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Brief report

Prospective surveillance reveals high rates of antimicrobial resistance in urinary tract infections among patients with cirrhosis.

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ABSTRACT

Introduction and Objectives: As antimicrobial resistance rises, selecting appropriate empirical antibiotics for treating urinary tract infections (UTIs) has become complex. This study aimed to estimate the antimicrobial susceptibility patterns of microorganisms that cause UTIs in patients with cirrhosis.
Materials and Methods: This study analyzed UTI episodes in patients with cirrhosis from Argentina and Uruguay (Dec 2020–July 2024). The coordinating center reviewed all antibiograms.
Results: A total of 277 UTI episodes in 233 patients were included (community-acquired: 119, healthcare-associated: 68, and nosocomial: 90). *Escherichia coli* and *Klebsiella pneumoniae* were the predominant pathogens (70.6 %, *n* = 202). Multidrug resistance and extensive drug resistance were observed in 51.6 % and 11.6 % of the episodes, respectively. Carbapenemase-producing organisms were particularly prevalent in nosocomial infections (30.3 %, 95 % CI: 21.5–40.8). In community-acquired UTIs, coverage rates for ceftriaxone, cefepime, and piperacillin-tazobactam ranged from 60–70 %. Aminoglycosides (82.2 %, 95 %CI: 74.1–88.2) and

Abbreviations: CI, Confidence intervals; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; IQR, Interquartile ranges; KPC, Klebsiella pneumoniae carbapenemase; MBL, Metallo-β-lactamase; MDRO, Multidrug-resistant organisms; UTI/UTIs, Urinary tract infection(s); XDRO, Extensively drug-resistant organisms

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carbapenems (90.0 %, 95 %CI: 83.0–94.2) provided coverage exceeding 80 %. For nosocomial UTIs, carbapenems demonstrated suboptimal coverage; in contrast, adequate coverage was observed with ceftazidime-avibactam plus aztreonam (83.0 %, 95 %CI: 73.4–89.6) or plus vancomycin (76.1 %, 95 %CI: 65.9–84.0).
Conclusions: The study highlights alarming antimicrobial resistance, particularly in nosocomial UTIs. Traditional antibiotics, such as ceftriaxone for community-acquired UTIs and carbapenems or piperacillin/tazobactam for nosocomial infections, fail to provide sufficient empirical coverage. More comprehensive approaches to empirical treatment, such as combination therapies or newer antibiotics targeting resistant pathogens, are needed.

1. Introduction

Bacterial infections are common and serious complications in patients with cirrhosis, affecting up to 50 % of those hospitalized and contributing to in-hospital mortality rates of up to 25 % [1,2]. While spontaneous bacterial peritonitis is the most common infection, urinary tract infections (UTIs) typically rank second, especially in the Americas and Europe, and together they account for up to 60 % of all infections [3,4].

UTIs can be challenging to diagnose in patients with cirrhosis, as typical symptoms may be absent or nonspecific. Diagnosis depends on urine cultures, which take 24 to 48 h and may not clearly distinguish actual infection from asymptomatic bacteriuria. This diagnostic uncertainty, along with their high frequency, often results in inappropriate antibiotic use [5].

Cirrhosis-related UTIs often involve multidrug-resistant organisms (MDRO) [1,2], complicating empiric treatment and potentially worsening sepsis outcomes [6]. The growing and regionally variable prevalence of MDRO makes it challenging to meet the recommended 80–90 % coverage targets [7].

This study aimed to evaluate the antimicrobial susceptibility of pathogens causing UTIs in hospitalized patients with cirrhosis.

2. Patients and Methods

This cross-sectional study analyzed data from a prospective multicenter registry of bacterial infections in patients with cirrhosis (ClinicalTrials.gov: NCT0634940), established in Argentina and Uruguay in December 2020 [8]. The registry includes consecutive episodes of culture-positive infections in hospitalized cirrhotic patients aged ≥17, excluding those with prior transplants or without informed consent. For the present analysis, a subset of episodes was selected and classified as UTIs, aiming to evaluate the antimicrobial susceptibility of the causative pathogens. UTIs were defined as the presence of symptoms (e.g., fever ≥38 °C, dysuria, urgency, frequency, or suprapubic tenderness) in addition to a positive urine culture (≥10^3 CFU/mL of bacterial growth). As of July 2024, the registry included 689 infection episodes, of which 277 were UTIs. The unit of analysis was the UTI episode, permitting multiple entries per patient. The registry adhered to a standardized protocol based on the WHO's Global Antimicrobial Resistance Surveillance System [9]. The supplementary material provides further methodological details, including information regarding data collection procedures, an extended description of the microbiological methods, and a detailed account of the statistical analysis performed.

