

Current Trends in Resistance Patterns in *Escherichia Coli* Associated Urinary Tract Infections in Adults in a Tertiary Hospital in Douala Cameroon

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Abstract

Urinary Tract Infections are frequently encountered in clinical practice and are a real burden to healthcare. This research was motivated by the frequent treatment failures observed following empirical therapy of Urinary Tract Infections (UTIs) especially with oral antibiotics. The research was a retrospective cross-sectional study. The data was extracted from the registers in the Laboratory used to record results for Culture and Sensitivity. Data collection covered the period from December 2023 to June 2024 and considered 203 samples for analysis for which culture results were positive for bacterial uropathogens in adult, non-pregnant patients above 14 years of age. The main objective was to identify the various other uropathogens besides *E. coli* commonly associated with UTI within the health facility and examine their sensitivity and resistance patterns that can inform therapeutic decisions in clinical practice, especially in the absence of a functional microbiology laboratory, as well as influence the essential medicines list.

The research identified the five leading causes of UTI to include *E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Citrobacter freundii* and *Enterobacter* spp. We observed massive resistance to oral and injectable antibiotics with no obvious trend, making empirical therapy very difficult, even for simple UTIs. Therefore, drawing from the results and the massive resistant patterns Culture and Sensitivity remain the gold standard in the management of UTI for both simple and complicated UTIs, and the therapeutic approach should consider combination therapy.

Keywords: Urinary Tract Infections, Antimicrobial Resistance, *Escherichia Coli*, Culture and Sensitivity, Uropathogens

Introduction

Background

In normal clinical practice, Urinary Tract Infections (UTIs) are encountered on a daily basis. Odoki, et al., found a prevalence of 32.2% in Bushenyi District in Uganda among patients attending hospitals, with higher preponderance in females than in males [1]. The exact burden in Cameroon has not been established. Nationwide, there is a paucity of literature on the exact burden of UTIs both in the hospital as well as in the community. However, some literature documents the burden in certain regions of the country. Ngong, Fru-Cho, Yung, & Akoachere, document a prevalence of above 54% within the North West and South West Regional capitals of Cameroon [2]. In other LMICs like Namibia, a study on Diabetic patients revealed a 9.8% prevalence, with the most causative agent being *E. coli*, the same leading causative agent in all settings [3].

Problem Statement

The driving force behind the choice of this topic was the increased rate of treatment failure of UTI treatment to empirical therapy in the hospital which receives patients from all over Douala II, as well as from other parts of the Littoral region. Treatment options classified as first-line were noticed to be increasingly becoming worthless, as patients were observed to return with the same or worsened symptoms after treatment, and upon repeat of Urinalysis, the same results as in the prior treatment period are obtained; in some cases, the symptoms and results were found to have worsened. Additionally, with some of the cases of UTI received in daily practice, culture reveals an irksome level of resistance of some of the uropathogens to 3rd and 4th generation fluoroquinolones. Equally, resistance to reserved molecules like the Carbapenems, 3rd and 4th generation cephalosporins, and Macrolides was as well observed. This observation, as well as the insufficiency of literature on the exact prevalence, and the susceptibility pattern of *E. coli* and other uropathogens led to the choice of the topic “Current Trends in Resistance Patterns in

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Escherichia coli associated Urinary Tract Infections in Adults in a tertiary hospital in Douala Cameroon”.

Research Objectives Main Objective

The purpose of this research was to highlight the current resistance pattern exhibited by *Escherichia coli*, the major pathogen implicated in UTI, as well as other leading uropathogens, and to recommend novel approaches in therapy to achieve better patient outcomes.

Specific Objectives

The specific objectives of this research are as follows:

- Establish the leading cause of UTI in the hospital,
- Investigate the other associated uropathogens,
- Determine the sensitivity patterns of various uropathogens, including *E. coli*,
- Identify the resistance pattern of the various uropathogens,
- Suggest better treatment approaches in empirical therapy,
- Propose better approaches in sensitivity testing based on the observed resistance pattern.

Materials And Method

Research Design

We conducted a retrospective cross-sectional research within a very heavily utilised tertiary Hospital in the Douala II Municipality. Data was extracted from the Hospital Laboratory Register from December 06, 2023, to June 06, 2024, as cut-off points.

Study Population

The study population was all the patients attended to at the tertiary hospital within the period of the study from December 06, 2023, to June 06, 2024, corresponding to about 130 127 patients.

