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**Review Article**

# ANTIMICROBIAL RESISTANCE PROFILES OF UROPATHOGENS AND THEIR IMPLICATIONS FOR EMPIRICAL TREATMENT OF URINARY TRACT INFECTIONS

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***Abstract***
*Antimicrobial resistance among uropathogens increasingly compromises empirical treatment of urinary tract infections and necessitates locally informed therapeutic strategies. This study characterized antimicrobial resistance profiles of Gram-negative uropathogens and evaluated their implications for empirical treatment. Secondary microbiological data were analyzed for 604 Gram-negative isolates, comprising Escherichia coli, Klebsiella spp., Pseudomonas spp., and Proteus spp. Susceptibility to seven antimicrobial agents was evaluated, alongside organism- and clinical-setting-specific resistance patterns and cumulative resistance burden. Escherichia coli was the predominant uropathogen (56.1%), followed by Klebsiella spp. (36.8%). Meropenem demonstrated the highest susceptibility (86.8%) and lowest resistance (10.6%), whereas amoxicillin-clavulanate showed the highest resistance (69.5%). Klebsiella spp. exhibited significantly greater resistance than E. coli to ciprofloxacin (41.9% vs. 31.3%) and meropenem (14.0% vs. 7.4%), with both differences remaining significant after false discovery rate correction (adjusted p=0.033). Overall, 43.2% of isolates were resistant to at least three of six universally tested agents. Clinical-setting differences did not remain significant after multiple-testing correction. These findings demonstrate substantial resistance heterogeneity among uropathogens and support routine local surveillance, culture-guided therapy, and antimicrobial stewardship to improve empirical UTI treatment while preserving effective antimicrobial options.*

**Key Words:** antimicrobial resistance, urinary tract infection, uropathogens, antimicrobial susceptibility, empirical therapy

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## 1. Introduction

UTI is one of the most prevalent bacterial infections in clinical practice and is a significant clinical problem at both community and hospital levels. They are from simple urinary tract infections to complicated infections of the upper urinary system and can result in complications, hospitalization and recurrence when not properly treated. The burden is different across different demographic groups, underlying health conditions, and healthcare exposure and geographical setting (Medina & Castillo-Pino, 2019). In addition, global evidence shows that UTs remain a significant public health and clinical challenge, highlighting the ongoing burden of this infection (Yang et al., 2022). The increasing knowledge about the pathogenesis of UTIs also highlights the role of interactions between bacterial virulence, host susceptibility, and exposure to antimicrobials in the development of the infection and its clinical outcome (Mancuso et al., 2023).

UTIs are typically bacterial in nature, with Escherichia coli being the most common uropathogen, but Klebsiella, Pseudomonas, Proteus, and other bacteria play a significant role, depending on the patient population (Chowdhury and Findlay, 2025). The differences between uropathogens are clinically relevant since their antimicrobial susceptibility is not consistent. Differences in phylogenetic background and virulence characteristics are associated with differences in antimicrobial susceptibility even within a single E. coli species, uropathogenic E. coli (Hyun et al., 2021). Urinary pathogen studies have also shown high levels of resistance to most effective antimicrobial drugs, further emphasizing the need for the identification of organisms and susceptibility testing for proper UTI management (Ahmed et al., 2019). Community-associated and hospital-associated infections can also have different resistance as healthcare exposure can have an impact on the distribution of pathogens and on antimicrobial selection pressure (Fekadu et al., 2025).

Antimicrobial resistance (AMR) is increasingly a significant problem for effective treatment of UTs. Resistance can develop by mutations or by gaining resistance determinants that help to inactivate the drug, modify the target, decrease permeability or pump out the antimicrobial. When antibiotic resistance genes are transferred among bacterial communities, the development and survival of resistant bacteria is further hastened (Jian et al., 2021). The greater the resistance, the less reliable are conventional empirical treatments and the more likely is that ineffective initial therapy will occur. This situation has exacerbated the urgency to make empirical antimicrobial choice decisions based on the latest evidence of antimicrobial susceptibility, instead of on assumptions based on antimicrobial prescribing practice from previous years (Bader et al., 2020). While non-antibiotic approaches are emerging as new options for prevention and treatment of uncomplicated infections, antibiotics play a key role in treating bacterial UTIs (Wawrysiuk et al., 2019).

