, comorbidities, history of cirrhosis and related complications, laboratory parameters, data on the site of the infection (SBP, spontaneous bacterial empyema, UTI, pneumonia, spontaneous bacteremia, skin and soft tissue, and others), type of infection (community-acquired, healthcare-associated or nosocomial), microbiological isolation, and patterns of antibiotic susceptibility and usage (initial adequate treatment and de-escalation) were obtained. Definitions for "type of infection" include: Community-acquired (infection diagnosed at the time of hospital admission or in the first 48 h in patients who do not meet the criteria for infection related to healthcare), healthcare-associated (infection diagnosed at the time of admission or in the first 48 h, in patients who had contact with the hospital in the previous 90 days, such as renal replacement therapy and/or evacuating paracentesis, or who live in a residence), and nosocomial (infection diagnosed in hospitalized patients after 48 h). For this study, "spontaneous infections" group together SBP, spontaneous bacterial empyema, and spontaneous bacteremia. The impact of infection was measured by different scores such as quick sequential organ failure assessment (*q*SOFA: at least two of three criteria must be met: altered mental status-Glasgow coma scale <15, respiratory rate ≥22 per minute, systolic blood pressure ≤100 mmHg), systemic inflammatory response syndrome (SIRS: when at least two of the following findings were present during the first 24 h of the diagnosis of the infection: fever (>38 °C) or hypothermia (<36 °C), as measured by axillary temperature; tachypnea, >20 breaths per minute or pCO2 <32 mmHg; tachycardia, >90 beats per minute; leukocytosis (>12,000 WBC/cc) or leukopenia (<4000 WBC/cc) or left shift (peripheral blood immature neutrophil count >10%), and ACLF score [17]. MDRO was defined as an organism presenting acquired resistance to three families of antibiotics. Adequate initial empirical antibiotic treatment was defined for culture-positive infections when the initial treatment included at least one antibiotic with in vitro activity for the microorganism involved [18]. Antibiotic de-escalation was defined as a modification of the empirical treatment to an antibiotic regimen with a lower spectrum or the suspension of any of the antibiotics used initially that will imply reducing the antibiotic spectrum [19]. Clinical outcomes registered during hospitalization were: the development of a second bacterial infection, type and the number of organ failures, type and the number of advanced life support requirements, days of hospitalization, and in-hospital mortality (See supplementary material for more definitions). Prospective data was collected in anonymized forms in each participating center and sent to the coordinating center. They were analyzed within no more than seven days by hepatologists and infectious diseases specialists to ensure data quality and detect inconsistencies.

2.4. Ethical statement

Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of Hospital Italiano de Buenos Aires (3879) and in all other participating center.

2.5. Statistical analysis

Categorical variables are presented as absolute numbers and percentages. Numerical variables are presented as median and 25th-75th percentiles (IQR). Results are presented for the global study population but also stratified according to pre-specified variables of interest: site of infection, type of infection, and antibiotic susceptibility patterns. The STATA v. 14.1 version was used for analyses.

3. Results

Throughout the study period, 493 patients met the inclusion criteria. Of those, 21 were excluded either because of transplantation history (n = 15) or by refusal to consent (n = 6). Finally, 472 patients were included and followed up until transplantation, death, referral to another center or hospital discharge (see supplementary material tables S1 and S2 for center data).

3.1. Characteristics of the patients

Patients were predominantly middle-aged males, with a median age of 59.5 (IQR: 51.5–66.0) years old. Bacterial infection was the reason for hospital admission in 271 (57.4%) patients; the rest developed the infection while hospitalized for other reasons. The most common etiology of cirrhosis was alcohol-related, followed by viral and non-alcoholic-steatohepatitis in almost equal proportions. One-third of the patients had diabetes. Common prior medication included beta-blockers (34.8%), rifaximin (27.7%), and norfloxacin prophylaxis (11.2%). During the three-month before the index bacterial infection, a significant number of the patients presented a bacterial infection (22.6%), received antibiotic treatments (33%), had an MDRO isolate (5.3%), underwent diagnostic or therapeutic invasive procedures (37.6%), and/or were admitted to an intensive-care unit (15.1%). Strikingly, 249 (52.8%) of the patients had experienced at least one of these situations, 61 (12.9%) had two, and 82 (17.4%) had three or more. For general descriptive characteristics of the study population, see Table 1.

