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ARTICLE

Prevalence and antimicrobial resistance of uropathogens in Karachi, Pakistan

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ABSTRACT Urinary tract infections (UTIs) are one of the major healthcare concerns causing an alarmingly high medical and financial burden in both developing and developed countries. There is a significant rise in multidrug-resistant (MDR) uropathogens, both in hospitalized and community settings, which threatens safe and effective therapy of these infections. The increased rates of resistance in UTIs requires the continuous surveillance of uropathogens in the specific area to inform safe and effective therapy. The present, retrospective, cross-sectional, descriptive study was carried out using samples collected between 01/06/2019 and 31/05/2020 in Karachi, Pakistan, during which, n = 1500 urine samples were collected. The samples were processed on Cystine Lactose Electrolyte Deficient (CLED) agar, identification was carried out by using standard biochemical tests and API 20E/20NE strips. Antimicrobial susceptibility testing was performed using standard disk diffusion test protocol, as per Clinical and Laboratory Standards Institute (CLSI) guidelines. Overall, n = 1189 urine samples (79.27%) showed significant bacterial growth. The median age of affected patients was 56 years (range: 1-100) with n = 811 females (68.21%), with patients between 61-80 years (n = 384; 32.29%) as the most numerous age group. Regarding uropathogen distribution, the overwhelming majority were Gram-negative bacteria (n = 986; 82.93%), the most common causative agent being *Escherichia coli* (n = 648; 54.49%), followed by *Klebsiella* spp. (n = 206; 17.33%) and *Enterococcus* spp. (n = 118; 9.92%). Resistance rates were highest for the tested fluoroquinolones (>70% for most species), trimethoprim-sulfamethoxazole, broad-spectrum penicillins, and cephalosporins, while fosfomycin, carbapenems and colistin largely retained their efficacy. The mitigation of UTIs and the emergence of resistance may be impeded by taking appropriate measures for the better management of patients; these interventions include improvements in the treatment recommendations, provision of health education, and continuous antimicrobial surveillance.
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Introduction

Urinary tract infections (UTIs) are one of the major healthcare concerns causing an alarmingly high medical and financial burden in both developing (low and middle-income countries; LMIC) and developed countries, however, the unmet treatment needs in LMICs are significant (Najar et al. 2009). UTIs predominately signify the presence of bacteria in the urine with corresponding symptoms, irrespective of the anatomical subregion of the urinary tract affected by the infection (Oluwole and Victoria 2016; Rusu et al. 2023). The clinical presentation of these infections may be asymptomatic (although many sources now consider asymptomatic bacteriuria as a separate entity outside UTIs, which does not require antibiotic treatment in most cases), or may result in serious illness – i.e. cystitis, pyelonephritis, and urethritis – with the corresponding symptoms (Derese et al. 2016; Khoshbakht et al. 2013). UTIs (especially uncomplicated infections) are more prevalent in females as compared to males, owing to principal anatomical differences

(Gajdács et al. 2021a; Petca et al. 2020); it has been reported almost 50% of females encounter an episode of UTI during their lifespan (Bultitude 2012). In men, the infection is less frequent (mostly occurring in men over 50 years of age), although, their presentation is usually more severe (Gajdács et al. 2021b; Olson et al. 2016). UTIs are categorized as uncomplicated and complicated, whereas the spectrum of microorganisms causing the complicated infection is much more extensive, in contrast to uncomplicated UTIs, although the possible causative pathogens found are closely matching for both upper and lower UTIs (Foxman 2014; Petca et al. 2020). The most common causative agent for both complicated and uncomplicated UTIs is *Escherichia coli* (i.e. uropathogenic *E. coli*; UPEC) (Bultitude 2012; Oluwole and Victoria 2016; Wagenlehner et al. 2020). Other relevant microorganisms involved in uncomplicated UTIs include *Klebsiella* spp., the *Proteus-Providencia-Morganella* group and *Staphylococcus saprophyticus* (Stefaniuk et al. 2016). In the case of other existing comorbidities (such as diabetes and spinal cord injuries) or in case of catheter-associated infections, *S. aureus, Enterococcus* spp., the *Citrobacter – Enterobacter - Serratia* group, *Pseudomonas aeruginosa*, and *Candida* spp. are present in higher rates along with *E. coli* (Foxman 2014; Wiedemann et al. 2014).