2.1. Ethical statement

All patients provided informed consent, directly or through a legal representative. The study received approval from the IRBs at all participating centers (#5821) and adhered to the Declaration of Helsinki.

3. Results

From December 2020 to July 2024, a total of 277 UTI episodes were recorded in 233 patients with cirrhosis across 19 centers in Argentina and Uruguay. These episodes yielded 286 bacterial isolates, as some infections involved more than one organism. Supplementary Table S1 provides details about the participating centers, and Table 1 summarizes the key clinical characteristics.

More than two-thirds of UTI episodes (68.6 %, *n* = 190) occurred while patients were on some form of antibiotic prophylaxis, primarily rifaximin (46.6 %, *n* = 129), with norfloxacin being less common (14.8 %, *n* = 41). Nearly half of these episodes (50.5 %, *n* = 140) occurred after patients had received at least five consecutive days of therapeutic antibiotics for another bacterial infection within the past three months. Additionally, 71.8 % of UTI episodes occurred in patients with hospital admissions due to bacterial infections within the previous year. Regarding the location where the infection was acquired, 119 UTI episodes were community-acquired (43.0 %), 68 were health-associated (24.5 %), and 90 were nosocomial (32.5 %).

Most UTI episodes were monomicrobial (96.8 %, *n* = 268), with only a small proportion involving two organisms (3.2 %, *n* = 9), resulting in 286 bacterial isolates. Gram-negative organisms predominated (*n* = 235, 82.2 %), with *Escherichia coli* accounting for 41.9 % (*n* = 120) and *Klebsiella pneumoniae* for 26.9 % (*n* = 77) of the isolates overall. Enterococcus was the third most frequent bacterium, comprising 14.0 % (*n* = 40) of the isolates. When evaluating the distribution of microorganisms based on where the infection was acquired, *E. coli* was the most common isolate in both community-acquired (59.2 %) and health-associated infections (41.2 %), while *Klebsiella pneumoniae* was the most prevalent in nosocomial infections (38.7 %). *Enterococcus* primarily represented the gram-positive organisms, with a higher prevalence in health-associated infections (25.0 %) compared to community-acquired (9.2 %) and nosocomial infections (12.9 %). Supplementary Table S2 provides further details regarding bacterial isolates.

MDRO was observed in 143 of the 277 UTI episodes (51.6 %, 95 % CI: 45.7–57.5), with prevalence increasing from 40.3 % (95 % CI: 31.8–49.5) in community-acquired infections to 50.0 % (95 % CI: 38.0–62.0) in healthcare-associated infections, and 67.8 % (95 % CI: 57.2–76.8) in nosocomial cases. Extensive drug-resistant isolates were reported in 11.6 % (95 % CI: 8.3–15.9) of the episodes, and pan-drug-resistant phenotypes were present in 2.2 % (95 % CI: 1.0–4.7). In a temporal analysis, MDRO significantly increased from 2021 (42.6 %, 95 % CI: 30.0–56.2) to 2023 (61.1 %, 95 % CI: 51.5–69.9) (Fig. 1). During this period, the proportion of extended-spectrum β-lactamase-producing organisms remained stable, while carbapenemase-producing organisms increased (Supplementary Figures S1 and S2).

When considering the total number of isolated bacteria (*n* = 286), 147 (51.4 %) MDRO were identified. Table 2 displays the key mechanisms of MDRO. The most frequent resistance mechanism was the production of extended-spectrum β-lactamase by *Enterobacteriaceae* (56.5 %), followed by carbapenemase-producing organisms (28.6 %) and vancomycin-resistant *Enterococcus* (9.5 %). As shown in Table 2,

Table 1
Patient characteristics registered at each episode of urinary tract infection (n = 277).