3.2. Characteristics of the bacterial infections

Regarding the type of infections, 247 (52.3%) were community-acquired, while 123 (26.1%) and 102 (21.6%) were nosocomial and healthcare-associated, respectively. Spontaneous bacterial peritonitis was the most frequent infection (n = 143, 47.7%), followed by UTI (n = 116, 24.6%), pneumonia (n = 63, 13.3%), skin and soft tissue infections (n = 52, 11.0%) and spontaneous bacteriemia (n = 34, 7.2%). Regarding the impact of the infection at diagnosis, 23.2% and 32.1% of the patients met *q*SOFA and SIRS criteria, respectively. Almost one-third of the patients (30.3%) met ACLF criteria, of whom 57.3% were grades 2 or 3 (Table 2).

3.3. Microbiological characteristics and antibiotic susceptibility patterns

Overall, 256 (54.2%) infections were culture-positive. Of them, 241 (94.1%) had a single bacterial isolate and 15 (5.9%) had two.

Table 1
Study population characteristics (n = 472).

Age in years, *median (IQR)*	59.5 (51.5–66.0)
Male sex, *n (%)*	314 (66.5)
Cirrhosis etiology, *n (%)*	
Viral	72 (15.3)
Alcohol related	204 (43.2)
Non-alcoholic-steatohepatitis	73 (15.5)
Cryptogenic	23 (4.9)
Autoimmune hepatitis	35 (7.4)
Primary biliary cholangitis	28 (5.9)
Other	37 (7.8)
Comorbidities, *n (%)*	
Diabetes (n = 470)	145 (30.9)
HIV infection (n = 459)	10 (2.2)
Medications at the time of the bacterial infection, *n (%)*	
Any pharmacological immunosuppression * (n = 471)	45 (9.6)
Corticosteroids for the treatment of alcohol related hepatitis	12 (2.5)
Rifaximin (n = 469)	130 (27.7)
Beta-blockers (n = 468)	163 (34.8)
Norfloxacin prophylaxis	53 (11.2)
Proton pump inhibitors (n = 467)	180 (38.5)
Previous events of interest (last 3 months), *n (%)*	
Use of therapeutic antibiotics for ≥ 5 consecutive days (n = 457)#	151 (33.0)
Bacterial infection (n = 439)	99 (22.6)
MDRO infection or colonization (n = 450)	24 (5.3)
Invasive procedures ¶ (n = 452)	170 (37.6)
ICU admission (n = 456)	69 (15.1)
Cirrhosis/Liver disease severity scores, *median (IQR)*	
Child Pugh score	10.0 (8.0–12.0)
MELD score	18.0 (13.0–24.0)
MELD Na score	21.3 (15.7–27.3)
Cirrhosis complications upon enrollment, *n (%)*	
Hepatocarcinoma § (n = 467)	53 (11.3)
Ascitis	364 (77.1)
Hepatic encephalopathy♦ (n = 469)	262 (55.9)
Laboratory results, *median (IQR)*	
Wite Blood Cell Count (x10^9/L)	7.8 (5.0–12.3)
Sodium (mEq/L)	134.0(130.0–138.0)
Creatinine (mg/dL)	0.98 (0.7–1.6)
INR	1.6 (1.3–2)
Bilirubin (mg/dL)	3.1 (1.6–6.5)
Albumin (g/dL)	2.7 (2.3–3)

IQR: interquartile range. HIV: human immunodeficiency virus, MDRO: multidrug-resistant-organism. ICU: intensive care unit. MELD: Model for End-stage Liver Disease, IRN: international normalized ratio.
* Current or in the last 30 days.
# 70% were beta lactam.
¶ Invasive procedures refer to paracentesis, central venous catheter, bladder catheter, and surgery.
§ 24 patients met Milan criteria.
♦ Mild grades (I/II): 192 (73.3%), Severe grades (III/IV): 70 (26.7%).

