Urinary tract infections caused by Gram-negative bacteria in elderly hospitalized patients: Epidemiology, clinical features and outcomes in the era of antimicrobial resistance

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A R T I C L E   I N F O

A B S T R A C T

Objective: Urinary tract infections (UTI) are among the most common infections in elderly hospitalized patients, often caused by multi-drug resistant (MDR) organisms and characterized by poor clinical outcomes. This study aimed to evaluate the clinical characteristics, microbiology, treatment patterns, and predictors of mortality in elderly hospitalized patients with UTI, with a focus on infections caused by MDR Gram-negative bacteria (MDR-GNB).

Methods: A retrospective analysis was conducted on 171 patients hospitalized between January 2022 and December 2023 at a large academic hospital in Siena, Italy. Data on demographics, comorbidities, infection characteristics, antimicrobial resistance, treatments, and outcomes were collected. Risk factors for MDR-GNB UTI and predictors of 14-d mortality were identified through univariable and multivariable analyses.

Results: Of 171 patients (median age: 82 y), 106 (62.0%) had a catheter-associated UTI, and 105 (61.4%) had a healthcare-associated UTI. MDR-GNB were isolated in 68.4% of cases. Common pathogens included *Escherichia coli* (74/171, 43.3%), *Klebsiella* spp. (39/171, 22.8%) and *Pseudomonas aeruginosa* (33/171, 19.3%). Among Enterobacterales 35.1% were Extended-spectrum β-lactamases-producers, 3.7% carried *Klebsiella pneumoniae* carbapenemase, and 3.0% metallo-β-lactamases. Overall, the 14-d mortality rate was 12.9%. Predictors of 14-d mortality included septic shock, infections caused by *Providencia stuartii,* infections caused by New Delhi metallo-β-lactamase-producing *K. pneumoniae*, and inappropriate empirical antibiotic therapy.

Conclusions: UTI significantly affect hospital length of stay and mortality in elderly patients. In the current context, resistance mechanisms including *K. pneumoniae* carbapenemase and metallo-β-lactamases production, must be considered when managing these infections. Prompt recognition of risk factors for infections caused by MDR organisms and optimized antimicrobial strategies are essential to improve outcomes in this vulnerable population.

1. Introduction

In recent decades, the global increase in life expectancy has led to an ageing population, which, in turn, has resulted in a significant rise in the number of elderly patients hospitalized [1,2]. Hospitalized elderly patients represent a unique cohort, often presenting with multiple comorbidities, complex polypharmacy, impaired

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immune function, and the need for invasive devices to support altered physiological functions (e.g. urinary catheters) [3,4].

The combination of these factors creates an extreme clinical vulnerability, making geriatric patients particularly prone to healthcare-associated infections [1,4,5].

Urinary tract infections (UTI) together with pneumonia, are among the most common nosocomial infections in hospitalized geriatric patients, contributing to high morbidity rates and mortality ranging from 0% to 33% [6–8]. Overall, UTI account for approximately 7 million hospital visits, 1 million emergency department visits, and 100.000 hospitalizations annually, representing about 25% of all infections in elderly individuals according to studies assessed in American region [9,10].

Moreover, they are one of the main reasons for prolonged hospital stays, leading to a significant impact on healthcare costs [11–13].

Gram-negative bacteria (GNB), including various species of Enterobacterales and, subsequently, non-fermenting GNB (NF-GNB), remain the primary causative agents of UTI, with a reported and concerning rise in multi-drug resistant (MDR) strains [14–18].

To date, while several studies have addressed the prevalence of UTI in such a fragile and unique clinical population, most were conducted during the early decades of the 2000s, with fewer studies available in recent years marked by the alarming global spread of MDR bacterial species [19–22].

In this study, we explored the epidemiological, microbiological, and clinical determinants of UTI caused by GNB in a cohort of hospitalized geriatric patients, identifying empirical and targeted therapeutic approaches as well as risk factors for mortality in the current era of antimicrobial resistance (AMR).

2. Material and methods

2.1. Study design and cohort enrolment

This study involved a retrospective analysis of observational data on elderly hospitalized patients with UTI caused by GNB between 1 January 2022 and 31 December 2023 in a large Academic Hospital in Siena, Italy. Patients eligible for study cohort enrolment met all the following criteria: (1) be admitted to one of the units between internal medicine, geriatrics or infectious diseases (a total of 74 beds with an overall patient load of approximately 2.330 per year), (2) age $\geq$70 y at hospital admission, (3) urine culture positive for GNB with a significant bacterial load ($\geq$100.000 colony-forming units/mL), along with clinical or laboratory findings suggestive of UTI, and (4) $\geq$72 h of hospital stay.

UTI was defined based on the presence of at least one of the following genitourinary symptoms: dysuria, urinary frequency or urgency, suprapubic pain, costovertebral angle tenderness, or gross hematuria. In catheterized or cognitively impaired patients, UTI diagnosis also included non-specific symptoms such as new-onset or worsening delirium, fever ($>$38°C), leukocytosis, and a dipstick test positive for leukocyte esterase and/or nitrite when other sources of infection were excluded.

Polymicrobial urine cultures and asymptomatic bacteriuria, with the latter defined as the urinary isolation of a significant bacterial load ($\geq$100.000 colony-forming units/mL) in the absence of symptoms suggestive of urinary or systemic infection, were excluded.

Enrolled patients' electronic medical records for the entire index hospitalization were consulted in order to extracting data on the patients' general characteristics, including age, sex, and comorbidities (including diabetes mellitus, chronic obstructive pulmonary disease, chronic renal failure, bedridden state, solid and haematological malignancies); length of hospital stay (total and as time at risk, i.e. days from hospital admission and the first posi-

tive urine culture collected); indwelling urethral catheter or central venous catheter, previous therapy with antibiotics, corticosteroids, chemotherapy and/or radiotherapy; previous MDR bacteria culture-positive surveillance rectal swabs; clinical, and microbiological features of the infection; characteristics of the antimicrobial treatment regimens; and case outcomes. Data collected and laboratory tests were entered on a case report form and recorded in a specific database.

2.2. Patient and infection profiles

The burden of patients' comorbidities was assessed in terms of individual conditions and Charlson Comorbidity Index (CCI) [23]. Illness severity at infection onset was classified based on the presentation as septic shock (i.e. sepsis associated with organ dysfunction and persistent hypotension despite volume replacement). Infections were considered healthcare-associated if the index culture was collected $>$48 h after hospital admission.

Catheter-associated UTI (CAUTI) was defined as a UTI that began in a patient with an indwelling urinary catheter for at least 2 d. Non-CAUTI were classified anatomically in upper-UTI (e.g. pyelonephritis and/or renal abscess) and lower-UTI (e.g. cystitis, prostatitis, and/or urethritis).

2.3. Microbiology

Urine samples were collected using sterile techniques according to the route of collection. For spontaneously voided samples, patients were instructed on midstream clean-catch collection after perineal cleansing. For catheterized patients, urine was aspirated aseptically from the sampling port of the indwelling catheter after disinfection with 70% isopropyl alcohol. Nephrostomy urine was collected by trained nurses directly from the nephrostomy tube using sterile containers. All samples were transported to the microbiology laboratory within 1 h of collection. If immediate transport was not possible, specimens were stored at 4°C and processed within a maximum of 4 h to prevent bacterial overgrowth or degradation. Standard operating procedures at our hospital ensure consistency in sample handling across wards.

