



A Review of the Antibacterial Resistance Patterns in Urinary Tract Infections

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ABSTRACT:

Antibacterial resistance is a global problem that threatens the use of medications and treatment of several diseases caused by negligence. One phenomenon that has emerged from this issue is increased antibiotic resistance, particularly in Urinary Tract Infections. Numerous studies indicate several factors, including drug class, pathogens, and age and gender-specific categories. In this study, articles investigating the trend of antibiotic resistance in UTIs are presented. This paper aims to reveal and analyze the difficulty of treating UTIs with antibiotics.

Introduction:

One of the most prevalent bacterial illnesses that affects people of all ages is urinary tract infection, causing morbidity and mortality [1]. Despite its prevalence, it remains understudied [2]. It is much more common in infants and neonates with a global incidence rate of 3-5% among girls and 1% among boys [1]. Between 1998 and 2011, there were twice as many cases of adult urinary tract infections, leading to more than 400 million hospitalizations annually. [3]. In order to treat this infection, antibiotics are used to prescribe to patients. However, over time, certain pathogens such as *E.coli*, *Klebsiella spp.*, and *S. saprophyticus* developed resistance to some medications: ampicillin and amoxicillin [4]. The efficacy of treatment was hampered by the uropathogens' rising antibiotic resistance trend. This has caused major concern among scientists and other health-related professionals and has led to some discoveries of its antibacterial susceptibility pattern.

In this study, the researchers aim to provide an article review that determines the patterns of pathogens relating to Urinary Tract Infection and the drugs associated with it among various patient categories in order to understand and provide a more accurate therapy against this urologic disease.

Methodology

The descriptive or *mapping* review was implemented to get published studies between 2012 and 2022, while assessing the degree to which data from a specific study issue demonstrates an interpretable pattern or trend in relation to previous propositions, techniques, theories, methodologies, or findings, which is the purpose of a descriptive review [5]. This literature search strategy in a study included searching Science direct, PubMed, Research gate, Biomed central, MDPI, Springer open, PAMJ, Biomedpress, PLOS ONE, BioMed Research International, The New England Journal of Medicine, and BMC.

The screening of all published studies was performed according to inclusion and exclusion criteria. Keywords used by search engines to find publications, UTI, Antibiotic resistance pattern, pathogens, antibiotic, Urinary tract, infection, and multidrug resistance. The terms were both searched separately and collectively [6]. Studies conducted before 2012 without specifying why the bacterial profile was omitted, and each article that are relevant articles that were retrieved to use for this study were carefully reviewed [7]. Likewise, the suitability of the search results and title were assessed for prospective inclusion in the study.

Urinary Tract Infection: History, Etiology, and Signs and Symptoms

One of the infectious diseases that is most common worldwide is UTIs, accounting for over 150 million cases annually [8]. This disease already existed prior to the discovery of disease-causing agents and the recognition of urology as an expertise [9]. According to the Ebers papyrus, the most effective way to cure urinary symptoms is with herbal remedies. [10]. Hippocrates identified the source of disease as an imbalance of the four humors. Moreover, Roman medicine further developed the conservative approach and was promoted by Greek physicians while allowing invasive procedures. Furthermore, Uroscopy was improved by Aetius, an Arabian physician [9]. This was used to develop a thorough classification of urine disorders. The advancement of determining urinary tract infections did not develop until 1930 [11].

Susceptible to UTIs include all ages and sex. It is the most prevalent bacterial infection in kids under 2 years old [12]. These pathogenic bacteria ascend from the perineum and rectum making women at more risk [13]. There are extremely few simple UTIs caused by blood-borne pathogens. *Escherichia coli* and *Klebsiella* are the two most prevalent bacteria that cause UTIs [14]. A substantial risk factor for UTIs are urethral manipulation and the use of a urine catheter [13]. Furthermore, risk factors include sexual intercourse, regular pelvic examinations and the occurrence of structural anomalies

Treatment for UTI relies majorly on antibiotics [15]. In addition, recurrences of UTIs pose an alarming concern. This is a factor in the increasing multi-drug resistance to UTIs as it is attributed to the uncontrolled usage of antibiotics [7]. This negligence brought about the emergence of bacterial strains that are resistant to treatment for urinary tract infections.

Results and Discussions:

Pathogens causing Urinary Tract Infection and their Antibiotic Resistance Pattern

Urinary Tract Infection or UTI is considered one of the most common bacterial infections [16] caused by several pathogens, both Gram-negative and Gram-positive bacteria as well as fungi [17]. In several studies, gram-negative bacteria were shown to be the most common cause of UTIs [18]. Among the most common UTI-causing bacteria, *Escherichia coli* accounts for the majority of cases [6] shortly followed by *Klebsiella pneumoniae* [19]. Overtime, multi-drug resistant uropathogens are continuously increasing making it a concern due to finite treatment options [20].