UTIs have a clinical and economic burden globally affecting more than 150 million people annually (Derese et al. 2016; Khoshbakht et al. 2013). In the USA, UTIs result in more than 7 million general practitioner visits per annum (Wagenlehner et al. 2020). A previously published literature review revealed that about 15% of antibiotic prescriptions are prescribed on account of UTIs in the USA and in some European countries (Bonkat et al. 2022). The projected financial burden of UTI is massive; an expenditure of greater than 6 billion US dollars per annum is involved including the cost of treatment and productivity losses (Eticha et al. 2014). The empirical treatment of UTIs involves broad-spectrum antibiotics. The availability of over-the-counter antibiotics and their inappropriate use (such as self-medication) has resulted in increased antibiotic resistance in common uropathogens (Prah et al. 2019). There is a significant rise in multidrug-resistant (MDR) uropathogens, both in hospitalized and community settings (Spellberg et al. 2013). According to the estimations of the European Centers for Disease Prevention and Control (ECDC), the mortality rate associated with MDR bacteria – which is around 25,000 individuals per year – is considerably affected bacterial strains implicated in complicated UTIs (McQuiston et al. 2013). The Infectious Disease Society of America (IDSA) has recognized so-called "ESKAPE pathogens" as the most concerning for global health, and the need for new antimicrobials. This has been further verified by the analysis of the Global Burden of Disease Study, which also highlighted the same pathogens of concern as important causes of morbidity and mortality (Antimicrobial Resistance Collaborators, 2022). These microorganisms comprise of *E. faecium*, *S. aureus*, *Klebsiella* spp., *Acinetobacter* spp., *Pseudomonas* spp. and *Enterobacter* spp (Sajnait and Indrawattana 2016). The increased rates of resistance in UTIs requires the continuous surveillance of uropathogens in the specific area to inform safe and effective therapy (Petca et al. 2021). Other contributing factors influencing correct global data on susceptibility includes the type of UTI, patient age and gender, along with the prior record of antibiotic treatments (Alós 2005). Furthermore, antimicrobial susceptibility of UTIs presents with specific spatio-temporal characteristics, which may vary considerably from one hospital setting to another. Susceptibility data is essential to control for irrational use of antibiotics and to inform local treatment guidelines and antimicrobial stewardship programs. The IDSA endorses surveillance on a regional level to follow antibiotic susceptibility variation under the specific region (Warren et al. 1999). However, there were limited number of recent studies conducted to determine the antimicrobial susceptibility patterns of UTI-causing bacteria in Karachi, Pakistan (Baig et al. 2018; Hussain et al. 2020; Nawaz et al. 2018; Zubair et al. 2019). Therefore, the present study was undertaken to determine the pathogen distribution and antimicrobial susceptibilities of uropathogens in Karachi, Pakistan, with special emphasis on etiology with respect to the gender and age of the patients.

Materials and methods

Study design and setting

The present, retrospective, cross-sectional, descriptive study was carried out using microbiological data and samples collected between 01/06/2019 and 31/05/2020, corresponding to the outpatient departments, from the Department of Microbiology, Patel Hospital Karachi (PHK). The PHK is a not-for-profit, tertiary-care hospital with a bed capacity of 250 beds, located in Gulshan-e-Iqbal, Karachi, Pakistan.

Study population

During the study period, n = 1500 urine samples were collected, out of which, a total of n = 1189 urine samples (79.27%) showed significant bacterial growth, defined as 10^5 < colony forming units [CFU]/mL (although this was subject to interpretation, based on the information provided by clinicians and relevant international guidelines), which were included in the analysis. To assess demographic characteristics, patient data was collected, which was limited to sex and age at the sample submission. Only one isolate per patient was included in the study, however, isolates with different antibiotic-susceptibility patterns were considered as different individual isolates. Individuals without complete socio-demographic information, who had been admitted to the hospital at least a week before their presentation at an outpatient department, catheter-specimens, or who received antibiotics two weeks prior were excluded from the analysis to debar hospital-acquired infections (Gajdács et al. 2021b).