Plates containing Columbia CNA agar with 5% sheep blood and MacConkey agar (bioMérieux, Marcy-l'Étoile, France) were inoculated with urine (10 μL per plate), incubated aerobically at 35°C and examined 24 h later for evidence of significant bacteriuria (i.e. $\geq$100.000 CFU/mL). MALDI Biotyper (Bruker Daltonik GmbH, Leipzig, Germany) was used to identify isolates. In vitro, antibiotic susceptibility testing (AST) was performed using a Phoenix M50 system (BD, Milan, Italy) or AST panels from MERLIN Diagnostika GmbH (Bornheim, Germany). Results were interpreted according to European Committee on Antimicrobial Susceptibility Testing clinical breakpoints [24]. Enterobacterales resistant only to penicillins and early (first- and second-) generation cephalosporins were supposed to be narrow-spectrum β-lactamases producers. The double-disk synergy test and the extended-spectrum β-lactamases (ESBL) 'Etest' were used to determine ESBL production. Carbapenemases detection was performed from grown colonies using lateral flow immunoassay approach (NG-Test CARBA 5 [NG Biotech, Guipry, France]; or by molecular methods (Xpert Carba-R assay [Cepheid, Sunnyvale, CA]).

Pseudomonas aeruginosa isolates were classified as MDR if they exhibited non-susceptibility to at least one antibiotic from a minimum of three different classes of antipseudomonal agents.

2.4. Treatment and outcomes

Empiric antibiotic therapy was defined as that started at the suspicion of UTI before the acquisition of microbial data and tar-

get therapy as that initiated based on microbiological isolation and AST. The empirical therapy was classified as inappropriate if antibiogram demonstrated resistance of isolates to the administered antimicrobial(s).

Data were collected for the duration of the index hospitalization.

The primary outcome was all-cause mortality 14 d after infection onset. Secondary outcomes included the appropriateness of empirical antimicrobial prescriptions, UTI recurrences during the hospital stay, antibiotic treatment failure (defined as the persistence or worsening of UTI symptoms requiring either a modification of the initial antibiotic regimen or a new course of antibiotic therapy within 14 d of treatment initiation), and the epidemiological analysis of GNB causing UTI in elderly hospitalized patients, including the report of AMR mechanisms.

2.5. Statistical analysis

Results are expressed as means ± standard deviations or medians and interquartile ranges (IQR) (continuous variables) or as percentages of the group from which they were derived (categorical variables). The Student t test and Mann–Whitney U test were used to compare normally and non-normally distributed continuous variables, respectively. Categorical variables were evaluated with the chi-square or two-tailed Fisher exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all associations emerged. Two-tailed tests were used to determine statistical significance reflected by a P-value <0.05. Multiple Cox regression models were performed to ascertain risk factors independently associated with 14-d mortality and logistic regression were used to investigate risk factors independently associated with treatment failure. To ensure the validity of Cox regression model, we assessed collinearity using variance inflation factors, which were all around 1, indicating no significant multicollinearity. We also tested the proportional hazards assumption using the Schoenfeld residuals test. The global test P-value was 0.11, with all individual covariate P-values >0.05, suggesting no violation of proportionality. Schoenfeld residual plots were also examined to confirm these findings. To account for potential overfitting and enhance multiple regression models robustness given the limited number of events, penalized logistic regression with LASSO regularization was applied. Bootstrap resampling ($n = 1000$ iterations) was used to derive adjusted hazard and odds radio corresponding CIs. The Kaplan–Meier method was used for survival analysis.

A post-hoc power analysis was performed to assess whether the study was adequately powered. The analysis focused on the variable with the lowest OR, considering an alpha level of 0.05 and the reported sample size (i.e. 171 patients). The resulting power was 0.91, confirming that our study had sufficient statistical power to detect significant associations.

All statistical analyses were performed with the IBM SPSS Statistics 25 and R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

As illustrated in Fig. 1, of 796 patients hospitalized in the selected wards during the study period, 171 were included in the final analysis.

Table 1 summarizes clinical and demographic characteristics of the patients, infection features, treatment strategies, and outcomes.

Of the 171 patients, just over half were females (96/171, 56.1%), with a median age of 82 y (IQR 72–86). The most common comor-

bidities were cardiovascular diseases (135/171; 78.9%), neurocognitive impairment (72/171, 42.1%), malignancies both solid (45/171, 26.3%) and haematological (15/171, 8.8%), and diabetes mellitus (48/171, 28.1%). The median of Charlson Comorbidities Index score was 6 (IQR 4–7).

A total of 158 out of 171 patients (92.4%) presented underlying urological conditions such as benign prostatic hyperplasia (29/171, 17.0%), urinary tract anomalies (24/171, 14.0%), urolithiasis (10/171, 5.8%), previous UTI (9/171, 5.3%) and neurogenic bladder (1/171, 0.6%).

Just under half of the patients (73/171, 42.7%) had been previously hospitalized, and the prevalence of a previous positive rectal swab for carbapenem-resistant Enterobacterales was 10.5% (18/171). Twenty-seven out of 171 patients (15.8%) were admitted from long-term care facilities, and more than two-thirds had an indwelling urinary catheter (132/171, 77.2%).

In the 90 d before the onset of UTI, 41.5% of patients (71/171) had been exposed to antibiotic therapy, predominantly with beta-lactams.

3.2. Characteristics of infections and microbiology

More than half of the patients (106/171, 62.0%) had CAUTI. Among non-CAUTI cases, lower-UTI were the most frequent (50/65, 76.9%). Most infections were healthcare-associated (105/171, 61.4%) and 15/171 (8.8%) were associated with concomitant bacteraemia. Of these, three cases progressed to septic shock.

As shown in Table 2, the most frequent etiological agents of UTI were Enterobacterales (134/171, 78.4%), predominantly *Escherichia coli* (74/171, 43.3%), and *Klebsiella* spp. (39/171, 22.8%). Just under a third of UTI (37/171, 21.6%) were caused by NF-GNB, mostly *P. aeruginosa* (33/171, 19.3%).

Fig. 2 reports cumulative AMR and susceptibility percentages for the most frequently isolated Gram-negative strains, as well as beta-lactamases production rates for Enterobacterales.

Enterobacterales were susceptible to all classes of antibiotics in 29.1% of cases (39/134). A resistance rate of 40.3% (54/134) to third-generation cephalosporins (3GC), 35.1% (47/134) to fourth-generation cephalosporins (4GC), 16.4% (22/134) to ceftolozane/tazobactam, and 14.9% (20/134) to piperacillin/tazobactam was observed. Resistance amounted to 8.2% (11/134) for ertapenem and 5.2% (7/134) for both meropenem and ceftazidime/avibactam. Resistance to fluoroquinolones reached 39.1% (52/134), and 44.8% (60/134) for cotrimoxazole. The most commonly detected resistance mechanism was ESBL production (35.1%, 47/134).

While antimicrobial susceptibility rates in *E. coli* largely reflected those observed across Enterobacterales, significant variations were noted in strains of the *Klebsiella* genus.