Characteristics	n = **277**
Male sex, *n (%)*	153 (55.2 %)
Cirrhosis etiology, *n (%)*	
Alcohol-related	94 (33.9 %)
Metabolic dysfunction-associated steatotic liver disease	83 (30.0 %)
Viral	27 (9.7 %)
Autoimmune hepatitis	26 (9.4 %)
Primary biliary cholangitis	21 (7.6 %)
Cryptogenic	13 (4.7 %)
Other	14 (5.1 %)
Prior medications, *n (%)*	
Norfloxacin prophylaxis	41 (14.8 %)
Ciprofloxacin prophylaxis	3 (1.1 %)
Rifaximin	129 (46.6 %)
Other antibiotics*	17 (6.1 %)
Beta-blockers	129 (46.6 %)
Proton pump inhibitors	169 (61.0 %)
Recent infections and/or recent antimicrobial treatments (last 3 months), *n (%)*	
Use of therapeutic antibiotics for ≥ 5 consecutive days #	140 (50.5 %)
Hospital admission within the last year for bacterial infection	199 (71.8 %)
Cirrhosis/Liver disease severity scores, *median (IQR)*	
Child Pugh score	10 (8–12)
MELD Na score	20 (14–25)
Listed for liver transplantation, *n (%)*	92 (33.2 %)

The unit of analysis for this table is the episode of urinary tract infection (N = 277), which involved 233 patients. Abbreviations: MELD Na: Model for End-stage Liver Disease Sodium, IQR: Interquartile Range.
* Other antibiotics different from those prescribed for prophylaxis. # Use of therapeutic antibiotics for ≥ 5 consecutive days within the last 3 months.

the multidrug resistance patterns varied based on where the infection was acquired.

The proportion of carbapenemase-producing organisms among *Enterobacteriaceae* varied based on the type of infection. In nosocomial infections, carbapenemase-producing bacteria represented 35.5 % (95 % CI: 25.5–47.0) of *Enterobacteriaceae* isolates, which was higher than in healthcare-associated infections at 7.7 % (95 % CI: 2.9–19.0) and community-acquired infections at 8.8 % (95 % CI: 4.6–16.2). The prevalence of carbapenemase-producing bacteria was even more pronounced when specifically focusing on *Klebsiella* species. Carbapenemase-producing *Klebsiella* accounted for 55.3 % (95 % CI: 39.0–70.4) of the isolates in nosocomial infections, while representing 23.5 % (95 % CI: 8.7–49.0) and 30.8 % (95 % CI: 15.8–51.3) in healthcare-associated and community-acquired infections, respectively.

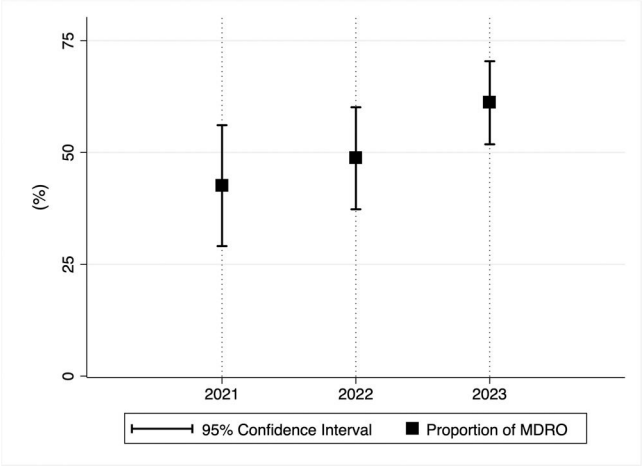

Fig. 1. Multidrug-resistant organisms proportion over time.
Footnote: The graph illustrates the proportion of urinary tract infection episodes with at least one Multidrug-resistant organism from 2021 to 2023: 2021 (42.6 %, 95 %CI: 30.0–56.2), 2022 (48.7 %, 95 %CI: 37.6–59.9), 2023 (61.1 %, 95 %CI: 51.5–69.9). The number of UTI episodes enrolled each year is as follows: 2021 = 54, 2022 = 76, 2023 = 108. Since 2020 had few episodes (n = 7) and 2024 is still in progress, they have been intentionally excluded from this graphic.

Table 3 presents the antibiotic susceptibility of UTI episodes. For community-acquired UTI episodes (n = 119), commonly used antibiotics such as ceftriaxone, cefepime, and piperacillin-tazobactam achieved 60–70 % coverage rates. Aminoglycosides and ertapenem provided approximately 80 % coverage, while imipenem or meropenem reached 90 %. Combining these with vancomycin or linezolid offered additional coverage.

In health-associated UTI episodes (n = 68), aminoglycosides alone (70.1 %, 95 % CI: 57.9–80.1), imipenem or meropenem alone (76.5 %, 95 % CI: 64.7–85.2), or in combination with vancomycin (82.4 %, 95 % CI: 71.1–89.8) were alternatives that covered approximately 80 % of episodes. If the clinical scenario requires higher coverage, options include the combination of imipenem or meropenem with linezolid (89.7 %, 95 % CI: 79.6–95.1) or ceftazidime-avibactam plus vancomycin (88.2 %, 95 % CI: 77.9–94.1).