Table 1.

Authors	Method	Result
Ahmed et al., 2019	Cross-sectional study and Retrospective analysis, Fully automated VITEK 2 compact system	The 89 (32%) of the 273 urine samples showed significant growth for UTI. Gram-negative bacteria <i>E. coli</i> (27%), <i>Klebsiella pneumoniae</i> (12.4%), <i>Enterobacter cloacae</i> (5.6%), <i>Enterobacter aerogenes</i> (5.6%), <i>Proteus mirabilis</i> (4.5%), <i>P. aeruginosa</i> (4.5%), and <i>Morganella morganii</i> (4.5%) were the most common uropathogens isolated from the sample. 82 (80%) of the 89 samples have show resistance to at least two drugs. UTI-causing bacteria were mostly resistant ampicillin (88.3%), piperacillin (72.7%), clindamycin (66.7%), amoxicillin/clavulanic acid (66.2%), and trimethoprim/sulfamethoxazole (50%) [16].
Kengne et al., 2017	Cross-sectional Study, VITEK 2 Compact Automated System	A total of 660 urine samples were obtained and analyzed with 263 (32.7%) showing significant bacteriuria. Frequent pathogens isolated were <i>E. coli</i> (59.2%), <i>K. pneumonia</i> (13.0%), and <i>E. cloacae</i> (5.1%). There is a high antibiotic resistance rate (>60%) of total isolates observed with ciprofloxacin, ampicillin, and cephalosporins. [21].
Vakili et al., 2018	Cross-sectional study, Frequency distribution, Chi-square test, Stata software version12	A total of 2014 positive urine cultures were obtained. <i>E. coli</i> accounted for 1369 (68%) of the cases, followed by <i>lebsiella</i> was 205 cases (10.2%), of beta-hemolytic Streptococci was 170 cases (4.8%), of Enterobacter was 61 cases (3%), of gram- negative Bacilli was 46 cases (2.3%), and of non-hemolytic Streptococci was 42 cases (1.2%). <i>Klebsiella</i> , Enterobacter, non-hemolytic Streptococcus, and gram-negative Bacilli were greatly resistant to ampicillin while <i>E. coli</i> and Streptococci were greatly resistant to cotrimoxazole [18].

Gunduz & Altun 2018	Retrospective study, non-randomised and convenient sampling, P-value method, SPSS (Statistical Package for the Social Sciences, version 23.0 for Windows, SPSS® Inc., Chicago, IL, USA) statistical analysis program	The most common causative agent both in total and among different age groups was <i>Escherichia coli</i> (64.2% of cases) followed by <i>Klebsiella pneumoniae</i> (14.9%), <i>Enterococcus</i> (5.4%), <i>Klebsiella oxytoca</i> and <i>Proteus mirabilis</i> (3.9%) and <i>Enterobacter</i> spp. (1.8%). Resistance to ampicillin (62.6%), co-trimoxazole (29.8%) and cefuroxime (28.7%) in all isolates was significant. [22]
Afroz, S. et al., 2020	Cross-sectional study, SPSS version 20 statistical software by the Chi-square test and Student's T-test for paired samples	430 (20.1%) of the 2136 urine samples collected showed significant bacterial growth. The most common pathogen isolated was <i>E. coli</i> (76.3%), <i>Pseudomonas</i> spp. (7.9%), <i>Proteus</i> spp. (7.2%), <i>Klebsiella</i> spp., <i>Citrobacter</i> spp. (1.9% each) and <i>Staphylococcus aureus</i> (1.6%). Resistance against Amoxicillin (86%-97%) and Cefradin (71%-100%) was the highest, followed by Cefixime (52%-85%), Ceftriaxone (50%-71%), Ciprofloxacin (50%-88%), Cotrimoxazole (50%-75%), Gentamicin (57%-75%) and Nitrofurantoin (43%-100%), and shows the least resistance to Imipenem (0%-15%) and Amikacin (0%-29%) [23].
Shakya S. et al., 2021	Cross-sectional study using routine laboratory records	A total of 11,776 urine samples were collected with 1,865 (16%) positive bacterial growth. <i>Escherichia coli</i> accounts for 1,159 (62%) of the cases. There is a high prevalence of resistance to at least one antibiotic (1,573; 84%) and multi-drug resistance (1,000; 54%). It was found that there is high resistance to commonly used antibiotics for UTIs like ampicillin, ceftazidime, cefepime, and levofloxacin [24].

