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The Resistance Crisis: Characterization and Antimicrobial Challenges of Uropathogenic Bacteria

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ABSTRACT

Urinary tract infections (UTIs) remain a significant clinical challenge, with increasing antibiotic resistance complicating treatment strategies. This cross-sectional study analyzed 124 urine samples from symptomatic UTI patients (84 females, 40 males; mean age 42.5±15.8 years) over a six-month period. Significant bacteriuria ($\geq 10^5$ CFU/mL) was identified in 104 samples (83.9%), which were processed for microbial identification and antibiotic susceptibility testing using standard microbiological techniques and disk diffusion method. Females showed significantly higher UTI prevalence (67.3% vs. 32.7%; $\chi^2=9.83$, $p=0.002$). Gram-negative organisms predominated (87% vs. 13% Gram-positive; $\chi^2=54.15$, $p<0.001$), with Escherichia coli being most prevalent (72%, $p<0.001$). Carbapenems (meropenem/imipenem) demonstrated 100% susceptibility, while fluoroquinolones exhibited significant resistance (ciprofloxacin 58% vs. moxifloxacin 30%; $\chi^2=12.7$, $p<0.001$). Azithromycin and cefixime showed 10% resistance each. This study highlights the sustained efficacy of carbapenems against uropathogens but reveals concerning resistance to fluoroquinolones, particularly ciprofloxacin. These findings emphasize the need for ongoing antimicrobial surveillance and cautious antibiotic selection in UTI management. This resistance can be reduced by taking precautionary measures like avoiding improper use of antibiotics and self-medication.

INTRODUCTION

UTIs can affect the bladder (cystitis) or kidneys (pyelonephritis). This is the second most frequent type of infection, leading to around 8.1 million visits to healthcare professionals annually (Klein and Hultgren, 2020). Women are particularly susceptible to UTIs than males.

Approximately 50% of women will have at least one UTI in their lifetime, with 20-30% lasting recurrent UTIs (Dospinescu et al., 2020). Clinical signs are contingent upon the type of organism, infection stiffness, the affected urinary tract segment, and the patient's immune response capacity (Hudson et al., 2020). UTIs have a significant negative impact on a person's quality of life and cause significant financial and public health costs (El-Sahrigy et al., 2019). UTIs affect approximately five percent of children and are most prevalent between the ages of 2 and 24 months. Compared to older infants, neonates (those under two months old) seem to have a comparable or greater ratio of UTI with fever (4.6% to 7.5%), with rates as high as 20% in infants with low birth weights, who are primarily male (Medina and Castillo-Pino, 2019). The most prevalent outpatient illness in the US is a urinary tract infection (Tenney et al.). The prevalence of UTIs rises with age, except for the highest rate in young women between the ages of 14 and 24. The prevalence is over 20% among women over 65, although it is only about 11% in the general population. Nearly 10% of postmenopausal women report having a UTI in the past year, and between 50% and 60% of adult women will experience at least one UTI in their lifetime (Medina and Castillo-Pino, 2019). They are a major cause of sepsis, resulting in significant death rates. Infants, pregnant women, patients with spinal cord injuries, diabetes, multiple sclerosis, acquired immunodeficiency disease syndrome, and underlying urologic abnormalities are at higher risk for UTIs. Catheter-associated urinary tract infections (Tenney et al.) are the most frequent nosocomial infection (Rexhepi et al., 2019).

Both Gram-positive and Gram-negative bacteria, as well as some fungi, can cause UTIs (Foxman, 2010). The most common causative agent for both uncomplicated and complicated UTIs is uropathogenic *Escherichia coli* (UPEC. *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *streptococcus* (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and Candida spp. are the most common agents involved in simple UTIs, followed by UPEC. The most prevalent causal agent for complicated UTIs is UPEC, followed by Enterococcus species, *K. pneumoniae, Candida species, S. aureus, P. mirabilis*, and *P. aeruginosa* (Lo et al., 2014).

UTI symptoms include painful urination (dysuria), frequent urination (frequency), difficulty initiating the urine stream (hesitancy), abrupt onset of urgency (desire to urinate), pain or discomfort in the suprapubic area, spasms in the bladder, and blood in the urine (hematuria) (Kaur and Kaur, 2021). Fever, chills, nausea, vomiting, and back/flank pain are more common symptoms of pyelonephritis or renal involvement than they are in patients with simple UTIs. Except for pregnant women, immunocompromised individuals, transplant recipients, and those who have recently had urologic surgery, asymptomatic bacteriuria is frequent and does not need to be treated. Additionally, before invasive urologic surgical treatments, significant bacteriuria should be addressed (Hudson et al., 2020).