Table 2
Infection characteristics and impact at diagnosis (n = 472).

Type of bacterial infection, *n (%)*	
Community-acquired	247 (52.3)
Healthcare-associated	102 (21.6)
Nosocomial	123 (26.1)
Site of bacterial infection, *n (%)*	
Spontaneous bacterial peritonitis	143 (30.3)
Urinary tract infection	116 (24.6)
Pneumonia	63 (13.4)
Spontaneous bacteremia	34 (7.2)
Skin and soft tissue	52 (11.0)
Spontaneous empyema	10 (2.1)
Other*	54 (11.4)
Infections impact scores at diagnosis, *n (%)*	
*q*SOFA: 2 criteria	74 (15.8)
*q*SOFA: 3 criteria	35 (7.4)
SIRS criteria (n = 467)	150 (32.1)
Acute on chronic liver failure	143 (30.3)
Grade 1	61 (42.6)
Grade 2	53 (37.1)
Grade 3	29 (20.3)

*q*SOFA: quick "Sequential Organ Failure Assessment". SIRS: systemic inflammatory response syndrome. The "site" of bacterial infection refers to the organ/system from which the infection develops and the "type" of bacterial infection refers to the site of acquisition of the infection. § 24 patients met Milan criteria.
* Others: catheter-associated bacteremia (n = 2), cholangitis/cholecystitis (n = 14), secondary peritonitis (9), pseudomembranous colitis (n = 2), others (n = 27).

Therefore, 271 organisms were finally identified. Gram negative-bacteria were the most commonly isolated microorganism (n = 161, 59.4%), not only in community-acquired infections (n = 71, 55.5%) but also in health-care associated (n = 44, 62.0%) and nosocomial (n = 45, 62.5%) episodes.

Table 3 describes general microbiological characteristics (for a more detailed description, see supplementary table S3). The most common Gram-negative isolates in SBP, spontaneous bacterial empyema, UTI, and spontaneous bacteremia were *Escherichia coli* and *Klebsiella pneumoniae*. The most common Gram-positive bacteria were *Staphylococcus aureus* and *Streptococcus viridans* in SBP, spontaneous bacterial empyema, spontaneous bacteremias, and in the skin and soft tissue infections; while in UTI, *Enterococcus faecalis* and *faecium* were the most frequent microorganisms. Regarding pneumonia, *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most frequent isolate.

Susceptibility patterns of the isolated microorganisms to frequently prescribed antibiotics by site and type of infection are shown in Table 4. The coverage of cefepime and ceftriaxone was over 70% for the empirical treatment of community-acquired spontaneous infections. However, ceftazidime's coverage was only 40%. The lower-spectrum antibiotics that provided coverage for at least 70% of the isolates for UTIs in any setting and for spontaneous infections in health-care and nosocomial context, were imipenem and meropenem.

Considering the entire study population (patients with culture-positive plus culture-negative infections), 103 (21.8%; 95%CI: 18.3% - 25.8%) patients presented infections caused by MDROs. The prevalence of infections caused by MDROs estimated only in patients with culture-positive infections was 40.2% (95%CI: 34.4%–46.4%). Extended-spectrum B-Lactamases enterobacteria and methicillin-resistant Staphylococcus aureus were particularly frequent, accounting for almost 50% of the MDROs. Of note, considering only the culture-positive population, almost half of the UTIs, pneumonias, and spontaneous bacteremias were caused by MDROs (details in Table 5).

3.4. Patterns of antibiotic usage

The median antibiotic treatment time for the entire cohort was 8.0 (IQR: 6.0–11.0) days. Considering patients with culture-positive infections (n = 256), 181 (70.7%) received adequate initial antibiotic

Table 3
General microbiological characteristics.