Identification and Confirmation of the Isolated Bacteria

Ten µL of uncentrifuged midstream urinary specimens were inoculated on Cystine Lactose Electrolyte Deficient (CLED) agar (Oxoid, Bakingstoke, UK) by the quantitative colony count method, by using a calibrated loop, using standard sterile microbiological techniques. After incubating the plates aerobically at 37 °C for 18-24 h, they were examined for bacterial growth. If no growth was observed, the plates were re-incubated and re-examined after an additional 24 h. A bacterial count of ≥ 10^5 CFU/ml was deemed significant. For presumptive identification of bacteria, standard microbiological methods (i.e. colony morphology, Gram-stain, biochemical tests and differentiating media, including catalase, oxidase, citrate, urease, bile esculin hydrolysis, Sulfur Indole Motility (SIM), and Triple Sugar Iron (TSI) were performed, while the final confirmation was carried out using API 20E and API 20NE kits (bioMérieux, Marcy-l'Étoile, France), as required.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was carried out by the standard disk diffusion test protocol, as per Clinical and Laboratory Standards Institutes (CLSI) guidelines (M100) (Wikler 2006; Wayne 2011). Using 0.5 McFarland turbidity standard, direct colony suspensions of the relevant bacterial isolates were plated on Mueller-Hinton agar plates (bioMérieux, Marcy-l'Étoile, France), on which antimicrobial-containing discs (Bioanalyse, Ankara, Türkiye; Oxoid, Bakingstoke, UK) were then placed. The following antibiotics were tested (when relevant for the bacterial species): amikacin (AMK; 30 µg), gentamicin (GEN; 10 µg), ampicillin (AMP; 10 µg), amoxicillin/clavulanic acid (AMC; 20/10 µg), ceftazidime (CFT; 30 µg), cefepime (CFP; 30 µg), cefoperazone/sulbactam (CFS; 70/30 µg), ceftriaxone (CRO; 30 µg), piperacillin/tazobactam (PTZ; 100/10 µg), imipenem (IMP; 10 µg), meropenem (MER; 10 µg), linezolid (LIN; 30 µg), ofloxacin (OFX; 5 µg), norfloxacin (NOR; 5 µg), ciprofloxacin (CIP; 5 µg), vancomycin (VAN; 30 µg), fosfomycin (FOS; 200 µg), nitrofurantoin (NIT; 300 µg), trimethoprim/sulphamethoxazole (SXT; 1.25/23.75µg) and colistin (COL; 10 µg). The plates were inverted and incubated at 37 °C for 16 to 18 h. The inhibition zone diameters were then measured with a caliper and recorded, breakpoints to assess susceptibility (S) or resistance (R) were based on CLSI guidelines (CLSI, 2018a; CLSI 2018b). Susceptibility to colistin was assessed according to the provisional breakpoints as advised by Galani et al., i.e. inhibition zones ≥14 mm were considered susceptible (Galani et al. 2008). Intrinsic resistance mechanisms were considered according to previously published guidelines (Leclerq et al. 2013). *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, *P. mirabilis* ATCC 35659, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213 were used as quality control strains.

Statistical analysis

Descriptive statistical analysis (ranges, percentages) to characterize data were performed using SPSS software version 24 (IBM SPSS Statistics for Windows 16.0, Armonk, NY, USA, IBM Corp.).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and national and institutional ethical standards. Study approval for the study protocol from the Hospital Ethics Committee, Patel Hospital, Karachi (Reference number: 97/2020). Informed consent was not required as data anonymity was maintained.

Results

Prevalence and distribution of uropathogens

Corresponding to the n = 1189 positive and clinically relevant urine samples, n = 378 males (31.79%) and n = 811 females (68.21%) attending the outpatient departments of the hospital has clinical evidence of a UTI, as examined by the physicians. The median age was 56 years (range: 1-100), with the following age distribution: 1-20 years: n = 114 (9.58%), 21-40 years: n = 313 (26.32%), 41-60 years: n = 300 (25.23%), 61-80 years: n = 384 (32.29%) and 81-100 years: n = 78 (6.56%).