Target Population

We targeted male and female, non-pregnant patients aged from 15 years and above received at the facility within this period, with a suspected infection, and for whom culture and antimicrobial susceptibility testing was considered a possible diagnostic procedure.

Simple Size Determination

The following formula extracted from Charan & Biswas, below was employed in the determination of the sample size for the research [4].

$$\text{Sample Size} = \frac{Z_{1-\alpha/2}^2 p(1-p)}{d^2}$$

Where $Z_{1-\alpha/2}$ = Standard Normal variate at 5% type 1 error ($p < 0.05$) = 1.96; p = expected proportion of resistant UTI in the population, estimated at less than 15% (0.15) for the current research; d = absolute error of precision, set at 5 (0.05) for this research.

Substitution into the formula gave 196 as the sample size. Thus, 203 samples were considered in the research, who included male and female non-pregnant patients over 15 years attended to in the Laboratory between December 06, 2023, and June 06, 2024, with symptoms suggestive of UTI, for whom culture and antibiotic susceptibility testing was considered as a diagnostic option, and who had a growth from the urine culture.

Urine Sample Collection

The Laboratory personnel systematically instruct patients to provide an adequate midstream urine (MSU) sample following step-by-step procedure, and then deliver the sample to the Microbiology Laboratory of the tertiary health facility immediately after collection.

Laboratory Procedure and Culture Technique

The laboratory personnel first performed dipstick and then subjected the samples to culture and antimicrobial susceptibility testing. Samples were cultured for three days using the following procedure in the following sequential manner:

- **Day 1:** Inoculation of sample on Cysteine-Lactose-Electrolyte-Deficient (CLED) Agar and incubating at 35-37°C and checking for growth after 18-24 hours according to clinical laboratory standards.
- **Day 2:** Plates with evidence of growth of greater than 10^4 colony forming units (CFU)/ml were then subject to identification of isolates using the 0.5 McFarlan's Standard and performing susceptibility testing using the Disc Diffusion Method. Plates with growth less than 10^4 CFU/ml were considered and reported as insignificant growth; plates with no visible colonies were reported as having no growth.
- **Day 3:** Reading and reporting the susceptibility results.

Inclusion Criteria

Only culture results for UTI in adult, non-pregnant patients were considered for evaluation in the study. While the research focused on *E. coli* associated UTIs, all causative organisms of UTI were equally examined.

Exclusion Criteria

All results in children under 15 years of age, as well as results of pregnant women were exempted from the research. Additionally, cultures with fungal isolates as well as multiple pathogens were as well excluded from the evaluation.

Ethical Consideration and Consent

The research was retrospective research extracting data from a database and did not involve any direct interaction with the patients. Therefore, no patient consent was obtained. However, administrative clearance was obtained. Data for the research was extracted from the registers in the Laboratory in the presence of the personnel to ensure that no data related to the identity of the patient was collected. Besides, the collected data was securely stored in a password protected laptop accessible only to the researchers to limit unauthorised access.

Results

Overview of Microbiological Exams within the Period

A total of 1740 Cultures were done within the period of the study, out of which 548 (31.49%) were Urine Samples. Of these 548, pathogens were isolated in 310 samples giving a clinical suspicion accuracy of 56.57%. From these 310 positive samples, 203 (65.48%) met the inclusion criterion and were thus analysed (Figure 1). The other samples were excluded based on the inclusion and exclusion criteria stated earlier.

Demographics

As seen in Figure 2, there was a preponderance of UTI in the age group 25-34, followed by 35-44 group. The least prevalence

was found in age group of 45-54 accounting just for 6.4% of all UTIs.

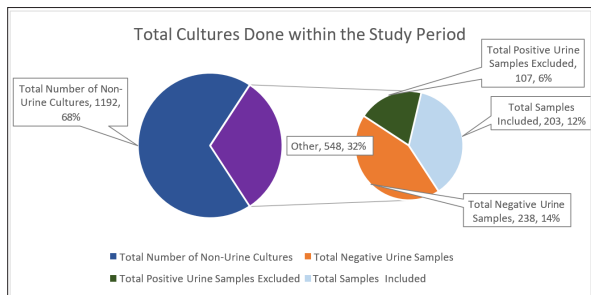


Figure 1: Total Cultures Done within the Study Period

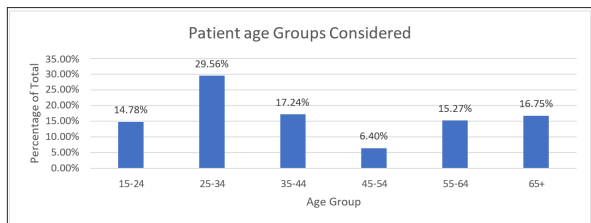


Figure 2: Age Group of Participants

These cases were distributed disproportionately between the male (69 out of 203, 33.99%) and female gender (134 out of 203, 66.01%).