Comparative susceptibility assessment can give clinically relevant information by highlighting antibiotics which will remain active in relevant bacteria. The evidence from the Gram-negative pathogens shows significant differences in antimicrobial susceptibility within bacterial species, suggesting that the pathogen-specific interpretation of resistance patterns is warranted (Moise et al., 2021). This type of surveillance is also essential for antimicrobial stewardship, a focus on maximizing antibiotic use and minimizing unnecessary exposure and selection for antimicrobial resistance (Majumder et al., 2020). Monitoring for changes in antimicrobial resistance patterns can offer a signal for antimicrobial policy and treatment changes (Tacconelli et al., 2018).

Although a lot of research has been carried out on AMR, there is a lack of generalised resistance estimates for a particular antimicrobial which can be applied to other healthcare settings due to the importance of local bacterial ecology and antimicrobial exposure. Thus, information from comparative analysis of clinical microbiology data may be useful in determining the distribution of pathogens and organism-specific susceptibility. Thus, the objectives of this study were to describe the antimicrobial resistance patterns of uropathogens and their relevance for the treatment of UTIs. It specifically looks at the distribution of clinically relevant uropathogens, and their in-vitro antimicrobial susceptibility patterns, and the antimicrobial agents with comparatively high in-vitro

activity that can provide evidence-informed empirical therapy and antimicrobial stewardship.

**Research Objectives**

1. To determine the distribution of clinically important uropathogens identified from urine culture samples.
2. To compare antimicrobial susceptibility and resistance patterns across the major uropathogens against commonly tested antibiotics.
3. To identify antimicrobial agents retaining comparatively high in-vitro activity and assessing their implications for empirical UTI treatment.

## 2. Materials and Methods

### 2.1 Study Design and Data Source

The design used to explore antimicrobial resistance profiles of uropathogens was retrospective secondary data analytics (Otaigbe et al, 2023). Data consisted of 3,612 clinical urine culture results from patients who were seen at a tertiary health care facility in South-West Nigeria. The variables that were available were patient gender, inpatient/outpatient status, culture results, type of microorganism, and antimicrobial susceptibility. No other patients were recruited, and no more laboratory experiments were conducted.

### 2.2 Data Preparation and Pathogen Classification

Duplicate records, missing observations, inconsistencies and variation in microorganism nomenclature were filtered out from the dataset. The names of the organisms and the categories of antimicrobial sensitivity were standardized prior to analysis, and antimicrobial results of unknown or unavailable were not imputed. Observations that were culture-positive were grouped by the uropathogen identified. Major organisms, representative of the data set, such as Escherichia coli, Klebsiella spp., Pseudomonas spp. were used for detailed comparative evaluations.

### 2.3 Antimicrobial Susceptibility Assessment

Susceptibility profiles were determined for the following antimicrobials: amoxicillin-clavulanate, ceftazidime, ceftriaxone, ciprofloxacin, meropenem, nitrofurantoin, piperacillin-tazobactam. The number of organisms isolated was used as denominator to quantify susceptible and resistant organisms for each organism–antibiotic combination. The percentages of susceptibility and resistance were then determined for each organism. This could allow direct comparisons of antimicrobial activity between the major uropathogens.

### 2.4 Statistical Analysis

Frequencies and percentages were used to summarize categorical variables, and cross tabulations were constructed to compare antimicrobial resistance by major uropathogens. Associations between categorical variables were evaluated using Pearson's chi-square test, with Fisher's exact test being used when the expected frequencies were too small. Available patient and healthcare characteristics were compared by resistance patterns as appropriate. All tests were two-tailed ($p<0.05$ was considered statistically significant) and were analysed with Python.

### 2.5 Assessment of Implications for Empirical Treatment

The observed susceptibility of the most common uropathogens was used to comparatively evaluate antimicrobial agents. Agents with higher and consistent susceptibility were interpreted as having more in-vitro activity while high resistance was interpreted as being less microbiologically reliable for empirical coverage within the studied population. The prevalence of pathogens was considered in addition to susceptibility for clinical interpretation. The implications drawn were limited to those

related to empirical selection and were not used to draw conclusions about the effectiveness of the treatment and/or the outcome of therapy.

## 3. Results

### 3.1 Distribution of Gram-Negative Uropathogens

Finally, 604 isolates of Gram-negative uropathogens were analyzed. Of the 397 isolates, 397 were from female patients (65.7%) and 207 were from male patients (34.3%). The majority of the isolates were from inpatients (382, 63.2%) and 222 (36.8%) were outpatients. The most common uropathogen was Escherichia coli (339 (56.1%) isolates), followed by Klebsiella spp. (222, 36.8%), Pseudomonas spp. (35, 5.8%), and Proteus spp. (8, 1.3%) (Table 1). The total Gram-negative isolates (92.9%) were mainly composed of E. coli and Klebsiella spp. as shown in Figure 1.