Culture-positive infections, *n (%)*	256 (54.2)
Culture-positive infections according to the site of infection*, *n (%)*	
Spontaneous bacterial peritonitis/Empiema (n = 153)	63 (41.2)
Urinary tract infection (n = 116)	97 (83.6)
Pneumonia (n = 63)	15 (23.8)
Spontaneous bacteremia (n = 34)	34 (100.0)
Skin and soft tissue (n = 52)	24 (46.2)
Other infections# (n = 54)	23 (42.6)
Infection episodes with single bacterial isolates (n = 256), *n (%)*	241 (94.1)
Infection episodes with two bacterial isolates (n = 256), *n (%)*	15 (5.9)

* The "site" of infection refers to the organ/system from which the infection develops.
# other infections: catheter-associated bacteremia, cholangitis/cholecystitis, secondary peritonitis, pseudomembranous colitis.

Table 4
Susceptibility to frequently used antibiotics by site and type of infection* (*n* = 256).

	Community acquired	Healthcare associated	Nosocomial
Spontaneous Bacterial Peritonitis/Empyema (*n* = 63), *n (%)*	**(*n* = 33)**	**(*n* = 11)**	**(*n* = 19)**
Ceftriaxone	24 (72.7)	8 (72.7)	11 (57.9)
Cefepime	25 (75.8)	9 (81.8)	11 (57.9)
Ceftazidime	14 (42.4)	6 (54.5)	6 (31.6)
Piperacillin-tazobactam	27 (81.8)	8 (72.7)	11 (57.9)
Imipenem/Meropenem	27 (81.8)	9 (81.8)	15 (78.9)
Ertapenem	25 (75.8)	7 (63.6)	12 (63.2)
Urinary tract infection (*n* = 97), *n (%)*	***n* = 48**	***n* = 24**	***n* = 25**
Ceftriaxone	29 (60.4)	15 (62.5)	14 (56.0)
Cefepime	29 (60.4)	15 (62.5)	14 (56.0)
Ceftazidime	25 (52.1)	15 (62.5)	14 (56.0)
Piperacillin-tazobactam	34 (70.8)	17 (70.8)	15 (60.0)
Imipenem/Meropenem	45 (93.8)	23 (95.8)	18 (72.0)
Ertapenem	41 (85.4)	20 (83.3)	17 (68.0)
Pneumonia (*n* = 15), *n (%)*	***n* = 7**	***n* = 4**	***n* = 4**
Ceftriaxone	5 (71.4)	2 (50.0)	1 (25.0)
Cefepime	5 (71.4)	2 (50.0)	1 (25.0)
Ceftazidime	–	2 (50.0)	–
Piperacillin-tazobactam	5 (71.4)	2 (50.0)	1 (25.0)
Imipenem/Meropenem	5 (71.4)	3 (75.0)	1 (25.0)
Ertapenem	3 (42.9)	3 (75.0)	–
Spontaneous bacteremia (*n* = 34), *n (%)*	***n* = 9**	***n* = 9**	***n* = 16**
Ceftriaxone	6 (66.7)	7 (77.8)	8 (50.0)
Cefepime	6 (66.7)	7 (77.8)	8 (50.0)
Ceftazidime	3 (33.3)	1 (11.1)	5 (31.3)
Piperacillin-tazobactam	6 (66.7)	8 (88.9)	9 (56.3)
Imipenem/Meropenem	7 (77.8)	8 (88.9)	11 (68.8)
Ertapenem	6 (66.7)	7 (77.8)	10 (62.5)
Skin and Soft tissue infection (*n* = 23), *n (%)*	***n* = 23**	***n* = 7**	***n* = 1**
Ceftriaxone	11 (47.8)	4 (57.1)	1 (100.0)
Cefepime	12 (52.2)	4 (57.1)	1 (100.0)
Ceftazidime	4 (17.4)	1 (14.3)	–
Piperacillin-tazobactam	12 (52.2)	4 (57.1)	1 (100.0)
Imipenem/Meropenem	11 (47.8)	4 (57.1)	1 (100.0)
Ertapenem	6 (26.1)	2 (28.6)	1 (100.0)
Spontaneous infections: peritonitis/empyema/bacteremia (*n* = 97), *n (%)*	***n* = 42**	***n* = 20**	***n* = 35**
Ceftriaxone	30 (71.4)	15 (75.0)	19 (54.3)
Cefepime	31 (73.8)	16 (80.0)	19 (54.3)
Ceftazidime	17 (40.5)	7 (35.0)	11 (31.4)
Piperacillin-tazobactam	33 (78.6)	16 (80.0)	20 (57.1)
Imipenem/Meropenem	34 (81.0)	17 (88.5)	26 (74.3)
Ertapenem	31 (73.8)	14 (70.0)	22 (62.9)