Regarding *Klebsiella* spp., resistance rate amounted to 51.3% (20/39) for 3GC and 4GC, 33.3% (13/39) to ceftolozane/tazobactam, and 28.2% (11/39) to piperacillin/tazobactam. Resistance rate was 20.5% (8/39) to ertapenem, 18.0% (7/39) to meropenem, and 12.8% (5/39) to ceftazidime/avibactam. The most represented resistance mechanism was ESBL production (46.2%, 18/39) followed by production of *Klebsiella pneumoniae* carbapenemase (10.3%, 4/39) and New Delhi metallo-β-lactamase (NDM) (7.7%, 3/39) carbapenemases.

Regarding *P. aeruginosa* cumulative resistance rates were 39.4% (13/33) to cephalosporins and piperacillin/tazobactam, 27.3% (9/33) to fluoroquinolones, 15.1% (5/33) to carbapenems, 12.2% (4/33) to ceftazidime/avibactam and 6.1% (2/33) to ceftolozane/tazobactam and amikacin. More than half (60.6%, 20/33) *P. aeruginosa* strains showed an MDR phenotype.
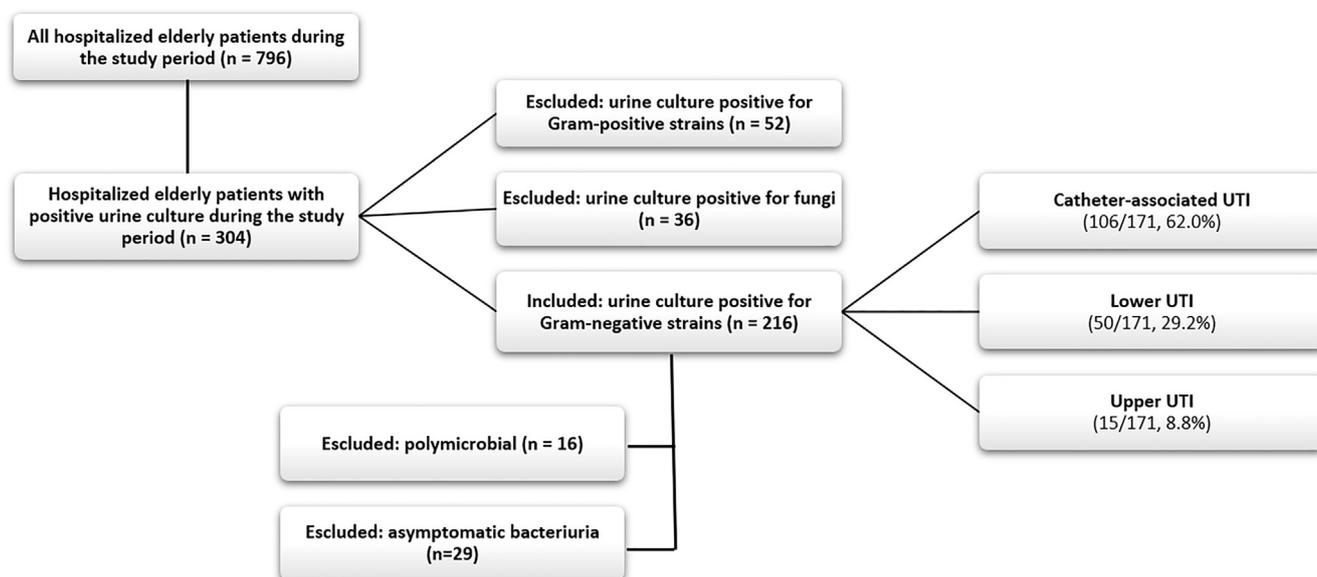
Fig. 1. Flowchart showing cohort enrolment. UTI, urinary tract infections.

Fig. 2. Cumulative antimicrobial resistance and susceptibility percentages of the most frequently isolated Gram-negative strains. Percentages are reported in black for resistance and in greys for susceptibility. On the right, beta-lactamase production rates are reported. 3GC, third-generation cephalosporins; 4GC, fourth-generation cephalosporins; AMK, amikacin; AMX/CL, amoxicillin/clavulanate; CAZ/AVI, ceftazidime/avibactam; ESBL, extended-spectrum beta-lactamase; FQ, fluoroquinolones; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug-resistant; NarrowSBL, narrow-spectrum beta-lactamase; NDM, New Delhi metallo beta-lactamase; PIP/TAZ, piperacillin/tazobactam; TMP/SMX, trimethoprim/sulfamethoxazole; TOL/TAZ, ceftolozane/tazobactam. *All isolates were tested against all listed antibiotics.

Table 1
Characteristics and outcomes of elderly hospitalized patients with urinary tract infections caused by Gram-negative bacteria.