**Table 1. Characteristics and distribution of Gram-negative uropathogen isolates**

| Characteristic | Category | n (%) |
|---|---|---|
| Sex | Female | 397 (65.7) |
| | Male | 207 (34.3) |
| Clinical setting | In-patient | 382 (63.2) |
| | Outpatient | 222 (36.8) |
| Uropathogen | Escherichia coli | 339 (56.1) |
| | Klebsiella spp. | 222 (36.8) |
| | Pseudomonas spp. | 35 (5.8) |
| | Proteus spp. | 8 (1.3) |

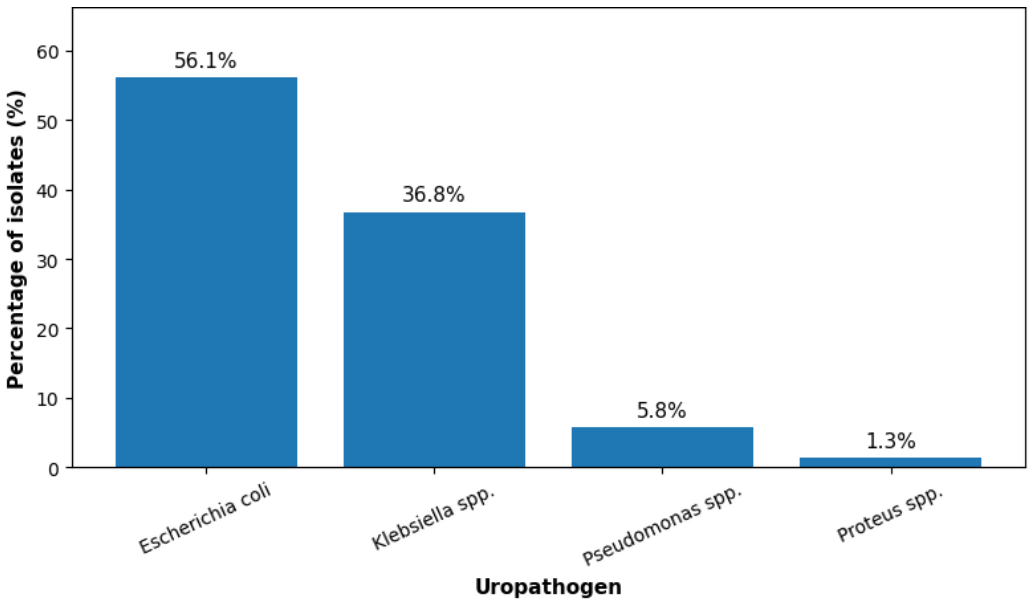


**Figure 1. Distribution of Gram-negative uropathogens among the analyzed isolates**

### 3.2 Overall Antimicrobial Susceptibility Profiles

Significant differences in antimicrobial susceptibility were found among the 7 agents tested (Table 2). Meropenem had the highest susceptibility in-vitro with 524/604 (86.8%) susceptible isolates and 64/604 (10.6%) resistant. The percentages of susceptibility to nitrofurantoin and ciprofloxacin were 55.1% and 54.6% respectively. Amoxicillin-clavulanate was the least susceptible (19.7%) and most resistant (69.5%). Piperacillin-tazobactam and ceftazidime had high levels of resistance as well (49.3% and 42.9%). Of the 339 isolates tested for which Ceftriaxone results were available, 49.6% were resistant. The differential sensitive, intermediate and resistant profiles are illustrated by the tested antimicrobial agents in Figure 2.

**Table 2. Overall antimicrobial susceptibility profiles of Gram-negative uropathogens**

| Antimicrobial agent | Tested, n | Sensitive, n (%) | Intermediate, n (%) | Resistant, n (%) |
|---|---|---|---|---|
| Meropenem | 604 | 524 (86.8) | 16 (2.6) | 64 (10.6) |
| Nitrofurantoin | 604 | 333 (55.1) | 33 (5.5) | 238 (39.4) |
| Ciprofloxacin | 604 | 330 (54.6) | 57 (9.4) | 217 (35.9) |
| Ceftazidime | 604 | 281 (46.5) | 64 (10.6) | 259 (42.9) |
| Piperacillin-tazobactam | 604 | 264 (43.7) | 42 (7.0) | 298 (49.3) |
| Ceftriaxone | 339 | 112 (33.0) | 59 (17.4) | 168 (49.6) |
| Amoxicillin-clavulanate | 604 | 119 (19.7) | 65 (10.8) | 420 (69.5) |