The leading causative agent for UTI among the 203 cases was *E. coli* accounting for 33% of all UTI cases followed by *Staphylococcus aureus* (22%) and *Klebsiella pneumoniae* (7.3%). The least causes are *Staphylococcus saprophyticus*, *Micrococcus*, *Yesinia spp*, *Shigella spp* and *Streptococcus spp* each accounting for 0.49% as illustrated Figure 3.

Major Causative Agents of UTI

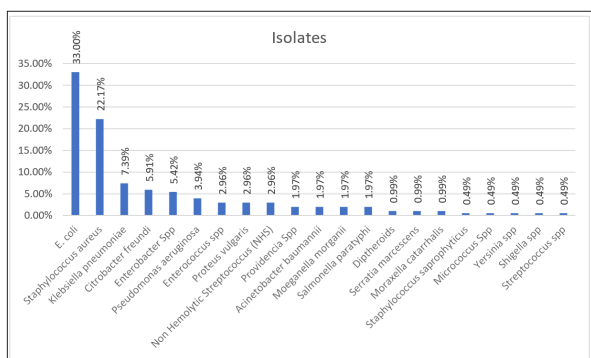


Figure 3: Various Isolates identified in the Study

E. coli Patterns

Escherichia coli, the leading cause of UTI exhibited the following characteristic Sensitivity and Resistance patterns as illustrated in Figure 4 and Figure 5 below, with the highest sensitivity to Meropenem, followed by Amikacin, the worst choice of antibiotics being TMP-SMX, Ampicillin, Ciprofloxacin, vancomycin and cefoxitin.

As shown in Figure 5, the leading resistance to *E. coli* associated UTI is noticed with Cefixime and Amoxicillin/Clavulanic acid, followed by Ofloxacin and Ceftriaxone. The least resistance is

noticed with Tobramycin, Norfloxacin, Oxacillin and Cloxacillin.

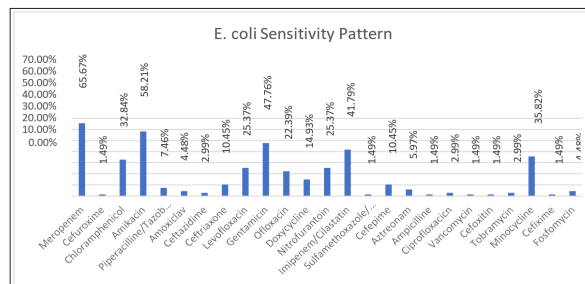


Figure 4: *E. coli* Sensitivity patterns

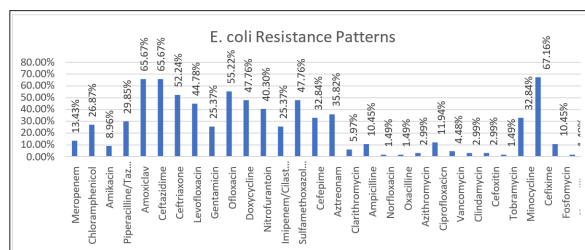


Figure 5: *E. coli* Resistance Patterns

Staphylococcus Aureus Patterns

Staphylococcus aureus was found to be the second leading cause of UTI responsible for 22% of all UTI cases. The sensitivity pattern exhibited by *Staphylococcus aureus* is as depicted in Figure 6, indicating that the aminoglycosides Gentamicin and Amikacin; and the tetracycline Minocycline, as well as Vancomycin and Imipenem/Cilastatin are the best antibiotics against this organism with sensitivity patterns of over 52%, The least sensitivity is with Ofloxacin, ampicillin, Cefoxitin and Cefixime.

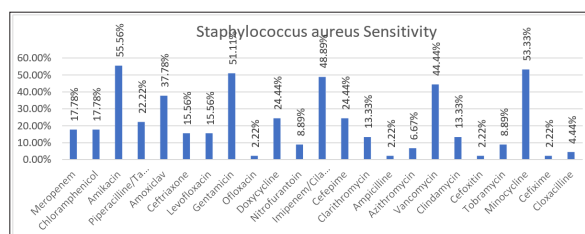


Figure 6: *Staphylococcus aureus* Sensitivity Patterns

Figure 7 below presents the resistance patterns of *Staphylococcus aureus* to various antimicrobial agents. We notice that Oxacillin, one of the antibiotics used in treating *Staphylococcus infections* is resistant in 66% of all isolates due to *Staphylococcus aureus*, followed by Ampicillin. The least resistance was noticed with Tobramycin, Fosfomycin, Ofloxacin and Norfloxacin.