In cases of nosocomial UTI episodes (n = 90), the options available for adequate coverage were limited. Commonly recommended antibiotics for nosocomial UTI, such as the combination of a carbapenem and a glycopeptide, achieved coverage rates of <70 %. In contrast, more effective options included ceftazidime-avibactam combined with aztreonam, which provided 83.0 % coverage (95 % CI: 73.4–89.6), and ceftazidime-avibactam combined with vancomycin, which offered 76.1 % coverage (95 % CI: 61.1–80.2). Overall, the explored antimicrobial regimens did not yield higher coverage rates for nosocomial UTI.

4. Discussion

In this study, we observed high rates of antimicrobial resistance among UTI isolates, particularly in nosocomial settings. Multidrug resistance rates approached 70 % in nosocomial UTIs, with one-third of the isolates demonstrating resistance to carbapenems. These findings challenge the adequacy of current empiric treatment strategies

Table 2
Key mechanisms of multidrug-resistance identified in multidrug-resistant organisms. Estimates are presented for the entire study population and by the place where the infection was acquired (n = 147).

Mechanism of Resistance % (95 %CI)	All (n = 147)	Community-acquired (n = 49)	Healthcare-associated (n = 34)	Nosocomial (n = 64)
Vancomycin-Resistant *Enterococci* (n = 14)	9.5 % (4.5–15.0)	2.1 % (−1.9–6.0)	14.7 % (2.8–26.6)	12.5 % (4.4–20.6)
Extended Spectrum β-Lactamases *Enterobacteriaceae* (n = 83)	56.5 % (48.4–64.5)	71.4 % (58.8–84.1)	67.6 % (51.9–83.4)	39.1 % (27.1–51.0)
Carbapenemase (KPC-Oxa-MBL) (n = 42)	28.6 % (21.3–35.9)	20.4 % (9.1–31.7)	11.8 % (0.9–22.6)	43.8 % (31.6–55.9)

KPC: Klebsiella pneumoniae producing carbapenemase; Oxa: Oxacillinase; MBL: Metallo-β-lactamase. The unit of analysis of this table is Multidrug resistant Organism. The calculation for the proportions of each resistance mechanism uses a total of 147 multidrug-resistant bacteria as the denominator (for the global estimates) or the respective denominators considering the absolute number of multidrug-resistant isolates of each type of infection (community-acquired, healthcare-associated, and nosocomial). No methicillin-resistant Staphylococcus aureus or *Pseudomonas aeruginosa* with difficult-to-treat resistance or multidrug-resistant *Acinetobacter* were found.

Table 3
Proportions of UTI episodes susceptibility to frequently used antibiotics, stratified by the place where the infection was acquired (n = 278).

Antibiotics	Community-acquired n = 119	Healthcare-associated n = 68	Nosocomial n = 90
Single antibiotics			
Nitrofurantoin #	82.4 % (73.0–89.0)	66.0 % (50.9–78.4)	55.4 % (42.9–67.2)
Quinolones	36.4 % (28.2–45.6)	25.8 % (16.5–37.9)	23.3 % (15.6–33.4)
TMS-SMX	42.7 % (34.0–52.0)	35.8 % (25.1–48.2)	25.6 % (17.5–35.7)
Ceftriaxone	51.3 % (42.2–60.2)	29.4 % (19.6–41.6)	21.1 % (13.8–31.0)
Cefepime	52.9 % (43.8–61.8)	30.9 % (20.9–43.1)	26.7 % (18.4–36.9)
Ceftazidime	47.1 % (38.2–56.2)	29.4 % (19.6–41.6)	22.2 % (14.7–32.2)
Aminoglycoside	82.2 % (74.1–88.2)	70.1 % (57.9–80.1)	62.9 % (52.3–72.5)
Piperacillin-tazobactam	60.5 % (51.3–69.0)	45.6 % (33.9–57.8)	29.2 % (20.6–39.7)
Ertapenem	79.0 % (70.6–85.5)	60.3 % (48.0–71.4)	46.7 % (36.5–57.2)
Meropenem/Imipenem	90.0 % (83.0–94.2)	76.5 % (64.7–85.2)	55.6 % (45.0–65.6)
Colistin	80.0 % (71.3–86.5)	63.3 % (50.1–74.8)	68.9 % (57.2–78.6)
Ceftazidime-avibactam	83.2 % (75.2–89.0)	67.6 % (55.4–77.9)	68.1 % (57.6–77.2)
Ceftolozane-tazobactam	85.3 % (77.5–91.0)	69.7 % (57.2–80.0)	72.6 % (61.9–81.2)
Combinations of antibiotics			
Piperacillin-tazobactam + Vancomycin	61.3 % (52.2–69.8)	51.5 % (39.4–63.3)	32.2 % (23.2–42.7)
Carbapenem + Vancomycin	90.8 % (84.0–94.9)	82.4 % (71.1–89.8)	57.8 % (47.2–67.7)
Carbapenem + Linezolid	91.6 % (85.0–95.5)	89.7 % (79.6–95.1)	64.4 % (53.9–73.8)
Aminoglycoside + Colistin	84.7 % (77.0–90.2)	71.2 % (58.9–81.0)	79.5 % (69.3–87.0)
Ceftazidime-avibactam + Aztreonam	86.6 % (79.1–91.7)	72.1 % (60.0–81.6)	83.0 % (73.4–89.6)
Ceftazidime-avibactam + Vancomycin	95.0 % (89.1–97.7)	88.2 % (77.9–94.1)	76.1 % (65.9–84.0)

