Evaluation of urinary tract infection agents in intensive care unit patients and monitoring of antimicrobial profile in Gram-negative bacteria

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Summary

Background: urinary tract infection is one of the most common complications in intensive care patients. This study aimed to determine the microorganisms grown in the urine cultures of patients treated in the intensive care units of our hospital and to evaluate the resistance status of the isolated Gram-negative bacteria to antibiotics.

Materials and Methods: the distribution of microorganisms isolated from urine cultures of intensive care patients in our hospital's microbiology laboratory between January 2018 and December 2022 and the resistance patterns of Gram-negative bacteria to antibiotics were evaluated retrospectively.

Results: there was significant growth in 391 (21%) of 1855 urine cultures. 84.6% (n=331) of the samples belonged to patients treated in the general intensive care unit. Gram-positive bacteria were found in 9.4% (n=37), Candida species in 28.9% (n=113), and Gram-negative bacteria in 61.6% (n=241) of the cultures. The most frequently isolated Gram-positive microorganism was *Enterococcus* spp., while the Gram-negative pathogen was *E. coli*. Ciprofloxacin resistance was 48.3% in *E. coli* and 65% in *K. pneumoniae*, and amoxicillin-clavonic acid resistance was 42.6% in *E. coli* and 80% in *K. pneumoniae*. Ciprofloxacin resistance in Proteus and Pseudomonas strains was 53.3% and 52.9%, respectively. All *A. baumannii* strains were resistant to carbapenem and ciprofloxacin.

Conclusions: considering the resistance rates obtained in the study, amikacin is considered an appropriate treatment option for patients in our hospital. Due to high resistance rates, the use of carbapenems and quinolones should be avoided in the treatment of *A. baumannii*. Carbapenem and amikacin are considered suitable treatment options for the treatment of *E. coli* and *K. pneumoniae* strains, and Trimethoprim/Sulfamethoxazole (TMP-SMX) for the treatment of *A. baumannii* strains.

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Key words: antibiotic resistance, bacteriuria, intensive care unit, urine culture, urinary tract infection.

Authors' contributions: NA, conceptualization, investigation, methodology, data curation, writing original draft preparation, supervision; PO, supervision, conceptualization, data curation, validation. Both authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Ethics approval and consent to participate: the study was approved by Nevşehir Hacı Bektaş Veli University (2023/12).

Informed consent: the manuscript does not contain any individual person's data in any form.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Received: 21 November 2024.
Accepted:2 January 2025.

Microbiologia Medica 2025; 40:13410
doi:10.4081/mm.2025.13410

Introduction

Urinary Tract Infections (UTIs) are the most common infections worldwide. UTIs are associated with a significant clinical and economic burden, decreasing patients' quality of life [20]. Urinary tract infections are heterogeneous in etiology, clinical presentation, and disease course [3]. Moreover, pathogenic microorganisms of urinary tract infection are diverse, differing by country or region, with significant changes over the years [23]. Multidrug-resistant pathogenic strains with various virulence factors make the management of complex infections more difficult [1,22,11]. Despite advances in their diagnosis and treatment, urinary tract infections are still associated with high incidence and mortality rates, especially in healthcare settings [8].

The microbial etiology of urinary tract infections is well established, and *E. coli* is the pathogen responsible for 50-80% of the cases [14,6]. Other agents are the Enterobacteriaceae family (Klebsiella, Proteus, Enterobacter), Enterococcus, Streptococcus, Staphylococcus, and Pseudomonas species [14].

Antibiotic treatment is the cornerstone of any bacterial infection. In recent years, the unconscious use of antibiotics for human health, veterinary practices, and agricultural-industrial use has led to a significant public health problem [14]. According to the European Association of Urology, the rational use of antimicrobials is the most essential step to prevent antimicrobial resistance. In addition, it recommends systematic evaluation of regional antibiotic resistance rates of pathogens and treatment accordingly [26]. The first antibiotics chosen in empirical treatment are generally Trimethoprim/Sulfamethoxazole (TMP-SXT), which can be used orally, as ciprofloxacin, nitrofurantoin, fosfomycin and beta-lactam group antibiotics [10]. Resistance rates are increasing due to the frequent use of these antibiotics.

Despite the prevalence of urinary tract infections and their burden on the health system, our study is the first to be conducted in Nevşehir, a city in the touristic Cappadocia region. This study aims to investigate the etiology of urinary tract infections and antimicrobial susceptibility-resistance trends in Gram-negative bacteria and provide scientific evidence on the situation specific to our region.