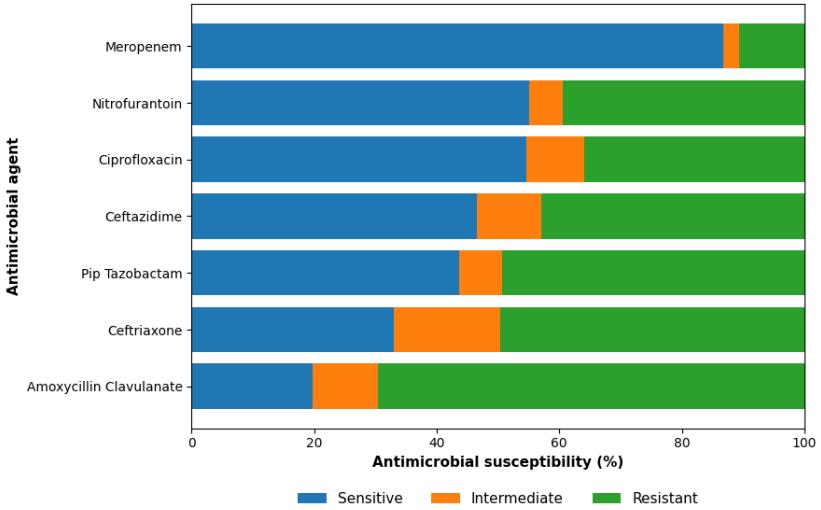


**Figure 2. Overall antimicrobial susceptibility profiles of Gram-negative uropathogens**

### 3.3 Organism-Specific Antimicrobial Resistance

The distribution of resistance pattern was different for the identified uropathogens (Figure 3). Amoxicillin-clavulanate (69.3%) was the most effective antibiotic against E. coli, followed by ceftriaxone (49.6%), piperacillin-tazobactam (46.6%), and ceftazidime (44.2%). The level of resistance to meropenem in E. coli was relatively low (7.4%). High resistance was also seen for Klebsiella spp. with amoxicillin-clavulanate (65.3%) and piperacillin-tazobactam (55.0%) and resistance to meropenem was 14.0%. Other less common organisms, 34/35 (97.1%) Pseudomonas spp. were resistant to amoxicillin-clavulanate. As there were only 35 Pseudomonas and eight Proteus isolates available these estimates were interpreted descriptively.

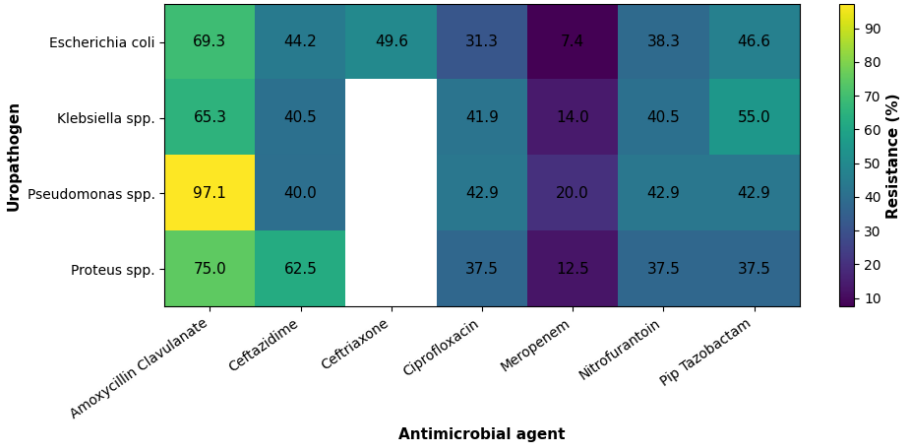

**Figure 3. Organism-specific antimicrobial resistance rates across Gram-negative uropathogens**

The two most well represented bacteria (E. coli and Klebsiella spp) were used for formal inferential comparison only (Table 3). The resistance rate for Ciprofloxacin was significantly lower in E. coli than Klebsiella spp. This was statistically significant before (OR=0.631, unadjusted p=0.010) and after (OR=0.631, adjusted p=0.033) false discovery rate (FDR) correction. The same situation was observed with meropenem: resistance was 7.4% for E. coli and 14.0% for Klebsiella spp. (OR=0.491, p=0.011; FDR-adjusted p=0.033). There was no FDR significant organism-level difference in the remaining agents.