Gender-based Pattern of Antibiotic Resistance of Uropathogens

All individuals are susceptible to UTIs; however, the prevalence of infection differs with age, sex, and certain predisposing factors [25]. Isolates obtained from males or females might have different resistance profiles [26]. This infectious disease is more common in women than men with a ratio of 14:1 [27]. Up to 70% of women will suffer from a UTI during their lifetime, and of those, 30% will have recurrent UTIs (rUTIs) [28]. It is a common occurrence in females during pregnancy, and in peri- and postmenopausal [29]. Female anatomy, age, sexual activity, certain types of birth control, and menopause are the most risk factors for UTI [30]. In contrast, the incidence of UTIs in males between 18-50 years of age is very low (5-8 per 10,000 patients/years), compared to the sharp increase in incidence over 50 years of age [31]. UTIs are uncommon in circumcised males; by definition, any male UTI is usually considered complicated [13]. Hence, antibiotic therapy is becoming increasingly necessary, and antibiotic-resistant uropathogens must be identified.

Table 2.

Authors	Method	Result
Petca et al., 2020	Multicenter Retrospective Study, Kirby-Bauer disk diffusion method, Descriptive Statistics	A total of 13,081 urine samples were obtained from females. The most common Gram-negative uropathogen was <i>Escherichia coli</i> (58.37%), with substantial resistance rates to levofloxacin (R = 29.66%), amoxicillin-clavulanic ac. Ceftazidime (R = 14.13%) and ceftazidime (R = 6.68%). The investigation discovered that imipenem and meropenem

		(both 98.16%), amikacin (S = 96.0%), and fosfomicin (S = 90.39%) had high sensitivity. <i>Klebsiella</i> (16.93%) was the second most common uropathogen, with the greatest amoxicillin-clavulanic acid resistance quota. (R = 28.62%), levofloxacin and nitrofurantoin (both R = 15.61%), ceftazidime (R = 15.24%), and imipenem (S = 93.93%), meropenem (S = 91.91%), and amikacin (S = 88.47%). The most common Gram-positive bacteria, <i>Enterococcus</i> (13.35%), had the strongest resistance to levofloxacin (R = 32.07%), penicillin (R = 32.07%), and ampicillin (R = 14.62%), as well as good sensitivity to vancomycin (S = 91.98%), fosfomicin (S = 94.4%), and nitrofurantoin (S = 89.15%) [32].
Haindongo et al., 2022	Retrospective analysis, Bacterial isolation and identification, Antimicrobial susceptibility testing (AST) procedure	There were a total of 22,259 urine cultures conducted. The most prevalent infections observed were <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , and <i>Proteus mirabilis</i> , which were mostly found in young females aged 28 to 32 years. <i>E. coli</i> has 77.7% ampicillin resistance and 84.9% in <i>K. pneumoniae</i> . Except for one site, resistance to the first-line empiric treatment antibiotic nitrofurantoin was less than 13% in <i>E. coli</i> . Third-generation cephalosporin (3GC) resistance was utilized as a surrogate for ESBL production. 3GC resistance was 22%, 31.4%, and 8.3% for <i>E. coli</i> , <i>K. pneumoniae</i> and <i>P. mirabilis</i> , respectively, in the year 2017 [33].
Ali et al., 2022	Cross-sectional study, Kirby-Bauer disk diffusion method, Univariable and multivariable logistic regression analyses	In 422 pregnant women, the frequency of UTI was 16.4%. <i>E. coli</i> was the most common bacterium isolate (43.5%), followed by <i>Coagulase negative staphylococcus</i> (CoNS) (16%), <i>S. aureus</i> (13%), <i>K. pneumoniae</i> (8.7%), <i>Pseudomonas aeruginosa</i> (7.2%), <i>Proteus mirabilis</i> (5.8%), <i>Citrobacter spp</i> (4.4%), and <i>M. morgani</i> (1.5%). In 85.5% of the bacteria identified, multidrug resistance was found [34].
Miotla et. al, 2017	Susceptibility and resistance testing, Vitek 2 Compact System, Statistica 12.0	Regardless of menopausal state, ampicillin resistance reached 40%. Notably, resistance to ciprofloxacin approached 25% in postmenopausal individuals. Furthermore, the resistance of all uropathogens to routinely used antimicrobials was much greater in postmenopausal women [35].
Chibelean et al., 2020	Multicenter Retrospective Study, Kirby-Bauer disk diffusion method, Vitek 2 Compact System	The frequency of diagnosed UTIs in the male population is highly connected with age, and it becomes more common beyond the age of 50. The most common bacterial predominance in male adults with UTIs is <i>E. coli</i> . The sensitivity of <i>E. coli</i> to nitrofurantoin and fosfomicin is appropriate,

		as there is still reasonable resistance to amikacin and cephalosporins. Amikacin remains a viable treatment choice for <i>Klebsiella</i> , despite disturbingly high resistance rates to fluoroquinolones and amoxicillin-clavulanic acid. <i>Enterococcus spp.</i> revealed concerning high levofloxacin and penicillin resistance [36].
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Age-based Pattern of Antibiotic Resistance of Uropathogens