* The "site" of infection refers to the organ/system from which the infection develops and the "type" of infection refers to the site of acquisition of the infection. Data is extracted from those infected patients with a positive sample to be analyzed (*n* = 256). The "n" from this table represents the number of culture-positive infections.

coverage. When analyzing the 75 patients with inadequate initial antibiotic treatment, 55 (73.3%) presented an infection caused by MDROs. Antibiotic de-escalation was performed in a third of the patients with culture-positive but in less than 10% of the patients with culture-negative infections.

3.5. Impact of bacterial infections and outcomes

Almost a third of the patients were transferred to an intensive care unit during hospitalization. A total of 114 (24.2%) patients required at least one type of advanced organ support, 8.3% a combination of two of them, and around 2.8% required three vital supports (invasive mechanical ventilation, vasopressors, and renal replacement therapy). A second bacterial infection was diagnosed in 46 (9.8%) subjects during hospitalization. Overall, 92 (19.5%, 95%CI 15.9%−23.1%) patients died during hospitalization. The median time between infection and death was 10.0 (IQR: 5.0−17.0) days. Patients' outcomes are detailed in Table 6.

4. Discussion

In this prospective multicenter study about the clinical and microbiological characteristics of bacterial infections in patients with cirrhosis, useful data was gathered for the region.

Among the most important clinical findings, it can be highlighted that alcohol is the leading cause of cirrhosis in patients with bacterial infections. The most frequent infection was not surprisingly, SBP, followed closely by UTI. This pattern of infection distribution has already been described in America and Europe [7]. When adding spontaneous bacterial infection and UTI, they accounted for almost two-thirds of all infections. This finding is relevant given its impact on the guidance of empirical treatments in patients with cirrhosis suspected of a bacterial infection.

Bacterial infections tend to present with subtle or no symptoms in patients with cirrhosis [20], and therefore different scores have been proposed for screening sepsis and/or quantifying mortality risk [21,22]. As shown in the present study, most patients presented a normal leukocyte count, and only one in three and one in four met SIRS and *q*SOFA criteria at the moment of the infection, respectively. Thus, this study reinforces that a high index of suspicion is necessary for early diagnosis and antibiotic initiation, considering common sources of infection and the local microbiological characteristics [23].

Overall, half of the patients presented culture-positive infections, with UTIs showing the highest microbiological yield (after spontaneous bacteremias in which cultures have to always be positive for their diagnosis). Importantly, UTI and spontaneous bacteremia have in common that they are highly dependent on the cultures to be

Table 5
Prevalence of MDRO according to site and type of infection (n = 103).

MDRO prevalence estimated over culture-positive infections by site of infection, *n (%)*	
Spontaneous bacterial peritonitis/Empyema (n = 63)	21 (33.3)
Urinary tract infection (n = 97)	49 (50.5)
Pneumonia (n = 15)	6 (40.0)
Spontaneous bacteremia (n = 32)	14 (43.8)
Skin and soft tissue (n = 23)	7 (30.4)
Other infections[#] (n = 24)	6 (25.0)
MDRO prevalence estimated over culture-positive infections by type of infection, *n (%)*	
Community acquired (n = 121)	41 (33.9)
Healthcare-associated (n = 64)	33 (51.6)
Nosocomial (n = 71)	29 (40.9)
Mechanism of resistance in isolated MDRO, *n (%)*	
Vancomycin-Resistant *Enterococci*	4 (3.9)
Methicillin-resistant *Staphylococcus aureus*	16 (15.5)
Extended Spectrum B-Lactamases *Enterobacteriaceae*	32 (31.1)
Carbapenemase (KPC, Oxa, MBL)—	4 (3.9)
Acinetobacter baumannii multidrug-resistant	2 (1.9)
Coagulase-Negative *Staphylococcus*	5 (4.9)
Other patterns of multidrug resistance	40 (38.8)