Regarding the distribution of uropathogens, the overwhelming majority were Gram-negative bacteria (n = 986; 82.93%). Overall, the most common causative agent was *E. coli* (n = 648; 54.49%), followed by *Klebsiella* spp. (n = 206; 17.33%), out of which, n = 68 were *K. pneumoniae*, while n = 64 were *K. oxytoca*) and *Enterococcus* spp. (n = 118; 9.92%). Other less common causative agents included *P. aeruginosa* (n = 69; 5.80%), *Acinetobacter* spp. (n = 57; 4.79%), *P. mirabilis* (n = 35; 2.94%), *P. vulgaris* (n = 27; 2.27%), *Enterobacter* spp. (n = 13; 1.09%), *Streptococcus* spp. (n = 9; 0.76%), *Citrobacter* spp. (n = 3; 0.25%), *S. marcescens* (n = 1;

0.08%), *S. epidemidis* (*n* = 1; 0.08%), and *S. saprophyticus* (*n* = 1; 0.08%), respectively. *E. coli* was found to be prevalent uropathogen in the age range of 21-40 and 51-70 years, being the causative agent among *n* = 165 patients and *n* = 216 patients, respectively.

Antimicrobial susceptibility of uropathogens

The summary of the antimicrobial susceptibility testing results are presented in Table 1. Regarding Gram-positive bacteria, highest rates of resistance were shown for CIP (85.3% in case of enterococci), in addition, a considerable rate of VAN-resistant isolates (20.6%) were also detected. On the other hand, LIN remained highly effective against *Enterococcus* spp. As two commonly used antibiotics in UTIs, FOS and NIT mostly retained their efficacy against enterococci. In case of Gram-negative pathogens, the reserve antibiotic COL retained its susceptibility in all tested strains. Excluding COL, FOS (in case of lactose-fermenters) and AMI (in case of all Gram-negative isolates) showed the lowest levels of resistance (14.2-25.7% and 7.7-44.4%, respectively), followed by the carbapenem antibiotics MER (18.0-61.8%) and IMI (16.3-57.9%). Overall, FOS displayed comparatively good results with *E. coli* (R: 14.6%), *Enterobacter* spp. (14.2%) and *Enterococcus* spp. (16.2%). While most of Gram-negative isolates had high levels of resistance against β-lactam antibiotics (i.e. AMC, PTZ, CFS, CRO, CFP), highest resistance rates were identified for SXT (>50% in most cases) and for fluoroquinolone antimicrobials, especially in *E. coli* and non-fermenters. Generally, resistance rates were lowest in *E. coli*, while they reached their highest values in *Acinetobacter* spp. and *Proteus* spp., however, a dissimilar resistance pattern was shown for SXT and the fluoroquinolones, where *E. coli* isolates had some of the highest rates of resistance (Table 1.).

Discussion

UTIs are a major burden for healthcare institutions worldwide, significantly affecting the quality of life and everyday functionality of millions of people each year (Flores-Mireles et al. 2015). While the prevalence of these infections is considerably higher in female patients, the outcomes in older male patients may be considerably worse, often resulting in sequelae (Chibelean et al. 2020). The treatment of both uncomplicated and complicated UTIs heavily relies on the availability of effective antibiotics, while the rise of antimicrobial resistance has been documented globally (González et al. 2020). Thus, many advances have been put forth to manage the dwindling supply of useful antibiotics to support antimicrobial stewardship activities. One such advancement is the AWaRe (Access, Watch, Reserve) classification of antibiotics by the World Health Organization (WHO), which aimed to support physicians in their therapeutic decisions and to preserve “last resort” antimicrobials (Bansal et al 2022). A 10-year surveillance study in Hungary on elderly patients’ UTIs has shown that uropathogens from inpatient samples showed significantly higher rates of resistance for the Access group of antibiotics, while Reserve drugs mostly retained their efficacy (Gajdács et al. 2021c).