UTIs, which are among the most common infections worldwide, are mostly caused by uropathogenic E. Sepsis, kidney injury, recurrence, or even death [37] are all potential outcomes of uropathogenic *Escherichia coli* (UPEC) infection. UTI is more prevalent in women than in men because of the anatomically less effective female urethra at preventing bacterial entry [38]. It's possible that the proximity of the urethra and genital tract [39], as well as the urothelial mucosa's adhesion to the mucopolysaccharide lining [40], play a part. The two major risk factors for UTI in women include pregnancy and sexual activity [41]. Patients aged 48 years and older were the most prone to UTI, followed by those aged 26 to 36 (58.11%), 15 to 25 (54.55%), and 37 to 47 (39.19%) [42]. Because of this, it's essential to utilize a sufficient and timely empirical antibiotic therapy. Women, older men, and newborns are particularly at risk for morbidity due to UTIs [43]. Due to the rising trends of multidrug resistance (MDR) and pandrug resistance (PDR) in UTI isolates, it was advised to use new and clinically more appropriate resistance categories in UTIs.

Table 3.

Authors	Method	Results
Fenta A et al., 2020	Antimicrobial susceptible profiling, MDR, XDR, and PDR resistance isolates and antibiogram	The highest age-specific prevalence (22.5%) was seen in the group of 73 individuals between the ages of 21 and 30, which is consistent with results from other studies showing that sexually active individuals, particularly women, are more likely to develop urinary tract infections [44, 45]. The findings of this study are consistent with those from Ethiopia [45] and India [46].
Shaki et al., 2020	Statistical Analysis (WHONET 5.6 software), χ^2 -test or Fisher's exact test	Shaki et al. (2020) characterized the etiological profile of UTI in babies under 2 years of age and showed that <i>E. coli</i> proportion increased. While <i>Klebsiella spp.</i> decreased with age, with several <i>Enterococcus</i> strains. Average percentages for age-related proportions fell, to 56.9, 14.1, and 11%, respectively. Adult data, however, differed from child data in some areas (47, 48). Therefore, etiological profile and antibiotic susceptibility may be impacted by age.
Huang et al., 2022	Statistical Analysis (WHONET 5.6 software), χ^2 -test or Fisher's exact test	Additionally, we found that the etiological profile in newborns was less varied than it was in adult, pediatric, and geriatric patients. This was probably caused by the largest proportion of adults among all age groups and the fact that most babies were born to inpatients who had nosocomial or complex UTIs [49, 50].
Bhargava et al., 2022	Statistical Analysis (WHONET 5.6 software), Chi-square test	Males were much less likely to have UTIs than females ($p = 0.00024$). The age group most at risk for UTI was 18 to 50, followed by 51 to 80, then 5 to 17 and older than 80 years

		(Figure 1). Between the ages of 51 and 80 and >80 years, men showed a higher prevalence of UTI than women (25.7 versus 1.5%), whereas women were more sensitive in the childhood and adolescent age ranges. The chi-square test ($p = 0.053$) ($\chi^2 = 7.69$; degree of freedom = 3) [51] found a significant correlation between age and gender.
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Conclusion:

The value of antibiotics, which have historically revolutionized the medical sciences, is in jeopardy due to the emergence of multidrug resistance among harmful microorganisms. Two criteria are frequently used to categorize UTIs; acute cystitis which affects the lower urinary tract, and acute pyelonephritis which affects the upper urinary system.

Numerous studies demonstrate that the two most common bacterial pathogens are *Klebsiella* and *E. coli*. Urinary tract infections are a serious clinical issue that frequently affects children and pregnant women. Patients with female urolithiasis have a distinct uropathogenic microbiological spectrum than male patients. Antibiotics with high susceptibility should be administered empirically according to gender to prevent the spread of microorganisms that are resistant to several drugs. UTIs can also appear as acute cystitis and pyelonephritis amongst children but it may be impertinent to base on the symptomatology alone.

In summary, there is a slight association between sex, age, and antimicrobial resistance. The resistance of the most common pathogen found in urine, *E.coli*, against antibiotics has shown an increase of roughly 10% over the decade. Because of this, some drugs such as ampicillin and amoxicillin are avoided as empirical therapy.

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