Materials and Methods

This study included intensive care patients with significant growth in urine cultures at Nevşehir Hospital between January 2018 and December 2022. The patients' urine cultures and antimicrobial sensitivity profiles were retrospectively (medical record) screened.

In the study, urine cultures of patients over 18 years of age, not considered as contamination and with antibiogram were evaluated. In this study, bacterial growth of ≥10□ colony forming units (CFU)/mL in urine was considered a significant bacteriuria. Samples producing less than 10□ CFU/mL were considered insignificant or potentially contaminated. Culture results were retrospectively analyzed via the hospital automation system. Patients' age, gender, intensive care unit information, bacterial susceptibility (ceftriaxone, amoxicillin clavonic acid, cefixime, cefoxitin, ciprofloxacin, amikacin, gentamicin, imipenem, meropenem, cefoperozone sulbactam, trimethoprim-sulfamethoxazole for enterobacteriacea; cefazidime, cefepime, ciprofloxacin, levofloxacin, amikacin, gentamicin, imipenem, meropenem, trimethoprim-sulfamethoxazole, piperacillin-tazobactam for nonfermenter bacteria; methicillin, TMP/SXT, ciproflaxacin, linezolid, vancomycin, teicoplanin, penicillin, cefoxitin for gram-positive bacteria) (Bioanalyse, Ankara, Turkey) were recorded. After the first growth, recurrent growths and polymicrobial growths belonging to the same patient were excluded from the study. The «percentage» value was used for descriptive statistics. Antimicrobial susceptibility-resistance tests were performed using the Kirby-Bauer disk diffusion method, following the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

The study was approved by Nevşehir Hacı Bektaş Veli University (2023/12).

Results

Between January 2018 and December 2022, our hospital performed 1855 urine cultures. The significant growth rate was 21.07% (391/1855), and 84.6% (331/391) of the samples belonged to patients treated in the general intensive care unit (Figure 1).

The proportion of female patients was 55.7% (218/391). The mean age of all patients was 75.07 years (min: 18- max: 96). Gram-positive bacteria were detected in 9.4% (37/391) of the cultures with significant growth, *Candida* spp. in 28.9% (113/391), and Gram-negative bacteria in 61.6% (241/391). The periods in which the most samples were studied were 2020 and 2021, and the distribution of microorganisms by year is given in Figure 2.

Enterococcus spp. isolates constituted 94.5% (35/37) of the Gram-positive bacteria identified in the cultures, with the remaining isolates being Staphylococcus aureus and Methicillin-Resistant Coagulase-Negative Staphylococci (MRCoNS). However, it is uncertain whether *Staphylococcus saprophyticus* is included among the MRCoNS, as specific species-level results were not provided in the data.

Among gram-negative bacteria, *E. coli* was found in 50.6% (122/241), *and K. pneumoniae was found in 24.8% (60/241)* (Figure 3). The change in the isolation numbers of the dominant species over the years is given in Figure 4.

There was no resistance to vancomycin, teicoplanin, or linezolid in any *S. aureus*, MRCoNS, and *Enterococcus* spp. isolates detected in the study.

When the antibiotic susceptibility status of Gram-negative bacteria was analyzed, one *Enterobacter* spp. the strain was identified, and the strain was resistant to all antibiotics, amoxicillin-clavonic acid, ampicillin-sulbactam, cefixime, ceftriaxone, ceftazidime, colistin, meropenem, ciprofloxacin, TMP-SXT, amikacin, gentamicin, piperacillin-tazobactam, cefoperozone-sulbactam. Two *Burkholderia cepacia* strains were isolated in the study, and the strains were susceptible to meropenem, ciprofloxacin, and levofloxacin and resistant to TMP-SXT.

All *E. coli* and *K. pneumoniae* bacteria were susceptible to carbapenem and colistin. Still, ciprofloxacin resistance was 48.3% in *E. coli* and 65% in *K. pneumoniae*, and amoxicillin-clavulanic acid

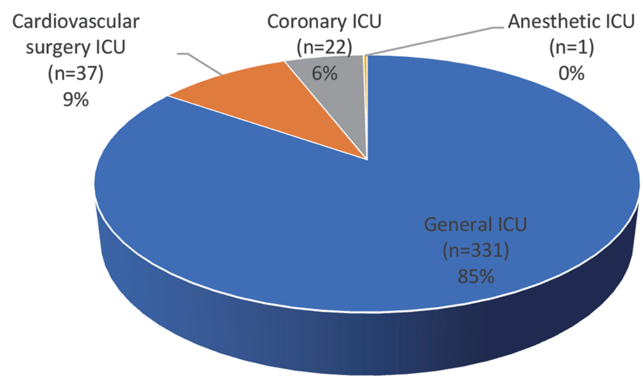

Figure 1. Distribution of causative microorganisms in clinics by year.