The current study aimed to offer valuable clinical and epidemiological insights by analyzing the rising trends of antimicrobial resistance in urinary tract infections (UTIs) observed in Karachi, Pakistan. This analysis can aid in enhancing empirical treatment strategies (Prakash and Saxena 2013; Wagenlehner et al. 2020). During the study, a high prevalence of UTIs among females was demonstrated (68.2%), which is in line with previously reported findings from the region (Afroz et al. 2019; Bahadin et al. 2011); this difference in prevalence – as described previously – occurs due to their anatomical characteristics, constituting the short urethra, the proximity of urethral meatus to the anus, incontinence, pregnancy, practices related to sexual intercourse, and unhygienic toilet use (Afroz et al. 2019; Bahadin et al. 2011; Hussain et al. 2020; Igbinosa et al. 2007; Naseem et al. 2018; Shah et al. 2019,) although in males, prevalence of UTIs progress in ages >50 years, mainly due to prostatic enlargement followed by subsequent obstruction and neurogenic bladder (Afroz, Habib et al. 2019; Chibelean et al. 2020; Gajdács et al., 2021b). Herein, UTIs were more prevalent in patients in the age groups of 61-80 years (32.29%) and 21-40 years (26.32%), with the median age of affected individuals in their mid-50s. A previous study in Karachi, Pakistan also reported that UTIs were prevalent in the same age groups, while a paper published in Nepal revealed that patients around age 31-40 years tend to suffer from UTI. This may account for environmental and cultural variability between the two geographical regions (Baral et al. 2014, Shah et al. 2019). While the study of Naseem et al. (2018) from the same geographical region reported that patients between 21-30 years of age were most likely to suffer from UTIs, followed by patients between the ages 51-60 years. Out of the *n* = 1189 relevant uropathogens, the majority (82.93%) were Gram-negative isolates, with *E. coli* being the most significant uropathogen (54.49%) overall, in both males and females, respectively. Similar findings were observed in other studies) (Afroz et al. 2019; Gajdács et al. 2021a; Moue et al. 2015; Naseem et al. 2018; Prakash and Saxena 2013). The second most common isolates were *Klebsiella* spp. (*K. pneumoniae* and *K. oxytoca*), while other common Gram-negatives were among non-fermenting bacteria. Several studies reported that *E. coli* and *Klebsiella* spp. were the most causative agents causing UTIs across

Table 1. Antimicrobial resistance rates of isolated uropathogens.

Antibiotics	Gram-negative bacteria							Gram-positive bacteria	
	Lactose-fermenters			Non-lactose fermenters					
	E. coli	*Klebsiella* spp.	*Enterobacter* spp.	*Acinetobacter* spp.	*P. mirabilis*	*P. vulgaris*	*P. aeruginosa*	*Streptococcus* spp.	*Enterococcus* spp.
	n = 648	n = 206	n = 13	n = 57	n = 35	n = 27	n = 69	n = 9	n = 118
AMP	88.2%	NR	NR	NR	79.4%	NR	NR	0%	42.3%
AMC	48.5%	44.7%	NR	NR	45.7%	84.0%	NR	NT	NT
PTZ	33.9%	38.8%	23.0%	60.7%	21.2%	34.6%	31.3%	NT	NT
CFS	33.8%	31.6%	23.0%	55.6%	32.4%	51.9%	40.2%	NT	NT
CRO	76.5%	54.2%	69.0%	92.8%	62.8%	88.0%	NR	0%	NR
CFP	73.9%	50.9%	46.1%	85.7%	65.7%	66.7%	47.0%	NR	NR
MER	18.0%	25.5%	30.7%	61.8%	34.2%	23.1%	31.8%	NR	NR
IMI	16.3%	29.3%	46.1%	57.9%	51.4%	53.8%	29.9%	NR	NR
GEN	36.8%	33.2%	15.4%	47.3%	35.2%	40.7%	35.3%	NR	NR
AMI	16.0%	23.6%	7.7%	51.8%	31.4%	44.4%	25.0%	NR	NR
CIP	73.9%	56.8%	22.2%	86.2%	55.5%	72.7%	64.0%	62.5%	85.3%
OFX	73.6%	62.6%	30.0%	66.0%	48.1%	76.0%	46.7%	NR	NR
NOR	72.6%	66.9%	25.0%	67.3%	46.9%	73.1%	44.4%	NR	NR
SXT	74.3%	69.1%	50.0%	62.2%	23.0%	76.1%	NR	50.0%	NR
FOS	14.6%	25.7%	14.2%	NR	NR	NR	NR	NR	16.2%
NIT	26.5%	75.9%	66.6%	NR	NR	NR	NR	0%	38.0%
VAN	NR	NR	NR	NR	NR	NR	NR	0%	20.6%
LIN	NR	NR	NR	NR	NR	NR	NR	0%	0%
COL	0%	0%	0%	0%	NR	NR	0%	NR	NR