The unit of analysis for this table is the episode of urinary tract infection. When an UTI episode has two isolated bacteria, sensitivity is calculated for a single antibiotic or combination that covers both isolations. # Nitrofurantoin was tested in 91 community-acquired cases, 47 health-associated cases, and 65 nosocomial infections. Nitrofurantoin achieves good concentrations in urine but does not concentrate well in plasma.

recommended by available clinical guidelines [10,11], raising concerns about their ongoing effectiveness. In addition, reconciling therapeutic recommendations is further complicated by the lack of consistency in how clinical scenarios are defined across these guidelines. Beyond the distinction between community-acquired and nosocomial infections, scenarios such as uncomplicated versus complicated UTIs, sepsis, and others are used variably, sometimes without standardized criteria.

Guidelines recommend fosfomycin or nitrofurantoin for patients with nosocomial uncomplicated UTIs, while carbapenem and a glycopeptide are suggested for critically ill individuals [10,11]. However, caution is warranted with nitrofurantoin. Although it provides excellent coverage for community-acquired and healthcare-associated UTIs, its effectiveness in nosocomial infections is more limited. Moreover, nitrofurantoin does not concentrate adequately in the kidneys or bloodstream, making it suitable only for cystitis [12]. A similar caution applies to fosfomycin, as it is ineffective in treating bacteremia [13]. Regarding the recommended use of carbapenem-glycopeptide combinations, such as carbapenem plus vancomycin [10,11], this strategy may still provide insufficient coverage. Alternatives targeting highly resistant *Enterobacteriaceae*, such as ceftazidime-avibactam (alone or combined with aztreonam), may improve coverage against these pathogens. However, the growing incidence of *Enterococcus* infections in healthcare-associated and nosocomial settings raises additional concerns. This suggests that broad-spectrum regimens directed primarily at resistant gram-negative bacilli may be inadequate as monotherapy, and that agents targeting gram-positive cocci —such as vancomycin or linezolid—may be required to ensure adequate coverage in these UTIs.

As a final note, the growing burden of multidrug resistance should be considered within the broader global context, particularly in light of the COVID-19 pandemic, which may have impacted resistance patterns through changes in antimicrobial use and healthcare practices [14].

5. Conclusions

Antimicrobial resistance has reached a critical point, especially in high-risk groups like hospitalized patients with cirrhosis. Our findings reveal key challenges for empiric treatment and suggest that emerging evidence could support more targeted therapeutic

strategies. Continued surveillance and coordinated efforts are essential to adapt to shifting resistance trends.

Author contributions

Study concept: CV, SM, AG, GGP; Study design: CV, SM, AG, GGP**; Enrolment of patients and data collection:** CV, GGP, EGB, IPI, CMB, ADS, MDM, AP, LT, JP, JB, BOS, MM, MA, GG, AR, AZ, PC, ME, MLG, MC, SS, JT, NV, DA, MD, FC, AG, SM**; Analysis and interpretation of data:** CV, SM, GGP**; Drafting of the manuscript:** CV, SM, GGP; **Critical revision for important intellectual content:** CV, GGP, EGB, IPI, CMB, ADS, MDM, AP, LT, JP, JB, BOS, MM, MA, DG, GG, AR, AZ, PC, ME, MLG, MC, SS, JT, NV, DA, MD, FC, AG, SM.

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Declaration of interests

None.

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Supplementary materials

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