**Table 3. Resistance comparison between Escherichia coli and Klebsiella spp.**

| Antimicrobial agent | E. coli, n/N (%) | Klebsiella spp., n/N (%) | OR | p-value | FDR-adjusted p |
|---|---|---|---|---|---|
| Amoxicillin-clavulanate | 235/339 (69.3) | 145/222 (65.3) | 1.200 | 0.321 | 0.463 |
| Ceftazidime | 150/339 (44.2) | 90/222 (40.5) | 1.164 | 0.385 | 0.463 |
| Ciprofloxacin | 106/339 (31.3) | 93/222 (41.9) | 0.631 | 0.010 | 0.033 |
| Meropenem | 25/339 (7.4) | 31/222 (14.0) | 0.491 | 0.011 | 0.033 |
| Nitrofurantoin | 130/339 (38.3) | 90/222 (40.5) | 0.912 | 0.603 | 0.603 |
| Piperacillin-tazobactam | 158/339 (46.6) | 122/222 (55.0) | 0.716 | 0.053 | 0.106 |
| Ceftriaxone | 168/339 (49.6) | Not tested | — | — | — |

OR represents the odds of resistance in E. coli relative to Klebsiella spp.

### 3.4 Resistance According to Clinical Setting

There were a few differences between inpatient and outpatient isolates prior to adjustment. There was no difference in resistance to ciprofloxacin between isolates from inpatient and outpatient settings, with resistance rates of 32.5% and 41.9%, respectively (p=0.020). Corresponding rates were 8.6% versus 14.0% for meropenem (p=0.040) and 46.1% versus 55.0% for piperacillin-tazobactam (p=0.035). However, none of these comparisons in the clinical setting remained significant after FDR correction (all adjusted p≥0.081). High prevalence of amoxicillin-clavulanate resistance was seen in both settings: 72.0% vs. 65.3% of inpatient/outpatient isolates, respectively. In the inpatient subset, susceptibility results were available and were compared across the different settings for ceftriaxone; however, this was not done for the other antibiotics.

### 3.5 Multiple-Antibiotic Resistance Burden

The six antimicrobial agents tested were used to assess the antimicrobial resistance burden. Overall, 43.2% (261/604) of the isolates were resistant to three or more of the six agents. Of the isolates, 184 (30.5%) were sensitive to none of these agents, 149 (24.7%) were resistant to five and 64 (10.6%) were resistant to all six antimicrobials tested. Resistance rates for E. coli, Klebsiella spp., Pseudomonas spp. and Proteus spp. were 44.2%, 41.9%, 42.9% and 37.5%, respectively, of organisms resistant to at least three agents. No significant association was found between this resistance burden classification and the 2 major uropathogens ($\chi^2$=0.215, p=0.643). Resistance to ≥3 agents were also higher in 44.0% of inpatient and 41.9% of outpatient isolates and was not significantly associated with clinical setting ($\chi^2$=0.171, p=0.679).

Taken together, these results indicate that there is significant inter-strain variation in

antimicrobial activity of Gram-negative urinary isolates. Meropenem had the best overall in-vitro activity, with high resistance rates for amoxicillin-clavulanate. Having multiple-testing corrected the results, the resistance difference between E. coli and Klebsiella spp. with the antibiotics ciprofloxacin and meropenem persists, pointing to the fact that empirical antimicrobial coverage can't be assumed across the predominant uropathogens.

## 4. Discussion

The present study revealed a significant burden of antimicrobial resistance in the Gram-negative uropathogens, and a high degree of variation among organisms for each individual antibiotic. E. coli was the most common isolate (56.1%) and Klebsiella spp. were the next most common (24.6%). (36.8%) again reinforcing the main role of Enterobacterales in the UTI. The susceptibility evidence that is generated locally is important for clinical decision making, as the etiology and resistance of UTIs have varied among patient populations as demonstrated by long term hospital surveillance, as well as susceptibility data from the literature (Huang et al., 2022). This type of surveillance is of special interest, because antimicrobial resistance is a significant contributor to infectious-disease mortality and morbidity throughout the world (Antimicrobial Resistance Collaborators, 2022).