Historically, the duration of antibiotic treatment has ranged from three days to six weeks. "Mini-dose therapy," which only requires three days of treatment, has outstanding cure rates. Variable regions of the nation have variable levels of *E. coli* resistance to conventional antibiotics. If the rate of resistance to any given antibiotic is greater than 50%, another medication should be selected (Bartoletti et al., 2016). Nitrofurantoin, sulfamethoxazole/trimethoprim, fosfomycin, and first-generation cephalosporins are first-line treatments for simple UTIs. Pivmecillinam is likewise regarded as a first-line treatment outside of the US (Foxman, 2014). Multidrug-resistant bacteria may grow because of these therapies, which may also cause long-term changes to the normal vaginal and gastrointestinal tract microbiota. Multidrug-resistant uropathogen colonization may become more likely if niches that the changed microbiota no longer fills become available. Crucially, the "golden era" of antibiotics is coming to an end, which means there is a growing demand for alternate and logically designed medicines (Mahony et al., 2020) (Foxman, 2014).

The widespread appearance of a variety of antibiotic resistance mechanisms has made treating UTIs more challenging. Members of the Enterobacteriaceae family, such as *K. pneumoniae and E. coli*, are especially concerning since they have developed resistance to extended-spectrum β-lactamases (ESBLs). Inhibitors of β-lactamase are similarly ineffective against other members of the Enterobacteriaceae family. Due to their inherent resistance to trimethoprim, clindamycin, cephalosporins, and penicillins, enterococci also frequently exhibit multidrug resistance. High-level resistance to glycopeptides, such as vancomycin, which is regarded as one of the final lines of defense against microbes resistant to several drugs, has recently been evolved by Enterococcus species (Lo et al., 2014). Increased frequency of urination, dysuria, bloody or murky urine, suprapubic soreness, fever, or costovertebral pain can all be indicators of a UTI. The manifestation of bacteriuria and pyuria is necessary for a conclusive diagnosis. Urine culture is necessary to differentiate between uncomplicated and complex UTIs (Tenney et al., 2018) (Lo et al., 2014). Accurate identification of bacterial uropathogens and determining their drug susceptibility pattern are critical for the efficient management of patients with UTIs. They are also associated with significant clinical and financial benefits, via the reduction of mortality rates and overall hospitalization costs. Therefore, the purpose of the study was to isolate and identify the bacteria that cause UTIs and their antibiotic susceptibility pattern.

MATERIALS AND METHODS

Study Area & Sample Collection

The current study was conducted at different clinical setups in District Abbottabad, KP Pakistan. 124 urine samples were taken from inpatients and outpatients at different Hospital in Abbottabad during the study period. 20-5ml midstream urine sample was taken in sterile condition in sterile urine bottle. Samples were bought into Abbottabad University of Science and Technology's microbiology lab after collection for further samples processing.

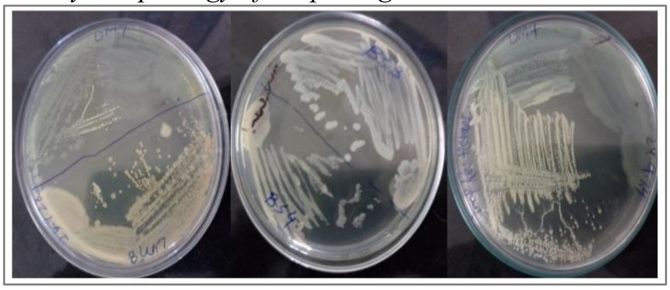
Sample Collection and Processing

Samples were collected in sterile cups, kept in an icebox, and transferred to the Abbottabad University of Science and Technology's Microbiology lab for further sample processing. During sample collection the inclusion criteria for urinary tract infections were followed. Urine samples were inoculated onto nutrient agar, CLED Agar, and MacConkey agar within 24 hours (as per standard) of collection and incubated at 37°C aerobically for 24-48 hours and the number of colonies was counted. Colony counts yielding bacterial growth of >105 / ml of urine (≥100,000 colonies) were regarded as significant for bacteriuria.