Variables	All infections ($n = 171$)	Non-MDR-GNB ($n = 54$)	MDR-GNB ($n = 117$)	P-value
Patient characteristics				
Males	75 (43.9)	19 (35.2)	56 (47.9)	0.120
Age – median [IQR]	82 [72–86]	82 [74–88]	81 [71–86]	0.196
Length of stay – median [IQR]	15 [10–23]	12.5 [9–22]	18 [12–24]	**0.017**
Time at risk – median [IQR]	3 [1–8]	2 [1–6]	3 [1–10]	0.758
Comorbidities				
COPD	32 (18.7)	10 (18.5)	22 (18.8)	0.965
Cardiovascular disease	135 (78.9)	42 (77.8)	93 (79.5)	0.799
Neurological disease	28 (16.4)	7 (13.0)	21 (17.9)	0.413
Neurocognitive impairment	72 (42.1)	24 (44.4)	48 (41.0)	0.674
Liver disease	14 (8.2)	2 (3.7)	12 (10.3)	0.146
Chronic renal failure	33 (19.3)	7 (13.0)	26 (22.2)	0.154
Diabetes mellitus	48 (28.1)	17 (31.5)	31 (26.5)	0.500
Bedridden state	24 (14.0)	5 (9.3)	19 (16.2)	0.222
Solid cancer	45 (26.3)	12 (22.2)	33 (28.2)	0.409
Haematological malignancy	15 (8.8)	5 (9.3)	10 (8.5)	0.878
Benign prostatic hyperplasia	29 (17.0)	6 (11.1)	23 (19.7)	0.186
Neurogenic bladder	1 (0.6)	1 (1.9)	0	0.140
Urolithiasis	10 (5.8)	0	10 (8.5)	**0.027**
Urinary tract anomalies	24 (14.0)	8 (14.8)	16 (13.7)	0.842
Previous UTI	9 (5.3)	6 (11.1)	3 (2.6)	**0.020**
CCI – median [IQR]	6 [4–7]	6 [4–7]	6 [5–7]	1
Pre-infection healthcare interventions				
Previous hospital admission[a]	73 (42.7)	15 (27.8)	58 (49.6)	**0.011**
Previous ICU admission[a]	9 (5.3)	5 (9.3)	4 (3.4)	0.112
Previous UTI episode[a]	22 (12.9)	5 (9.3)	17 (14.5)	0.339
Previous bacterial infection[a]	25 (14.6)	6 (11.1)	19 (16.2)	0.378
Previous surgery[a]	10 (5.8)	2 (3.7)	8 (6.8)	0.417
Admitted from LTFs	27 (15.8)	4 (7.4)	23 (19.7)	**0.041**
Endoscopy[b]	13 (7.6)	6 (11.1)	7 (6.0)	0.240
Indwelling devices[b]				
Central venous catheter	19 (11.1)	7 (13.0)	12 (10.3)	0.601
Bladder catheter	132 (77.2)	47 (87.0)	85 (72.6)	**0.037**
Nephrostomy	8 (4.7)	0	8 (6.8)	**0.049**
Ureteral stent	3 (1.8)	0	3 (2.6)	0.235
Steroid therapy	14 (8.2)	2 (3.7)	12 (10.3)	0.146
Chemotherapy	10 (5.8)	3 (5.6)	7 (6.0)	0.912
Previous antibiotic therapy[c]	71 (41.5)	15 (27.8)	56 (47.9)	**0.013**
With cephalosporins	28 (16.4)	5 (9.3)	23 (19.7)	0.088
With penicillins ± BLI	26 (15.2)	6 (11.1)	20 (17.1)	0.311
With carbapenems	15 (8.8)	5 (9.3)	10 (8.5)	0.878
With cotrimoxazole	12 (7.0)	2 (3.7)	10 (8.5)	0.249
With fluoroquinolones	3 (1.8)	0	3 (2.6)	0.235
Previous positive rectal swab	18 (10.5)	2 (3.7)	16 (13.7)	**0.048**
KPC	9 (5.3)	1 (1.9)	8 (6.8)	0.175
VIM	6 (3.5)	1 (1.9)	5 (4.3)	0.424
NDM	3 (1.8)	0	3 (2.6)	0.235
Infection characteristics				
Catheter-associated UTI	106 (62.0)	41 (75.9)	65 (55.6)	**0.011**
Lower UTI	50 (29.2)	10 (18.5)	40 (34.2)	**0.040**
Upper UTI	15 (8.8)	3 (5.6)	12 (10.3)	0.310
Healthcare-associated	105 (61.4)	27 (50.0)	78 (66.7)	**0.037**
Concomitant bacteraemia	15 (8.8)	3 (5.6)	12 (10.3)	0.312
Septic shock	3 (1.8)	1 (1.9)	2 (1.7)	0.947
Treatment characteristics				
Days of treatment – *median (IQR)*	9 [4–12]	10 [5–12]	9 [4–13]	0.870
Empirical therapy	101 (59.1)	35 (64.8)	66 (56.4)	0.299
Inadequate empirical therapy	41 (24.0)	5 (9.3)	36 (30.8)	**0.002**
Targeted monotherapy regimen	157 (91.8)	48 (88.9)	109 (93.2)	0.340
Infectious diseases consultation	24 (14.0)	6 (11.1)	18 (15.4)	0.455
Outcomes				
All-cause 14-d mortality	22 (12.9)	9 (16.7)	13 (11.1)	0.312
Treatment failure	39 (22.8)	10 (18.5)	29 (24.8)	0.364
Infection relapse	4 (2.3)	0	4 (3.4)	0.169

Statistically significant P-values ($P < 0.05$) are shown in bold.
Unless otherwise stated, data are expressed as numbers (%).
BLI, beta-lactamases inhibitors; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; LTFs long-term care facilities; MDR-GNB, multidrug-resistant Gram-negative bacteria; NDM, New Delhi metallo-β-lactamase; UTI, urinary tract infections; VIM, Verona integron-encoded metallo-β-lactamase.

[a] During the 360 d preceding infection onset.
[b] During the 30 d preceding infection onset.
[c] During the 90 d preceding infection onset.

Table 2
Aetiology of urinary tract infections.

Variables	All infections (n = 171)	CAUTI (n = 106)	Non-CAUTI (n = 65)	P-value	Lower UTI (n = 50)	Upper UTI (n = 15)	P-value
Cultural Identification							
Enterobacterales	134 (78.4)	78 (73.6)	56 (86.2)	0.053	43 (86.0)	13 (86.7)	0.948
Escherichia coli	74 (43.3)	42 (39.6)	32 (49.2)	0.218	23 (46.0)	9 (60.0)	0.341
Klebsiella spp.	39 (22.8)	23 (21.7)	16 (24.6)	0.659	12 (24.0)	4 (26.7)	0.833
Klebsiella pneumoniae	35 (20.5)	21 (19.8)	14 (21.5)	0.786	10 (20.0)	4 (26.7)	0.582
Klebsiella oxytoca	3 (1.8)	2 (1.9)	1 (1.5)	0.866	1 (2.0)	0	1
Klebsiella aerogenes	1 (0.6)	0	1 (1.5)	0.380	1 (2.0)	0	1
Proteus spp.	12 (7.0)	8 (7.5)	4 (6.2)	0.729	4 (8.0)	0	0.258
Proteus mirabilis	10 (5.8)	7 (6.8)	3 (4.6)	0.591	3 (6.0)	0	0.331
Proteus vulgaris	2 (1.2)	1 (0.9)	1 (1.5)	0.725	1 (2.0)	0	1
Enterobacter cloacae	2 (1.2)	1 (0.9)	1 (1.5)	0.725	1 (2.0)	0	1
Morganella morganii	3 (1.8)	1 (0.9)	2 (3.1)	0.302	2 (4.0)	0	1
Providencia stuartii	2 (1.2)	2 (1.9)	0	0.265	0	0	–
Serratia marcescens	2 (1.2)	1 (0.9)	1 (1.5)	0.725	1 (2.0)	0	1
Non-fermenting Gram-negative bacilli	37 (21.6)	28 (26.4)	9 (13.8)	0.053	7 (14.0)	2 (13.3)	0.948
Pseudomonas aeruginosa	33 (19.3)	25 (23.6)	8 (12.3)	0.070	6 (12.0)	2 (13.3)	0.890
Acinetobacter baumannii	2 (1.2)	1 (0.9)	1 (1.5)	1	1 (2.0)	0	1
Stenotrophomonas maltophilia	1 (0.6)	1 (0.9)	0	0.432	0	0	–
Alcaligenes xylosoxidans	1 (0.6)	1 (0.9)	0	0.432	0	0	–

Statistically significant *P*-values (*P* < 0.05) are shown in bold.
CAUTI, catheter-associated urinary tract infections; UTI, urinary tract infections.

3.3. Risk factors for MDR-GNB UTI

Grouping the cohort based on whether an MDR species was isolated, it emerged that patients harbouring MDR-GNB were more frequently hospitalized for longer time (median hospital stay: 18 vs. 12.5 d, $P = 0.017$). They were also more likely to suffer from urolithiasis (8.5% vs. 0%, $P = 0.027$), to have had previous hospital admissions (49.6% vs. 27.8%, $P = 0.011$), or to have a nephrostomy (6.8% vs. 0%, $P = 0.049$). Furthermore, these patients were more frequently exposed to prior antibiotic therapy (47.9% vs. 27.8%, $P = 0.013$), had a previous positive rectal swab (13.7% vs. 3.7%, $P = 0.048$), had healthcare-associated UTI (66.7% vs. 50.0%, $P = 0.037$), and received an inappropriate empirical therapy (30.8% vs. 9.3%, $P = 0.002$).