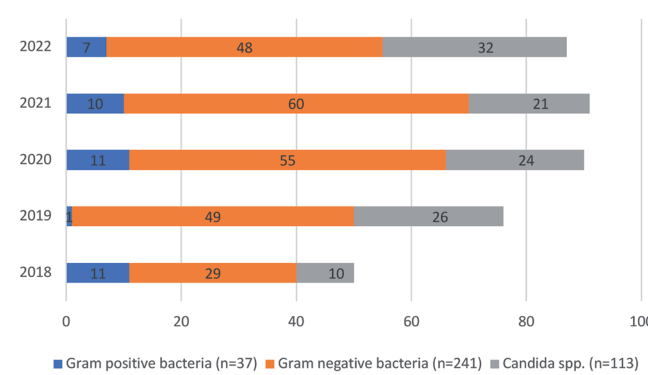

Figure 2. Distribution of microorganisms detected in urine cultures of hospitalized patients between 2018 and 2022 by year.

resistance was 42.6% in *E. coli* and 80% in *K. pneumoniae*. Ciprofloxacin resistance in Proteus and Pseudomonas strains was 53.3% and 52.9%, respectively. Carbapenem and ciprofloxacin resistance and colistin sensitivity were determined as 100% and 100%, respectively, in *A. baumannii* strains (Table 1).

Discussion

Urinary tract infections are common among patients treated in intensive care units due to the catheters commonly used in patients [16,19,27]. Since the urethra in women is shorter, the intestinal flora can easily reach the urinary system, making women more susceptible to urinary tract infections [25]. In our study, we found that the urine culture positivity rate in female patients was 55.7%. This aligns with findings from another study conducted in Turkey, which reported a culture positivity rate of 56% in women, highlighting a consistent trend in our results [12].

The presence of Candida species in urine or candiduria is usually asymptomatic [18]. Candiduria is more common in hospitalized patients and especially in those in intensive care [2]. Since Candida species are known commensals of the genitourinary system, their presence in urine specimens creates uncertainty in making a definitive diagnosis of candidal UTI. One of the biggest problems is that candiduria has been observed as the only indicator of more serious invasive candidiasis in immunocompromised

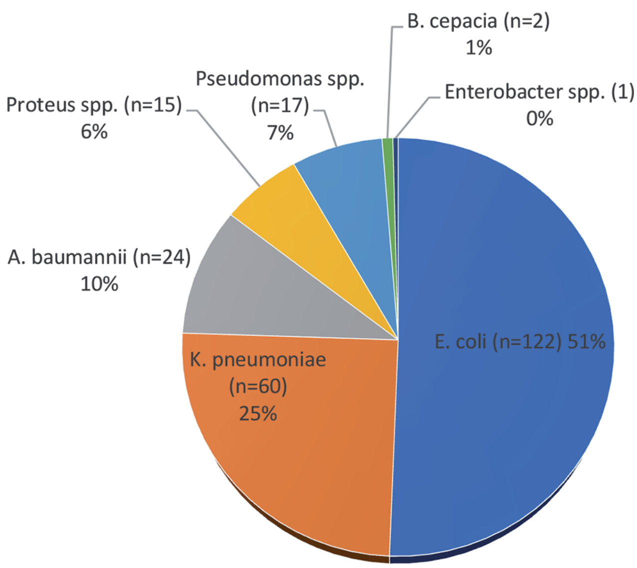

Figure 3. Distribution of Gram-negative bacteria.

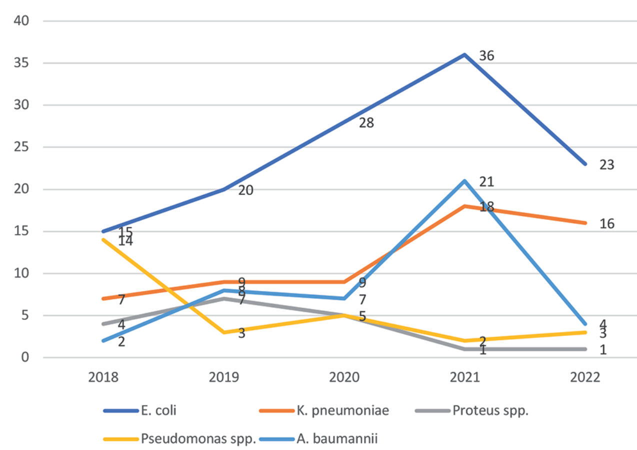

Figure 4. Distribution of dominant Gram-negative species between 2018-2022.