Identification of Isolates

Pure isolates of the bacterial pathogen were preliminary characterized by colony morphology (Figure 1), Gram-stain, and biochemical tests (Said et al., 2021).

Figure 1
Colony morphology of uropathogens bacteria



Biochemical Characterization

Biochemical assays, including catalase, oxidase and methyl red were carried out. Briefly described as follow:

Catalase Test

This analysis reveals the presence of the catalase enzyme, which promotes the oxygen release from hydrogen peroxide (H2O2). It is used to distinguish between bacteria that produce the catalase enzyme. On a sterilized slide, one colony was carefully combined with hydrogen peroxide to perform the catalase test. The test was deemed successful if gas bubbles appeared on the culture material's surface (Reiner, 2010a).

Oxidase Test

An enzyme that is present during aerobic respiration, cytochrome C oxidase, also known as cytochrome a3, can be detected with the oxidase test. Any aerobic, oxidase-positive bacterium that is capable of respiration can use oxygen as a terminal electron acceptor. Oxidase deficient bacteria can be facultative or anaerobic. The result only shows that these species lack cytochrome c oxidase, which is required to oxidize the test reagent. During respiration, they may use a variety of oxidases to transfer electrons. The oxidase test can be carried out in a number of methods. Among them are the filter paper test and the filter paper spot test (Shields and Cathcart, 2010).

Filter Paper Test Method

A tiny piece of filter paper was treated with 1% Kovac's oxidase reagent and left to air dry. A well-isolated bacterial colony from a freshly cultivated (18–24 hour) bacterial plate was moved onto filter paper using a sterile loop. Color differences were analyzed for each test colony. After an oxidase-positive test, the color turns dark purple in ten to fifteen seconds. The color either remains the same or reacts more slowly than two minutes when oxidase-negative organisms are present (Shields and Cathcart, 2010).

Methyl-red Test

When methyl red indicator is added at the conclusion of the incubation period and changes color, it indicates that enough acid was created by the fermentation of glucose and that the conditions were maintained so that the pH of an old culture remained below 4.5. A culture of the bacterial strains was injected into a tube containing MR broth, which was high in glucose and peptone, in order to conduct the Methyl Red (MR) Test. After adding two loopful of each bacterial culture to the broth in test tubes and labeling them with the organism's name, the soup was incubated for 48 to 72 hours at 37°C. A few drops of methyl red indicator were added to the incubated tubes at the end of the incubation period. Each tube was examined to look for a specific red hue that indicated positive results and a yellow tint that indicated negative reactions (Tille and Bailey, 2014).

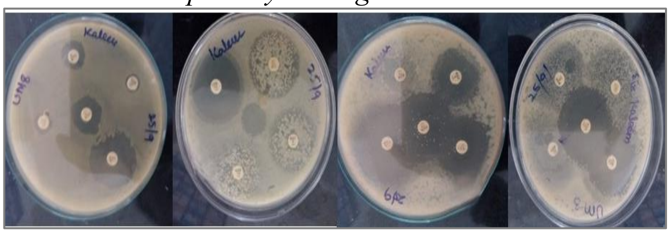
Indole Test

A culture of the bacterial strains was injected into a tube filled with tryptophan broth and left at 37 °C for 24 to 48 hours in order to conduct the Indole test. Add 0.5 ml (5 drops) of Kovac's reagent and mix gently. Look at the topmost layer of the liquid; if purple or red rings appear there, a positive result is shown; if yellow rings appear, a bad result is shown (KOMAL, 2019).

Antibiotic Susceptibility Tests for Uropathogens

The antibiotic susceptibility test was done by the standard disk diffusion method on Mueller-Hinton agar (MHA) using commercial disks. Turbidity standard protocol was followed to have homogenized bacterial inoculum suspension (Seifu and Gebissa, 2018). The following antibiotic discs were used for the disc diffusion tests: imipenem, moxifloxacin, ciprofloxacin, meropenem, azithromycin, and cefixime. (Figure 2).

Figure 2
Antibiotic susceptibility Testing



RESULT

During the study period, 124 urine samples were collected from symptomatic UTI patients (84 females [67.7%], 40 males [32.3%]; mean age 42.5±15.8 years). Significant bacteriuria ($\geq 10^5$ CFU/mL) was detected in 104 samples (83.9%), demonstrating significantly higher prevalence in females (67.3% vs 32.7% in males; $\chi^2=9.83$, $p=0.002$, OR=2.06, 95% CI: 1.30-3.26), as detailed in Table 1.