Non-MDR-GNB were mostly isolated from patients who had indwelling bladder catheter currently or in the previous 30 d (87% vs. 72.6%, $P = 0.037$) and a CAUTI (75.9% vs. 55.6%, $P = 0.011$).

3.4. Treatment characteristics and regimens

As shown in Table 1, the median duration of antibiotic therapy for UTI was 9 d (IQR 4–12 d). Empirical therapy was initiated at the onset of suspected UTI in 101/171 (59.1%) patients. In nearly a quarter of cases, empirical therapy proved to be inappropriate (41/171, 24.0%).

Over 90% (157/171) of all infections were managed with a targeted monotherapy regimen.

Fig. 3 illustrates the therapeutic approaches employed for UTI treatment.

Piperacillin/tazobactam was the most prescribed antibiotic both as empirical and targeted therapy (20% and 26%, respectively), followed by ceftriaxone chosen as empirical therapy in 19% of cases and as targeted in 15%. Meropenem ranked third among targeted therapies (14%), while its use in empirical therapy was limited to 4% of cases.

3.5. Outcomes

Fourteen days after onset of infection, 22/171 (12.9%) patients had died. Among patients with CAUTI, the mortality rate was 17.0% (18/106), and 14.3% (15/105) in those with healthcare-associated UTI. All patients presenting with septic shock at infection onset died.

Mortality rates were 16.7% (9/54) in patients with non-MDR-GNB UTI and 11.1% (13/117) in those with MDR-GNB UTI.

The 14-d mortality rate was 13.5% (5/37) for patients with UTI caused by NF-GNB and 12.7% (17/134) for those caused by Enterobacterales. All the patients who died with UTI caused by NF-GNB had urine culture positive for *P. aeruginosa*. Among Enterobacterales-related UTI, mortality was higher in infections caused by *K. pneumoniae* (6/35, 17.1%) compared to those caused by *E. coli* (8/74, 10.8%). All the two patients with UTI due to *Providencia stuartii* and the three patients with UTI due to NDM-*K. pneumoniae* died, though one of the latter at the 18th d of infection onset.

Mortality among patients who received inappropriate empirical antibiotic therapy reached 29.3% (12/41).

Four patients experienced UTI recurrence within a median of 22 d [IQR 21–28]. All four patients were male, suffering from benign prostatic hypertrophy resulting in chronic renal failure, and three of them were affected by urolithiasis. All four relapses were caused by ESBL-producing *E. coli*.

3.6. Predictors of mortality in elderly hospitalized patients with UTI

In the univariable analysis (Table 3), patients who died within 14 d of infection onset were more likely to have been admitted from long-term care facilities and tended to have previous infections caused by carbapenem-resistant strains, prior exposure to cephalosporins, previous positive rectal swab, CAUTI, UTI with concomitant bacteraemia, UTI caused by *P. stuartii* or NDM-producing *K. pneumoniae*. Mortality was also associated with septic shock at infection onset and with inadequate initial antibiotic therapy.

Non-infection-related factors, such as cardiovascular or neurological diseases, malignancies, bedridden state, and the overall burden of comorbidities (assessed by the CCI), did not show associations with 14-d mortality.

In the multivariable analysis (Table 4), 14-d mortality was independently associated with septic shock at infection onset, inadequate initial antibiotic therapy, and UTI caused by *P. stuartii* or NDM-producing *K. pneumoniae*, with the last of these not retained by penalized regression.

Table 3
Univariable analysis of factors associated with 14-d mortality.

Variable	No. (%) of patients		P-value	OR (95% CI)
	Non-survivors n = 22	Survivors n = 149		
Patient characteristics				
Males	8 (36.4)	67 (45.0)	0.448	1.37 (0.61–3.09)
Age – median [IQR]	83 [73–90]	81.5 [72–86]	0.580	–
Length of stay – median [IQR]	11 [9–23]	16.5 [10–24]	0.071	–
Time at risk – median [IQR]	4 [1–12]	3 [1–7]	0.467	–
Comorbidities				
COPD	3 (13.6)	29 (19.5)	0.513	1.46 (0.46–4.63)
Cardiovascular disease	15 (68.2)	120 (80.5)	0.185	1.75 (0.77–3.97)
Neurological disease	3 (13.6)	25 (16.8)	0.710	1.24 (0.39–3.91)
Dementia	10 (45.5)	62 (41.6)	0.733	0.87 (0.40–1.91)
Liver disease	2 (9.1)	12 (8.1)	0.869	0.89 (0.23–3.43)
Chronic renal failure	3 (13.6)	30 (20.1)	0.471	1.51 (0.78–4.82)
Diabetes mellitus	7 (31.8)	41 (27.5)	0.675	0.84 (0.39–1.92)
Bedridden state	2 (9.1)	22 (14.8)	0.474	1.63 (0.41–6.54)
Solid cancer	7 (31.8)	38 (25.5)	0.530	0.77 (0.33–1.76)
Haematological malignancy	1 (4.5)	14 (9.4)	0.453	2.02 (0.29–13.98)
Benign prostatic hyperplasia	2 (9.1)	27 (18.1)	0.292	2.04 (0.51–8.26)
Neurogenic bladder	0	1 (0.7)	0.700	0.87 (0.82–0.92)
Urolithiasis	0	10 (6.7)	0.210	0.86 (0.81–0.92)
Urinary tract anomalies	2 (9.1)	22 (14.8)	0.474	1.63 (0.41–6.54)
Recurrent UTIs	1 (4.5)	8 (5.4)	0.872	1.17 (0.18–7.73)
CCI – median [IQR]	6 [5–7]	6 [4–7]	0.533	–
Pre-infection healthcare interventions				
Previous hospital admission[a]	10 (45.5)	65 (43.6)	0.872	0.83 (0.43–2.05)
Previous ICU admission[a]	0	9 (6.0)	0.236	0.87 (0.81–0.92)
Previous UTI episode[a]	1 (4.5)	21 (14.1)	0.212	3.10 (0.44–21.91)
Previous bacterial infection[a]	5 (22.7)	20 (13.4)	0.249	0.58 (0.24–1.44)
By carbapenem-resistant strains	2 (9.1)	0	**<0.001**	0.12 (0.08–0.18)
Previous surgery[a]	0	10 (6.7)	0.210	0.87 (0.81–0.92)
Admitted from LTFs	7 (31.8)	20 (13.4)	**0.027**	0.40 (0.18–0.90)
Endoscopy[b]	1 (4.5)	12 (8.1)	0.562	1.73 (0.25–11.84)
Indwelling devices[b]				
Central venous catheter	5 (22.7)	14 (9.4)	0.063	0.43 (0.18–1.02)
Bladder catheter	19 (86.4)	113 (75.8)	0.272	0.53 (0.17–1.71)
Nephrostomy	1 (4.5)	7 (4.7)	0.975	1.03 (0.16–6.73)
Ureteral stent	0	3 (2.0)	0.502	0.87 (0.82–0.92)
Steroid therapy	3 (13.6)	11 (7.4)	0.318	0.57 (0.19–1.68)
Chemotherapy	0	10 (6.7)	0.210	0.87 (0.81–0.92)
Previous antibiotic therapy[c]	13 (59.1)	58 (38.9)	0.073	0.49 (0.22–1.09)
With cephalosporins	7 (31.8)	21 (14.1)	**0.036**	0.42 (0.19–0.93)
With penicillins ± BLI	2 (9.1)	24 (16.1)	0.392	1.79 (0.45–7.22)
With carbapenems	1 (4.5)	14 (9.4)	0.453	2.02 (0.29–13.98)
With cotrimoxazole	0	12 (8.1)	0.167	0.86 (0.81–0.92)
With fluoroquinolones	0	3 (2.0)	0.500	0.87 (0.82–0.92)
Others	3 (13.6)	13 (8.7)	0.463	1.56 (0.48–5.05)
Positive rectal swab	5 (22.7)	13 (8.7)	**0.046**	0.40 (0.17–0.95)
KPC	2 (9.1)	7 (4.7)	0.389	0.56 (0.15–2.02)
VIM	1 (4.5)	5 (3.4)	0.777	0.77 (0.12–4.78)
NDM	2 (9.1)	1 (0.7)	**0.005**	0.18 (0.07–0.44)
Infection characteristics				
Catheter-associated UTI	18 (81.8)	88 (59.1)	**0.040**	0.36 (0.13–1.02)
Lower UTI	3 (13.6)	47 (31.5)	0.085	2.62 (0.81–8.45)
Upper UTI	1 (4.5)	14 (9.4)	0.453	2.02 (0.30–13.98)
Healthcare-associated	15 (68.2)	90 (60.4)	0.482	0.74 (0.32–1.72)
Concomitant bacteremia	5 (22.7)	10 (6.7)	**0.013**	0.33 (0.93–1.92)
Septic shock	3 (13.6)	0	**<0.001**	0.11 (0.07–0.17)
Enterobacterales	17 (77.3)	117 (78.5)	0.894	1.09 (0.42–2.70)
Escherichia coli	8 (36.4)	66 (44.3)	0.483	1.34 (0.59–3.01)
Klebsiella spp.	6 (27.3)	33 (22.1)	0.593	0.79 (0.33–1.88)
Klebsiella pneumoniae	6 (27.3)	29 (19.5)	0.397	0.69 (0.29–1.62)
Klebsiella oxytoca	0	3 (2.0)	0.502	0.87 (0.82–0.92)
Klebsiella aerogenes	0	1 (0.7)	0.700	0.87 (0.82–0.92)
Proteus spp.	1 (4.5)	11 (7.4)	0.627	1.59 (0.23–10.79)
Proteus mirabilis	1 (4.5)	9 (6.0)	0.780	1.30 (0.20–8.74)
Proteus vulgaris	0	2 (1.3)	0.585	0.87 (0.82–0.92)
Enterobacter cloacae	0	2 (1.3)	0.585	0.87 (0.82–0.92)
Morganella morganii	0	3 (2.0)	0.502	0.87 (0.82–0.92)
Providencia stuartii	2 (9.1)	0	**0.016**	0.12 (0.08–0.18)
Serratia marcescens	0	2 (1.3)	0.585	0.87 (0.82–0.92)
ESBL	5 (22.7)	42 (28.2)	0.592	1.29 (0.50–3.30)
KPC	1 (4.5)	4 (2.7)	0.502	0.63 (0.11–3.82)
VIM	0	3 (2.0)	0.502	0.87 (0.82–0.92)
NDM	2 (9.1)	1 (0.7)	**0.044**	0.18 (0.07–0.43)