MDRO: multidrug-resistant organisms.*The "site" of infection refers to the organ/system from which the infection develops and the "type" of infection refers to the site of acquisition of the infection.
[#] Other infections: catheter-associated bacteremia, cholangitis/cholecystitis, secondary peritonitis, pseudomembranous colitis.

positive for their diagnosis, as opposed to other infections like SBP or pneumonia. Since cultures are usually available not sooner than 24 to 48 h after the infection is suspected, the treating physician is challenged not only by having to decide whether to start empiric antibiotics or not but also by not being able to define with precision the site of the infection. These two infections represented a third of the total sample in the present study and accounted for 40% of the infections in prior publications [7]. All in all, these could be responsible for mistakes in selecting empirical antibiotics, either by under or over-prescription.

As aforementioned, appropriate antibiotic treatment should ideally be guided by the most granular and up-to-date microbiological data. Gram-negative bacteria slightly predominated in the present study, regardless of where the infection was acquired. The increasing representation of Gram-positive isolations occurring over time is hypothesized to be due to the increasing exposure of patients with cirrhosis to antibiotic prophylaxis, invasive procedures, and frequent hospitalizations, among others [24], all of which were frequent in this cohort.

Table 6
Patient outcomes (n = 472).

Organ failure during follow-up, *n (%)*	
Kidney failure	118 (25.0)
Hematological failure	93 (19.7)
Liver failure	79 (16.7)
Respiratory failure	32 (6.8)
Neurological failure	101 (21.4)
Advanced life support at bacterial infection diagnosis or during follow-up, *n (%)*	
ICU admission	142 (30.1)
Mechanical respiratory assistance (n = 470)	44 (9.4)
Vasopressors	104 (22.0)
Renal replacement treatment	31 (6.6)
Second event of bacterial infection during follow-up (n = 449), *n (%)*	46 (10.2)
End-of-follow-up events	
Liver transplantation during follow-up, *n (%)*	17 (2.4)
Days between infection and liver transplantation, *median (IQR)*	10.0 (9.0–21.0)
Hospital transfer[*], **(n = 460)**, *n (%)*	11 (2.4)
Days between infection and hospital transfer, *median (IQR)*	8.0 (4.0–17.0)
Hospital discharge, *n (%)*	352 (74.6)
Days between infection and hospital discharge, *median (IQR)*	9.0 (6.0–14.0)
In-hospital mortality, *n (%)*	92 (19.5)
Days between infection and death, *median (IQR)*	10.0 (5.0–17.0)

ICU: intensive care unit. IQR: interquartile range.
[*] transferred patients are considered lost to follow-up for other events.

The empiric antibiotic selection is mainly supported by prior knowledge of antibiotic susceptibility patterns of the most commonly isolated microorganisms. When analyzing antibiotic usage patterns in our study, four of every five patients were adequately covered by the initial treatment. It is known that a high level of protection is warranted for this population, particularly in those with organ failures [8]. In accordance with this and considering the present study's findings, some traditional antibiotic options might be left aside. That was the case for ceftazidime which harbored an unacceptable low coverage for most spontaneous bacterial infections, mainly because it does not cover Gram-positive bacteria. Of note, this antibiotic is still used empirically to treat SBP in many centers of Argentina and Uruguay. In addition, a high prevalence of UTI was noticed in this study, which harbored a high resistance pattern, regardless of where the infection was acquired (half of the culture-positive UTIs were caused by MDROs). Of concern, ceftriaxone or cefepime, which offer good coverage for spontaneous community-acquired infections, may not be sufficient for UTI. As previously suggested, in the scenario of nosocomial infections, no less than carbapenems and probably a combination of antibiotics might be necessary depending on the site of infection and the clinical condition of the patient [3].