Table 1
Representing the gender wise distribution of urine samples and bacterial growth

Gender	Total samples	Positive bacterial growth	Negative bacterial growth
Male	40	34	6
Female	84	70	14
Total	124	104	20

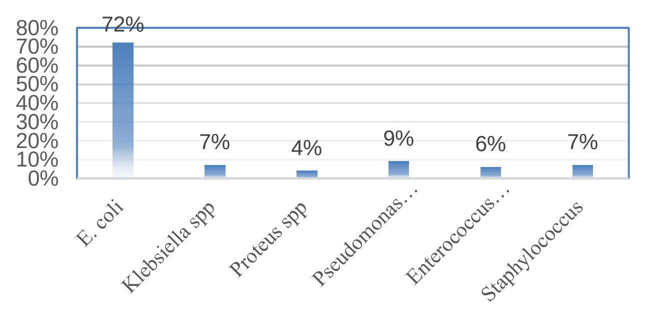
After bacterial isolation from urine sample the bacteria were then identified by using gram staining, bacterial morphology and other different biochemical tests. Like *E. coli* showed Gram Negative, rod shaped, catalase and indol positive and methyl red and oxidase negative as shown in Table 2.

Table 2
Biochemical tests and Gram reaction of bacterial isolates from urine samples.

Identified Bacteria	Gram staining & morphology	Catalase test	Oxidase test	Methyl red test	Indole test
E. coli	Gram – rod	+	-	-	+
Klebsiella	Gram – rod	+	-	-	-
Proteus	Gram – rod	+	-	-	+
Enterococcus facelis	Gram + cocci	-	-	-	-
Staphylococcus	Gram + cocci	+	-	-	+
Pseudomonas aureginosa	Gram - rod	+	+	-	-

Of the 104 culture-positive urine samples, bacteriological analysis revealed a statistically significant predominance of Gram-negative organisms (n=90, 87%) compared to Gram-positive isolates (n=14, 13%; χ^2=54.15, p<0.001, OR=6.69, 95% CI [3.45-12.98]). Among the identified pathogens, *Escherichia coli* demonstrated marked prevalence (n=75, 72%), showing statistically significant dominance over other uropathogens (χ^2=215.4, p<0.001). The remaining isolates exhibited the following distribution: *Pseudomonas aeruginosa* (n=9, 9%), *Klebsiella species* (n=7, 7%), *Staphylococcus species* (n=7, 7%), *Enterococcus faecalis* (n=6, 6%), and *Proteus species* (n=4, 4%) (χ^2=178.3, p<0.001 for inter-pathogen distribution differences). This pathogen distribution pattern is visually presented in Figure 3.

Figure 3
Frequency of isolated uropathogenic bacteria



Antimicrobial susceptibility testing
The susceptibility testing revealed striking resistance profiles among uropathogens (Table 3). Carbapenems demonstrated exceptional efficacy, with meropenem and imipenem both showing 0% resistance (100% susceptibility). In contrast, fluoroquinolones exhibited significant resistance variation, with ciprofloxacin resistance (58%) being nearly twice as prevalent as moxifloxacin (30%; χ^2=12.7, p<0.001, OR=3.23, 95% CI: 1.72-6.07). Among other tested agents, both azithromycin (macrolide) and cefixime (third-generation cephalosporin) showed identical resistance rates (10%; p=1.00), though through potentially different resistance mechanisms.

Table 3
The susceptibility of uropathogens to commonly used antibiotics.