Table 3 (*continued*)

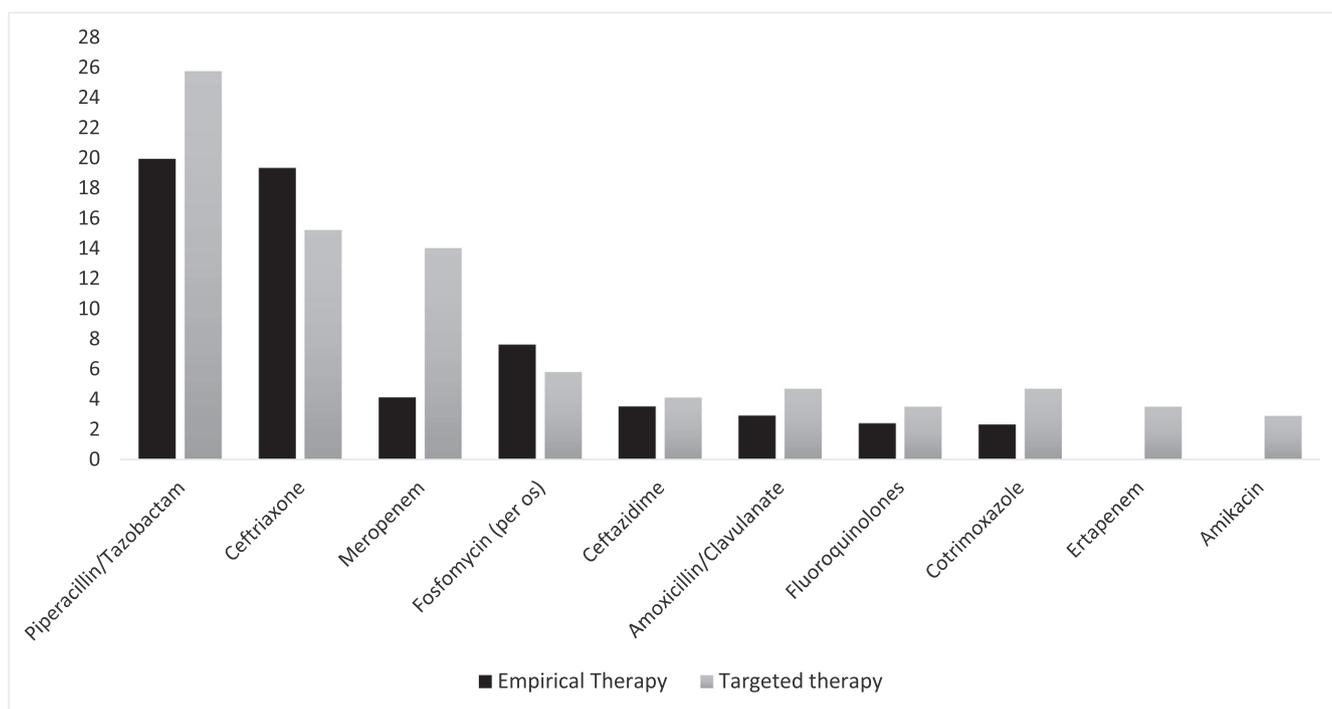|	No. (%) of patients		*P*-value	OR (95% CI)
Variable	Non-survivors *n* = 22	Survivors *n* = 149		
Non-fermenting Gram-negative bacilli	5 (22.7)	32 (21.5)	0.894	0.94 (0.37–2.38)
Pseudomonas aeruginosa	5 (22.7)	28 (18.8)	0.662	0.81 (0.32–2.04)
Acinetobacter baumannii	0	2 (1.3)	0.585	0.87 (0.82–0.92)
Stenotrophomonas maltophilia	0	1 (0.7)	0.700	0.87 (0.82–0.92)
Alcaligenes xylosoxidans	0	1 (0.7)	0.700	0.87 (0.82–0.92)
Treatment characteristics				
Days of treatment – *median (IQR)*	8 [2–9]	10 [5–13]	**0.015**	–
Inadequate empirical therapy	12 (54.5)	29 (19.5)	**<0.001**	0.26 (0.12–0.58)
Targeted monotherapy regimen	20 (90.9)	137 (91.9)	0.870	1.21 (0.29–4.31)

Data are expressed as numbers (%) unless otherwise stated.