Table 1. Antibiotic resistance in Gram-negative bacteria.

Antibiotics	*Escherichia coli* (n=122)	*Klebsiella pneumoniae* (n=60)	*Proteus* spp. (n=15)	*Pseudomonas aeruginosa* (n=17)	*Acinetobacter baumannii* (n=24)
Ceftriaxone	62.2% (76)	83.3% (50)	26.6% (4)	*	*
Amoxicillin clavonic acid	42.6% (52)	80% (48)	26.6% (4)	*	*
Cefixime	53.2% (65)	78.3% (47)	26.6% (4)	*	*
Cefoxitin	50.8% (62)	73.3% (44)	26.6% (4)	*	*
Cefazidime	*	*	*	11.7% (2)	91.6% (22)
Cefepime	*	*	*	*	66.6% (16)
Ciprofloxacin	48.3% (59)	65% (39)	53.3% (8)	52.9% (9)	100% (24)
Levofloxacin	*	*	*	*	100% (24)
Amikacin	6.5% (8)	20% (12)	6.6% (1)	5.8% (1)	95.8% (23)
Gentamicin	26.2% (32)	31.6% (19)	33.3% (5)	5.8% (1)	95.8% (23)
Imipenem	0	0	0	0	100% (24)
Meropenem	0	0	0	17.6% (3)	100% (24)
Cefoperozone sulbactam	1.6% (2)	11.6% (7)	*	*	*
Trimethoprim-Sulfamethoxazole	45.08% (55)	58.3% (35)	80% (12)	41.1% (7)	41.6% (10)
Piperacillin-Tazobactam	8.1% (10)	*	*	17.6% (3)	100% (24)
Colistin	0	0	*	*	0

*Not tested.

patients. Because the presence of long-term urinary catheterization, antibiotic use and concomitant diabetes are thought to be risks for candiduria, according to management strategies, candiduria should be evaluated in the context of the clinical setting, determining its significance and making an appropriate decision as to whether antifungal therapy is needed [2]. In a study conducted in our country, it was reported that Candida species yeasts grew in 64 (26.8%) of 238 (25.6%) cultures with positive microorganism growth [12]. In our study, where retrospective analysis of urine cultures of patients treated in intensive care units was performed, the rate of *Candida* spp. was found to be 28.9% (113/391). Considering that the average age of the hospitalized patients in our study was 75.07, it was concluded that they were in the risk group because they probably had other underlying diseases.

Urinary tract infections are a severe public health problem caused by various pathogens but are most commonly caused by *E. coli, K. pneumoniae, P. mirabilis, E. faecalis*, and *S. saprophyticus* [7]. In our study, microorganisms from the Enterobacterales order were found to be the primary causative agents. One of the reasons for this is that they are commonly found in the digestive system and facilitate the contamination of the urethra by providing natural colonization of the perineum. In our study, 31.2% of UTIs were caused by *E. coli* (122/391), 15.3% by *K. pneumoniae* (60/391), and 3.8% by *Proteus* spp. (15/391). In a study conducted in our country, the growth of Gram-negative bacteria in culture was determined as 47.4% and the most frequently isolated bacteria was reported to be *E. coli* (46%). The second most frequently isolated bacteria was reported to be *K. pneumoniae* (24.7%) [12]. Majumder et al. reported that the leading cause of UTI in their study population was *E. coli* (75%), followed by Klebsiella species (10.7%) and Enterococcus species (6%) [17]. It was reported that these changes developed depending on geographical region, racial differences, and hygiene conditions [15].

The European Association of Urology Guidelines on Urological Infections suggests that consideration of local sensitivity rates is essential in the empirical treatment of UTIs [26]. The antibiotics initially chosen by physicians are usually TMP-SXT, ciprofloxacin, nitrofurantoin, fosfomycin, and beta-lactam antibiotics with or without beta-lactamase inhibitors [10,24]. In our country, Avcıoğlu and Behçet determined the TMP-SMX resistance of E. coli as 40% in their study [4]. In our research, the TMP-SMX resistance of *E. coli* was found to be 45.08% and the TMP-SMX resistance of *K. pneumoniae* was found to be 58.3% (Table 1). When the resistance rate against ciprofloxacin is below 10%, it is an antibiotic from the quinolone group that is appropriate to choose empirically [10]. Avcıoğlu and Behçet found ciprofloxacin resistance at 41% in their studies [4]. In our study, ciprofloxacin resistance in *E. coli* was 48.3%, and ciprofloxacin resistance in *K. pneumoniae* was 65%. In this case, it is thought that it would be appropriate to plan the treatment protocol according to the culture result.