S.No	Antibiotic Tested	Resistance Rate	Sensitivity Rate
1	Meropenem	0%	100%
2	Imipenem	0%	100%
3	Ciprofloxacin	58%	42%
4	Moxifloxacin	30%	70%
5	Azithromycin	10%	90%
6	cefixime	10%	90%

DISCUSSION

Globally, urinary tract infections are prevalent, and regional variations exist in the pattern of antibiotic resistance and are the most prevalent bacterial infections in outpatient settings in the US, resulting in seven million office visits and 100,000 hospitalizations annually (Faine et al., 2022). Forty to fifty percent of women will get a UTI in their lifetime, and one in three will need antimicrobial treatment for a UTI before the age of twenty-four. Evaluation and treatment of UTIs are anticipated to cost $1.6 billion annually. Even with improvements in antibiotic treatment, urinary tract infections continue to be a major source of morbidity. The number of incident instances of these three urologic benign disorders increased significantly worldwide between 1990 and 2019. One of the most prevalent microbial illnesses in people is a urinary tract infection (Ortega Martell et al., 2019). The isolation of bacterial pathogens from the urinary system is the focus of the current investigation. 124 urine samples were taken from inpatients and outpatients at different Hospitals in Abbottabad during the study period. When urinating four hours later or on the first morning, a midstream urine sample was taken under sterile conditions. A similar study was conducted by (Ronald, 2002) who isolated 50 urine samples from hospitalized patients for bacterial specimen isolation. After the sample was first examined, the findings showed that every sample was developing well in its growth medium and the study conducted by (Ortega Martell et al., 2019) shows out of 50 samples 30 bacterial pathogens were grown on the surface of nutrient agar medium. Gram staining of the separate cultures revealed that the organisms were both gram-positive and gram-negative. Bacterial isolates can be found alone, in pairs, or occasionally even in chains. A similar study by (Kurts et al., 2013) demonstrates that isolated bacterial pathogens manifest as rods, cocci, and even chains. Notably, the majority of bacteria were Gram-negative, with Gram-positive cocci being less common.

In the current study, 23% of the bacterial isolates tested positive for the catalase test, indicating the presence of the catalase enzyme, whereas the majority of them (73%) tested negative. These results are consistent with a previous study, which found 10% catalase-positive isolates out of 30%. The oxidase test yielded 39% positive results, indicating the existence of cytochrome oxidase, whereas 60% were negative. Similar research by Shetty et al. found that just 1% of 80 isolates from urine samples were oxidase-positive, whereas 29% were negative (Shetty et al., 2009). The Methyl Red (MR) test showed negative results for all isolates, indicating that glucose fermentation does not produce stable acid. JF (2000) found that 60% of urinary tract bacterial infections showed MR-negative findings, which supports this finding. In the indole test, 17% of the isolates were positive (a red ring appeared after adding Kovac's reagent), whereas 82% were negative. This finding is consistent with (JF, 2000), who obtained 80% indole-negative findings in a comparable setting.

Antibiotic sensitivity testing was performed to determine the susceptibility patterns of the isolated bacterial strains. Meropenum and imipenem exhibited 0% resistance indicating the highest efficacy against the tested isolates and the results align with the findings of (Dhillon, 2018) Among fluoroquinolone, ciprofloxacin should have a resistance rate of 58% whereas moxifloxin exhibited a lower resistance rate of 30%. The macrolide (Azithromycin) had a resistance rate of 10% while cefixime also showed 10% resistance. Alike study by (Astal and Sharif, 2002) demonstrates that amikacin and ciprofloxacin were the most effective antimicrobial medicines against urinary tract infections with high sensitivity rate (81%–100%). In contrast, the isolated bacterial pathogen showed complete resistance to both tobramycin and kanamycin.

CONCLUSION

Infections of the urinary tract are widespread throughout the world. One of the leading causes of morbidity is still UTIs. It is crucial to address the issue of urinary tract infections and determine the dangerous bacterial sources. Both sexes are susceptible to urinary tract infections, but women are more likely to have them because of their physiology, which makes the infection more likely to arise. Antibiotics such as azithromycin, ciprofloxacin, moxifloxin, and meropenum had the highest antimicrobial sensitivity. Therefore, the study was based on clarifying the positive and Gram-negative bacterial isolates that affect the urinary tract and identifying these isolates' antibiotic sensitivity profiles. As these isolates were defined by morphological, and biochemical methods, the results showed that the bacteria were represented in *E. coli* (72%), *Klebsiella spp* (7%), *Proteus spp* (4%). *Enterococcus facelis* 6% and *Staphylococcus* were 7% of the isolates and *Pseudomonas aureginosa* (9%) showed sensitivity to most antibiotics. Therefore, this study concludes that to maintain the effectiveness of antibiotics in treating such kinds of infections, it is mandatory to use antibiotics at the correct dosage, avoid self-medication, and perform proper culture and sensitivity testing before starting any antibiotic treatment.

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