BLI, beta-lactamases inhibitors; CCI, Charlson Comorbidity Index; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; ESBL, extended-spectrum β-lactamases; ICU, intensive care unit; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; LTFs long-term care facilities; NDM, New Delhi metallo-β-lactamase; OR, odds ratio; UTI, urinary tract infections; VIM, Verona integron-encoded metallo-β-lactamase.

[a] During the 360 d preceding infection onset.
[b] During the 30 d preceding infection onset.
[c] During the 90 d preceding infection onset.

Fig. 3. Most used antibiotics for both empirical and targeted therapy of urinary tract infections. Values are expressed as percentages.

Table 4

Cox regression analysis for 14-d mortality in 171 elderly hospitalized patients with urinary tract infections due to Gram-negative bacteria.

Variables	*P*-value	HR (95% CI)	aHR (95% CI)
Septic shock at infection onset	<0.001	36.82 (9.06–149.71)	10.94 (1.00–37.07)
Providencia stuartii	<0.001	22.00 (4.48–108.01)	2.99 (1.00–11.49)
NDM-producing *Klebsiella pneumoniae*	0.003	10.19 (2.23–46.55)	– (1.00–8.52)
Inadequate empirical antimicrobial therapy	0.001	4.87 (1.94–12.22)	1.32 (1.00–3.44)

Adjusted hazard ratios (aHR) obtained from LASSO penalization and corresponding 95% bootstrap confidence intervals are also reported.

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; NDM, New Delhi metallo-β-lactamase.

3.7. Predictors of antibiotic treatment failure in elderly hospitalized patients with UTI

Table 5 reports the univariable and multivariable logistic regression analyses for antibiotic treatment failure. In the univariable analysis, the presence of carbapenem-resistant GNB, inadequate empirical antimicrobial therapy, previous treatment with cephalosporins, infection by *P. stuartii* or NDM-producing *K. pneumoniae*, septic shock at infection onset, were all associated with treatment failure while infection by *E. coli* was associated with decreased odds of treatment failure.

Table 5

Univariable and multivariable analysis (standard and LASSO penalized) for treatment failure in 171 elderly hospitalized patients with urinary tract infections due to Gram-negative bacteria.

Variables	Univariable analysis		Multivariable analysis		
	P-value	OR (95% CI)	*P*-value	OR (95% CI)	aOR (95% CI)
Carbapenem-resistant Gram-negative bacteria	<0.001	7.24 (2.44–21.53)	0.001	7.11 (2.20–22.94)	6.73 (2.61–20.27)
Inadequate empirical antimicrobial therapy	<0.001	4.05 (1.87–8.81)	0.002	3.85 (1.67–8.90)	3.60 (1.65–8.78)
Previous treatment with cephalosporins	0.001	3.90 (1.66–9.18)	0.003	3.01 (1.18–7.71)	2.94 (1.00–7.53)
Providencia stuartii	0.009	17.67 (0.83–375.30)			
NDM-producing *Klebsiella pneumoniae*	0.001	25.41 (1.28–502.60)			
Septic shock at infection onset	0.001	25.41 (1.28–502.60)			
Escherichia coli	0.004	0.31 (0.14–0.70)			

aOR, adjusted odds ratio; CI, confidence interval; NDM, New Delhi metallo-β-lactamase; OR, odds ratio.

In the multivariable analysis, carbapenem-resistant GNB, inadequate empirical therapy, and previous treatment with cephalosporins remained independently associated with treatment failure.

The penalized regression confirmed the predictors identified in the standard multivariable model, except for the upper bound of the CI for previous treatment with cephalosporins, which was slightly lower.

4. Discussion

This non-interventional medical chart review on epidemiological features, microbiological characteristics, and treatment patterns of UTI in elderly hospitalized patients takes into account an epidemiological context different from that of previous decades due to a greater spread of MDR bacterial species.

Despite the inherent limitations of retrospective studies, our findings highlight the significant impact of UTI on clinical outcomes in this population [25–27], with a 14-d mortality rate of 12.9%, exceeding previous reports [28,29] but aligning with recent data from regions with high endemicity of MDR organisms (MDROs) [30].

In a Spanish cohort of patients with UTI enrolled in 2015 and comparable to ours in age, Artero et al. [31] reported a mortality rate of 9.3%. The higher rate observed in our study could be attributed to the greater prevalence of MDR bacterial species. The aforementioned study reported lower rates of ESBL-producing *E. coli* (20% vs. 34%) and less frequent isolation of *K. pneumoniae* (10.0% vs. 22.2%) and *P. aeruginosa* (8.7% vs. 20.5%), pathogens notoriously more difficult to treat.

Furthermore, according to the European Antimicrobial Resistance Surveillance Network (EARS-Net) data reported by the European Centre for Disease Prevention and Control (ECDC) [32], the carbapenem resistance rate of *K. pneumoniae* in Spain in 2015 was 1%–5%, approximately half the rate observed in our cohort. In contrast, the 17.6% mortality reported by Ioannou et al. [19] in a similar high MDR-GNB endemicity setting aligns with our findings. These results are consistent with World Health Organization projections, which predicted a rising mortality from infections caused by MDR organisms in the coming years.

Microbiological findings shown in Fig. 2 reveal high rates of AMR, particularly among *K. pneumoniae* isolates. Resistance to carbapenems was observed in 38.5% of cases, increasing to 51.3% when combined with resistance to ceftazidime/avibactam. Similarly, *P. aeruginosa* exhibited an MDR phenotype in 60.6% of isolates. When these data are considered alongside treatment prescription patterns reported in Fig. 3, a clear therapeutic gap emerges. The presence of carbapenemase-producing strains, along with other resistance mechanisms that impair the activity of newer agents such as ceftazidime/avibactam, further restricts the available therapeutic arsenal,

Managing UTI is increasingly challenging, requiring a balance between avoiding overtreatment, minimizing adverse effects of antimicrobials, and preserving reserve antibiotics, while addressing the risks of inadequate therapy in the era of AMR.

Evidence suggests that delayed or inadequate treatment worsens outcomes. Gharbi et al. [33] found that a conservative 'wait-and-see' approach in elderly patients doubled the mortality risk compared to immediate antibiotic therapy.