For the abbreviations of antibiotics, see the Materials and Methods section.
NR: antibiotic not tested, as intrinsic resistance is present (i.e. resistance is considered 100%). NT: AMP susceptibility was used to infer susceptibility to other beta-lactam antibiotics, such as AMC, PTZ and CFS.

the globe (Bahadin al. 2011; Dobbyn et al. 2022; Gajdács et al. 2021a; Kalsoom et al. 2012; Kothari and Sagar 2008; Stapleton et al. 2020). Similar findings were also reported in the studies conducted in Pakistan (Hussain et al. 2020; Naseem et al. 2018; Zubair et al. 2019). On the other hand, few studies have noted the importance of *Pseudomonas* species as common infectious agents in UTIs (Afroz et al. 2019; Jhora and Paul 2011).

The results of our study showed a high rate of resistance to commonly prescribed antibiotics. The rate of resistance against many β-lactam antibiotics is especially concerning, as the drugs constitute the only safe and effective therapeutic alternatives for many patient populations, such as children, pregnant women, and the elderly (Silago et al. 2022). Our results correspond to the previously reported resistance rates published for the region (Aiyegoro et al. 2007; Naseem et al. 2018; Prakash and Saxena 2013). These high levels of resistance towards β-lactam antibiotics (especially broad-spectrum penicillins and 3rd generation cephalosporins) is most probably due to the high carriage rate of plasmids encoding for extended-spectrum β-lactamase (ESBL) enzymes (Dadashpour et al. 2020; Hassena et al. 2022). Furthermore, the unjudicious use of cephalosporins (such as overuse, indiscriminate use without antimicrobial sensitivity testing and self-medication) has led to rapidly increasing cephalosporin resistance (Afroz et al. 2019). Unfortunately, with the emergence of ESBLs, clinicians were forced to use the remaining, broad-spectrum β-lactams – carbapenems – as therapeutic alternatives (Adekanmbi et al. 2021). This practice is not ideal, as on one hand, carbapenems are only available in intravenous formulation (which may make their administration cumbersome in resource-limited settings); in addition, their extended use has led to increased carbapenem resistance in Gram-negative bacteria, due to the rapid spread of plasmid-borne carbapenemases (Queenan and Bush 2007). Non-susceptibility to aminoglycosides was more common in non-fermenters than among members of the Enterobacterales order. Among the tested uropathogens, the most significant rates of resistance were shown for fluoroquinolones: high rates of non-susceptibility for ofloxacin were seen in *E. coli*, *Klebsiella* spp. and *P. vulgaris*, while for norfloxacin, similar rates of non-susceptibility was shown in *E. coli* and *Klebsiella* spp. For ciprofloxacin, high levels of non-susceptibility was seen for both Gram-positive (*Enterococcus* spp.) and Gram-negative bacteria. Studies conducted in different parts of the world including the countries of the European Union, Canada, India, Iran, and Bangladesh all reported a high incidence of fluoroquinolone resistance (Afroz et al. 2019; Das et al. 2022; Dobbyn et al. 2022; Gobernado et al. 2007; Sabharwal 2012; Stapleton et al. 2020; Yakout and Ali 2022). One of the contributing factors that account for widespread fluoroquinolone resistance is heavy over-the-counter fluoroquinolone dispensing without restriction, and the habitual prescribing patterns of physicians, leading to their irrational use (Afroz et al. 2019; Dobbyn et al. 2022; Iffat et al. 2010; Prakash and Saxena 2013; Yakout and Ali 2022). Although few studies reported that nitrofurantoin was considered the drug of choice for UTIs, a greater percentage of uropathogens were found to be susceptible (i.e., where intrinsic non-susceptibility is not present) (Afroz et al. 2019; Enayat et al. 2008; Rusu et al. 2023). This increased resistance to nitrofurantoin is a foremost concern which pose a considerable threat to UTI management (Afroz et al. 2019).