Achieving high rates of adequate empiric coverage does not mean efficiency, and that's why around one in three enrolled patients with culture-positive infections in our study experienced de-escalation of the initial regimen. De-escalation is a strategy to reduce the undesired effects of broad-spectrum antibiotics, and therefore all efforts should be made to facilitate it as a central part of antibiotic stewardship programs [19]. Not surprisingly, this was possible in only 10% of the patients with culture-negative infections, highlighting the importance of obtaining adequate microbiological samples in all patients suspected of a bacterial infection and before starting antibiotics.

Prescribing an empiric antibiotic regimen with enough coverage but not excessive in terms of the spectrum is a challenging task, especially for a critically ill patient. One downside of prescribing broad-spectrum antibiotics to all patients is that it favors the development

of bacterial resistance, which might appear very early during the first days of treatment [25,26]. In our study, we found a slightly higher prevalence of infections caused by MDROs compared with the 34% that was reported in the global study of Piano et al., estimated on patients with culture-positive infections [7]. Notably, we found that among patients with culture-positive infections, half of the episodes of UTI, pneumonia, and spontaneous bacteremias were caused by MDRO strains, which might have led to inadequate initial antibiotic treatment.

Even with high rates of adequate antibiotic coverage, nearly one in four included patients needed some sort of advanced life support, and one in five died. This positions bacterial infections as one of the most severe acute syndromes in patients with cirrhosis, with higher in-hospital mortality rates than acute variceal bleeding [27] and similar rates to alcohol-related hepatitis [28].

The present study has some limitations and strengths to be acknowledged. Among the shortcomings, the sample size may need to be increased to draw conclusions for certain infections, like pneumonia and skin and soft tissue infections. Additionally, since patients' treatment and work-up were according to each participant center's own protocols, and because cultures were not centralized, there might be issues regarding misclassification of the source of infection, and heterogeneous quality of biological samples and patient management. However, all cultures' results and antibiograms were sent to the coordinating center for their central reading by an infectious disease specialist.

Within the strengths, the prospective and multicenter nature of the study allowed the collection of a large number of variables with uniform criteria and a great granularity level. This is the region's first study large enough to serve as a platform to suggest evidence-based recommendations for the empirical treatment of bacterial infections in patients with cirrhosis in Latin America. Additionally, the study had a central real-time monitoring team which favored that all research activities were implemented according to the approved study protocol and good clinical practices. Finally, the results provided by this study in a region in which the lack of local data prevented the development of evidence-based guidelines, highlight the importance of generating regional information.

5. Conclusions

One in five hospitalized patients with cirrhosis and bacterial infection dies. The high prevalence of MDRO is worrisome, especially when considering frequent infections such as urinary tract infections and spontaneous bacteremias, where this phenomenon accounts for half of the episodes. Appropriate empiric antibiotic treatment is a crucial goal for the optimal management of infections in this population, and its choice has to be based on the most granular and up-to-date microbiological data in every region. This article emphasizes the need to reassess the choice of certain traditional antibiotics as empirical regimens. Furthermore, given the high prevalence of MDROs in patients with urinary tract infections and spontaneous bacteremias, and since the diagnosis of these infections is based on culture results that may not be available before 48 h, broad-spectrum antibiotics should be considered with early de-escalation strategies. We are confident that the data presented here will be useful in revising current practices of patients with cirrhosis and bacterial infections in Argentina and Uruguay, and it will serve as a platform for others to revise them.

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Author contributions

All authors participated in the conception and design of the study, and/or acquisition of data, and/or analysis and interpretation of data, and/or drafting the article and/or revising it critically for important intellectual content and final approval of the version to be submitted.

Declaration of Competing Interests

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2023.101097.

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