Similarly, Esparcia et al. [34] reported a significant association between initial inappropriate treatment and increased mortality (OR 3.47; 95% CI, 1.42–8.48).
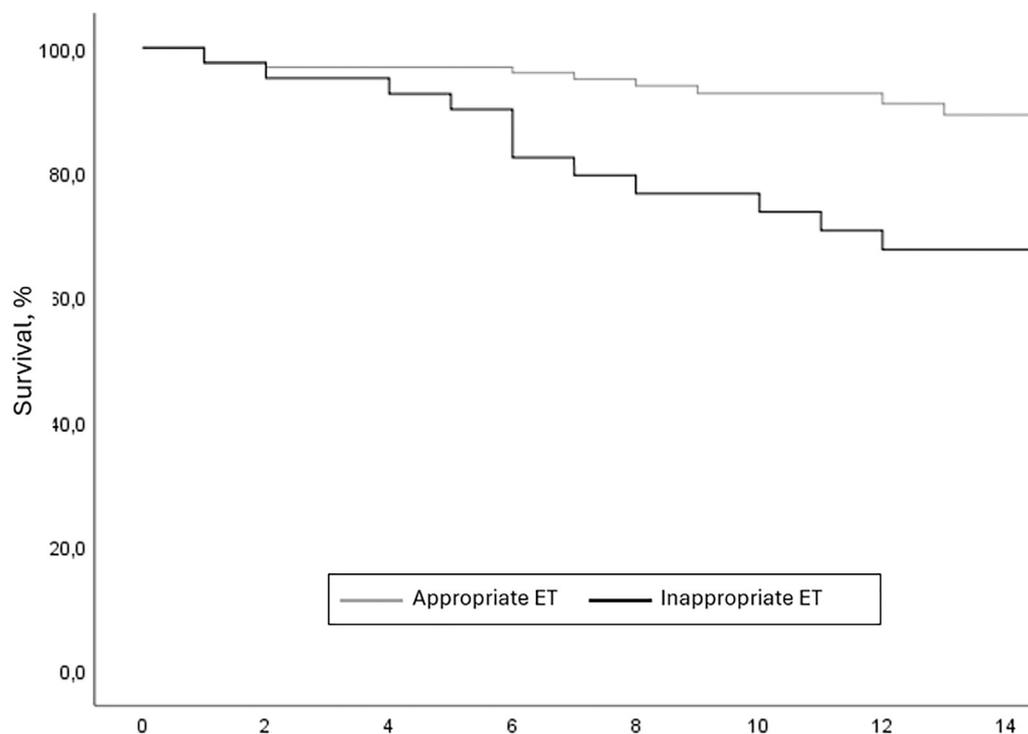
In our cohort, nearly one-third of patients with MDR-GNB UTI received inadequate empirical therapy, significantly reducing their survival probability, as shown by the Kaplan–Meier curves in Fig. 4 (*P* = 0.001).

As early as 2016, Cardwell et al. [35] emphasized the need to consider ESBL- and AmpC-producing GNB when selecting empirical antibiotic therapy for UTI. They reported a higher rate of inappropriate empirical therapy in patients with MDR-GNB infections, resulting in prolonged hospital stays and increased healthcare costs. Compared to the prior decade, the current landscape requires addressing additional resistance mechanisms, including *K. pneumoniae* carbapenemase and metallo-β-lactamases production. Shields et al. [36] demonstrated that UTI caused by carbapenem-resistant Enterobacterales are not only more prevalent in the elderly but also linked to higher risks of complications, including bacteraemia, relapses, and prolonged hospitalization.

Similarly, Falcone et al. [37] observed a mortality rate of up to 29.7% among 343 patients with metallo-β-lactamases-producing Enterobacterales infections, predominantly NDM-1 type. Consistent with our results, they identified older age as a significant predictor of 30-d mortality (aHR 1.05 [CI 1.03–1.08]; *P* < 0.001), while appropriate empirical therapy within 48 h emerged as a protective factor (aHR 0.48 [CI 0.26–0.8]; *P* = 0.007). In such a shifting microbiological context, a broad-spectrum empirical therapeutic model tailored to high-risk patients, followed by rapid de-escalation, when possible, may be warranted [38].

The analysis of risk factors for antibiotic treatment failure is consistent with the predictors of mortality identified, further reinforcing the critical role of adequate empirical antimicrobial therapy. Treatment failure was independently associated with the presence of carbapenem-resistant GNB and prior inadequate empirical treatment.

A reasoned antibiotic strategy, integrating individual risk factors and local epidemiology, and the implementation of antimicrobial stewardship programmes remain crucial in hospitalized elderly patients. As suggested by Alves et al. [38], stewardship interventions should address both diagnostic (e.g. limiting unnecessary urine cultures through clinical decision support tools; use of biomarkers to tailor treatment duration) and therapeutic aspects. Concerning the latter, our results support the need for broader adoption of predic-

Fig. 4. Kaplan–Meyer analysis of the impact of appropriateness of empiric antibiotic therapy on 14-d survival for 171 elderly hospitalized patients with urinary tract infections due to Gram-negative bacteria. Significantly better survival was observed when appropriate empirical treatment was started vs inappropriate empiric antibiotic therapy ($P = 0.001$). ET, empirical therapy.

tive models to stratify the risk of MDR-GNB UTI, which could help optimize treatment outcomes [39–41]. Among key antimicrobial stewardship programmes components, ensuring the appropriateness of antimicrobial therapy – not only by reducing overall prescriptions but also by tailoring the choice of agent, route of administration, and duration to each patient's clinical context – emerges as a critical priority.

In our studies, both patients with *P. stuartii* UTI died. The role of this pathogen in causing UTI has emerged in some studies, highlighting a correlation between ESBL-strains and older age [42].

Malviya et al. [43] identified *Providencia* spp. as significant UTI pathogens in elderly patients, with a 27.1% cumulative mortality, though not directly infection-related. In our study, one patient developed bloodstream infection and septic shock, while the other had a high comorbidity burden (CCI = 7) including liver cirrhosis and hepatocellular carcinoma. Although attributing causality in geriatric mortality remains challenging, infections caused by specific bacterial strains appear to contribute significantly to adverse outcomes.

The median duration of therapy for UTI in our study was 9 d (IQR 4–12), slightly longer than the recommended duration for uncomplicated infections. This may reflect real-world clinical practice, where factors such as infection severity, MDR pathogens, and the frailty of elderly patients influence treatment decisions. Moreover, the higher prevalence of complicated infections in our cohort, for which a longer duration of therapy is recommended, likely contributed to this finding. Balancing treatment duration is crucial to ensuring clinical efficacy while minimizing the risk of antibiotic resistance and adverse effects associated with prolonged therapy.

This study has some limitations. Its observational design may introduce biases such as confounding, misclassification, and data coding errors. However, given that randomized clinical trials often exclude geriatric populations, studies like ours provide essential insights. Additionally, as we assessed overall rather than infection-

attributable mortality, our findings should be interpreted in the context of broader clinical conditions affecting elderly patients.

Moreover, the internal validation analyses using bootstrap and Lasso regression suggest that our Cox model's estimates, while directionally consistent, are subject to uncertainty, likely due to the limited number of events. These results highlight the risk of overfitting in multivariable modelling with small sample sizes. Therefore, the findings should be interpreted with caution, and further research with larger cohorts is warranted to validate these predictors.

In conclusion, our study highlights the significant impact of UTI in hospitalized elderly patients, emphasizing that even infections typically considered low-risk can lead to severe outcomes. These findings reinforce the need for a tailored empirical antibiotic approach in this vulnerable population. Further research is essential to refine treatment strategies and improve outcomes in the context of rising AMR.

Ethical approval

Clinical practices described have been approved by the Regional Ethics Committee for Clinical Trials of the Tuscany Region (Section: Area Vasta Sud-Est) with protocol number 23538.

Declaration of competing interests

The authors declare that they have no conflicts of interest.

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