In the present study, both carbapenems tested (meropenem and imipenem) had mostly retained their activity against *E. coli* (with resistance rates at 18% and 16.3%, respectively). Similar results were reported in a study conducted in India (Prakash and Saxena 2013), papers from other geographical regions showed lower non-susceptibility rates (0-10%) in Gram-negative bacteria (Al-Zahrani and Akhtar 2005; Das et al. 2022; Joly-Guillou et al. 2010). Fosfomycin resistance in *E. coli* and *Enterobacter* spp. was <15%; many studies have reported the renewed interest of many physicians regarding fosfomycin as a viable alternative for UTI treatment, due to an increase in the emergence of MDR Gram-negative bacteria, and the lack of availability of newer antibiotics (Mezzatesta et al. 2017). Similar findings were reported in a study where fosfomycin showed to be highly effective against MDR ESBL-producing *E. coli* and was considered a substantial therapeutic alternative to UTI management (Jain et al. 2022).

One of the major reasons for antibiotic prescribing is uncomplicated UTIs. However, overuse of antibiotics on account of them being low-priced and readily available, the extensive usage of broad-spectrum antibiotics has led to the escalated risk of developing antibiotic resistance in the relevant pathogens (Bahadin et al. 2011). To ensure appropriate antibiotic usage among patients, physicians need to have timely access to data on the local prevalence of antibiotic resistance and the information needs to be updated periodically in the form of local or hospital antibiograms (Joshi 2010). Furthermore, there is a need to balance optimal patient outcomes – aided by antimicrobial stewardship activities – without unnecessarily contributing to potential antibiotic resistance through the widespread empiric use of these drugs (Majumder et al. 2020). The present study results can facilitate a more rational antibiotic use for the management of UTIs. The results of our study suggested that presently, only a few promising antimicrobial agents were effective against the majority of uropathogens, including fosfomycin, carbapenem and colistin. It is widely accepted that the emergence of antimicrobial resistance occurs as a natural response of microbes to the inappropriate and unmonitored use of antibiotics in human and animal medicine (Prestinaci et al. 2015). The mitigation of UTIs and the emergence of resistance can be impeded by taking appropriate measures for a clearer diagnosis and management of patients. Therefore, emphasis should be made on prescribing rational and optimal antibiotic use and continuous monitoring and surveillances programmes. Limitations of the study should be acknowledged when evaluating the results of the present study, like the cross-sectional and retrospective study design, the limited availability of clinical data to assess the patients' independent risk factors. In addition, due to limited laboratory capabilities, the molecular study of the exact mechanism of action behind the phenotypic resistance of the isolates was also not carried out.

Conclusions

The present study revealed that in our settings, UTIs were most common in young to middle-aged women. with *E. coli* being the most predominant microorganisms causing UTI. Most of microorganisms showed high rates of resistance against antibiotics that are commonly used for UTI treatment – both as empiric therapy and as self-medication – non-susceptibility for fluoroquinolones, broad-spectrum penicillin derivatives and cephalosporins reached worrying levels. Overall, only a few promising antimicrobial agents remained that are effective against uropathogens, which are fosfomycin, carbapenems and colistin for Gram-negative bacteria, while fosfomycin, linezolid and vancomycin for Gram-positives. On the other hand, aminoglycosides may serve as adjunctive therapy for both groups of pathogens. The mitigation of UTIs and the emergence of resistance may be impeded by taking appropriate measures for the better management of patients; these interventions include improvements in the treatment recommendations, provision of health education and continuous antimicrobial surveillance.

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