In our study, carbapenems and aminoglycosides were found to have the highest sensitivity among intravenous options for *E. coli*. Our findings showed amikacin resistance was 6.5%, and gentamicin resistance was 26.2% in *E. coli* (Table 1). Our study's low resistance rate found against amikacin shows that this agent is an essential option for our region.

Klebsiella spp. is recognized as the second most frequently isolated strain in urinary tract infections, following *E. coli*, and it typically exhibits higher antibiotic resistance rates compared to *E. coli* [5]. In line with this trend, *K. pneumoniae* was identified as the second most common pathogen in our study's urine culture results. Specifically, the resistance rates observed in our study for *K. pneumoniae* were significant: ciprofloxacin resistance was noted at 65%, TMP-SMX resistance at 58.3%, amikacin resistance at 20%, and gentamicin resistance at 31.6%. In our study, both *E. coli* and all *K. pneumoniae* strains were susceptible to carbapenems and colistin. According to the results of our study, all Enterococcus species commonly found in urine cultures were susceptible to vancomycin, teicoplanin, and linezolid. Proteus species, typical members of hospital-acquired pathogens, are naturally resistant to nitrofurantoin and colistin and have reduced susceptibility to imipenem [9]. In our study, resistance of Proteus species to ciprofloxacin used in the empirical treatment of urinary tract infection was found to be 53.3%; resistance to amoxicillin clavonic acid was 26.6%. Detection of these resistance rates emphasizes the importance of urine culture and antibiogram in treating urinary tract infections caused by Proteus species. In treating urinary tract infections caused by Pseudomonas species, our data suggest using aminoglycosides or carbapenems (Table 1).

The global annual estimated incidence of *A. baumannii* infections is 1 million cases, of which approximately 50% are multidrug-resistant, including carbapenems [21]. It is currently considered one of the most highly resistant organisms encountered by clinicians, and this high level of resistance results from the simultaneous and concerted activity of several mechanisms [13]. In our study, all *A. baumannii* strains were also resistant to carbapenems and quinolones. The most suitable antibiotic for this bacterium was TMP-SMX, with a resistance rate of 41.6% (Table 1). Cephalosporins and quinolones have been commonly utilized as empirical therapy in intensive care units, often with minimal restrictions. This extensive use may contribute to the elevated resistance rates observed in microorganisms like *A. baumannii*, particularly in immunosuppressed patients. Effective management of urinary tract infections in such vulnerable populations necessitates carefully reevaluating empirical treatment options and adherence to stricter guidelines to mitigate the emergence of resistant strains [13].

The years with the highest number of patients considered in our study were 2020 and 2021 (Figure 2). These periods coincide with the COVID-19 pandemic and our results were thought to be compatible when we took into account the average age of the patients. However, well-designed studies are needed to compare the spectrum and susceptibility of urinary tract infection agents in our region during the pandemic and pre-pandemic periods.

In patients treated in intensive care units, urinary tract infection agents must be monitored by culture, and treatment and prevention should be guided by culture results. Regional infection agents and antibiotic resistance should be reviewed at certain intervals to ensure the continuation of treatment use of low-resistance antibiotic groups, and empirical treatments and prophylactic antibiotic selection should be evaluated following the results.

Conclusions

Our findings revealed that the causative agents of UTI in intensive care patients were Gram-negative bacteria, Candida species and Gram-positive bacteria, respectively. According to our results, *E. coli, K. pneumonia, A. baumannii, P. mirabilis* and *P. aeruginosa* represented Gram-negatives. The best drug choices for enterobacteriacea members and *P. aeruginosa*, whose antibiotic status was evaluated, were imipenem, meropenem, amikacin, gentamicin, cefoperazone sulbactam and colistin. Since all *A. baumannii* strains in our study were resistant to carbapenems and quinolones, the most suitable antibiotic for this bacterium was TMP-SMX.

There are several important limitations in our study. First, the results are based on data from a single hospital, and the analyses are limited by their retrospective nature. Since the data were obtained only from the microbiology laboratory, information such as urinary system malformations, prophylactic antibiotic use, previous UTI diagnosis, current cystitis-pyelonephritis diagnosis, immune suppression status, etc. could not be obtained; only the age and gender of the patients are known. Despite this, since the data reflect the UTI agents and antimicrobial susceptibility/resistance status of the patients admitted to our hospital, it is thought that our results will contribute to the empirical treatment of UTI agents in intensive care patients.

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