The most worrisome was the overall resistance to amoxicillin-clavulanate (69.5%). The resistance rates for piperacillin-tazobactam (49.3%), ceftazidime (42.9%) and nitrofurantoin (39.4%) were also high. These patterns indicate that a few agents are not as reliable when treatment is based on no susceptibility data. Bacterial resistance can develop by several mechanisms: enzymatic inactivation of the drug, modification of the drug target, decreased uptake of the drug, efflux mechanisms and acquisition of transferable resistance determinants (Urban-Chmiel et al., 2022). Therefore, the choice of antibiotic based on empirical therapy may have a higher risk of discordant therapy if it is done in the way it is done conventionally. This is clinically relevant as inappropriate empirical treatment of Enterobacterales UTIs with nonsusceptible bacteria has been found to be associated with worse outcomes (Dunne et al., 2022).

Meropenem had the highest percentage of susceptibility (86.8%) and resistance (10.6%). However, Klebsiella spp. showed a much greater resistance rate than E. coli (14.0% versus 7.4%) and after FDR correction this difference was still significant ($p=0.033$). Similarly, the resistance of Klebsiella spp. to Ciprofloxacin was higher than E. coli (41.9% vs. 31.3%, adjusted $p=0.033$). The results show that percentage results are not necessarily applicable to every organism and indicate clinically relevant differences from the antibiotic patterns of the organisms. It is therefore essential to have surveillance systems that can detect these patterns to maintain antimicrobial effectiveness and guide empirical treatment strategies (Tacconelli et al., 2018). Even though meropenem appears to be a very active antibiotic, it is not to be considered a ‘standard first choice empirical agent' and should be avoided unless there is a clear need. It is important to note that the use of broad-spectrum antibiotics can increase selective pressure. The principles of stewardship, on the other hand, promote targeted prescribing and conservation of critically important antibiotics (Majumder et al., 2020).

Another issue was the compound resistance load. Overall, 43.2% of isolates were resistant to three or more of the six agents tested universally; five (24.7%) resistant to five agents and 10.6% resistant to all six agents. There was no significant difference in the percentage resistant to at least 3 agents between E. coli and Klebsiella spp. The results showed that there was no significant difference between the extent of resistance ($p=0.643$) and that extended to one of the major uropathogens. A robust antimicrobial stewardship program can help minimize inappropriate exposures, and better antibiotic selection, including making sure that antibiotic prescribing decisions consider microbiological data (Khadse et al., 2023). An essential part of this is ‘culture-guided modification of therapy' (Altaf et al., 2023).

Many differences between clinical and non-clinical settings were also observed in the initial analyses for ciprofloxacin, meropenem and piperacillin-tazobactam; however, none of these differences remained significant after FDR correction. Therefore, these differences are not to be regarded as good evidence of setting-specific resistance. However, the information on surveillance should be combined with each person's clinical and microbiological data, rather than being used as a guide for selecting empirical therapy (de la Court et al., 2022).

The study has the following limitations: The design was a retrospective secondary data analysis; the numbers of Pseudomonas and Proteus isolates were small; some isolates were not tested for ceftriaxone. Patient-level factors, prior antibiotic use, treatment response and clinical outcomes were not available. However, the results indicate high degree of antibiogram variability across the region and further highlight the need for regular antibiogram monitoring, culture-based treatment and use of appropriate antibiotics in empirical treatment of UTIs to ensure availability of effective treatment.

## 5. Conclusion

This study clearly shows the significant and variable degree of antimicrobial resistance of uropathogens, which has implications for empirical therapy of UTIs. Most isolates were of Escherichia coli followed by Klebsiella spp. uropathogens. Amoxicillin-clavulanate showed the highest level of resistance, and significant resistance was seen for piperacillin-tazobactam, ceftriaxone, ceftazidime and nitrofurantoin. Meropenem was the most active antimicrobial agent overall in vitro, but meropenem resistance has been identified with the increased number of isolates, especially Klebsiella spp., thus requiring prudence in use. They’re remain significant differences in ciprofloxacin and meropenem susceptibility between organisms, even after multiple comparisons, suggesting that estimates of aggregate susceptibility may mask clinically relevant differences between the major uropathogens. Moreover, 43.2% of isolates were susceptible to only three of the six antimicrobial drugs that are tested globally, which shows a high level of combined resistance. In contrast, resistance patterns did not differ significantly between inpatient, and outpatient isolates after adjustment for multiple testing. These results indicate the routine use of local antibiograms, periodic surveillance of resistance and the use of culture-based treatment to guide the empirical prescribing to be beneficial. To maintain therapeutic efficacy and further selection of resistant uropathogens, antimicrobial stewardship and judicious use of broad-spectrum agents will be critical.

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