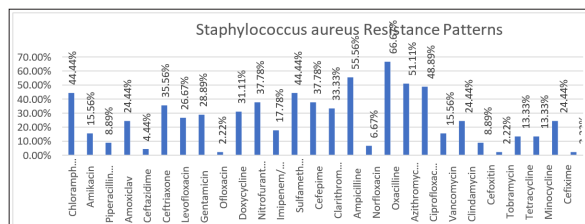


Figure 7: *Staphylococcus aureus* Resistance Patterns

Klebsiella Pneumoniae Patterns

The third leading cause of UTI, *Klebsiella pneumoniae* (7.39%), manifested the following patterns as on Figure 8 to Figure 9.

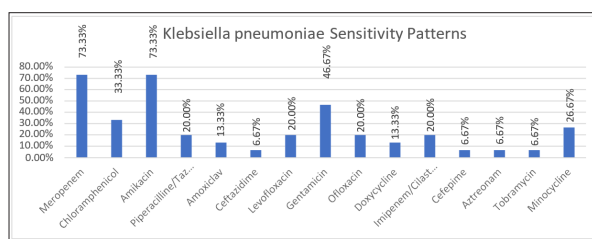


Figure 8: *Klebsiella pneumoniae* Sensitivity patterns

We observe again that for *Klebsiella pneumoniae*, Amikacin and Meropenem are the antibiotics to which *Klebsiella pneumoniae* exhibited the most sensitive of all the antibiotics used in the study with over 70% sensitivity (Figure 8).

Amoxicillin/Clavulanic Acid, Cefepime and TMP-SMX are the leading antibiotics to which there is massive resistance with over 73% of the isolates resistant to them (Figure 9).

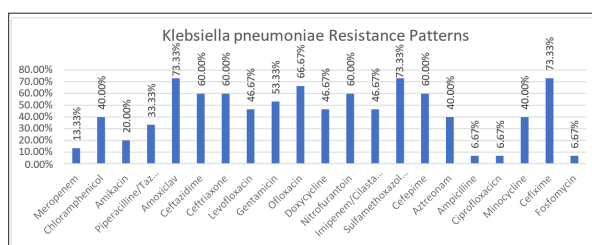


Figure 9: *Klebsiella pneumoniae* Resistance Patterns

Citrobacter Freundi Patterns

12 samples out of the 203 considered in this research (5.91%) were UTIs caused by *Citrobacter freundii*. Its patterns are illustrated in Figure 10 to Figure 11 that follow. We observe again that Meropenem and Amikacin remain the ideal choices of antimicrobial agents against *Citrobacter freundii* infections, each with sensitivity to over 66% of the isolates.

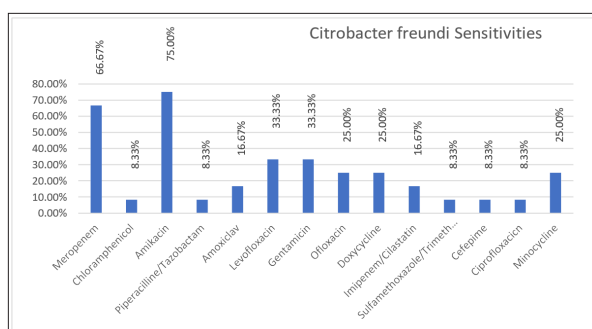


Figure 10: *Citrobacter freundii* Sensitivity Patterns

Nitrofurantoin, Amoxicillin/Clavulanic Acid, Imipenem/Cilastatin all appear as in Figure 11 to be the worst choices of antimicrobial agents used to empirically treat *Citrobacter freundii* associated infections with resistance patterns well above 52% for each of the antimicrobials.

Enterobacter Spp Patterns

Enterobacter spp. was found to be the fifth leading cause of UTI. It exhibited sensitivity patterns as on Figure 12. Meropenem and Amikacin are the ideal antibiotics for these infections

with over 63% sensitivity. The least sensitivity is noticed with Piperacillin/Tazobactam, Levofloxacin, Gentamicin; Ofloxacin, Doxycycline, Nitrofurantoin, Cefixime and Fosfomycin with less than 10% sensitivities.

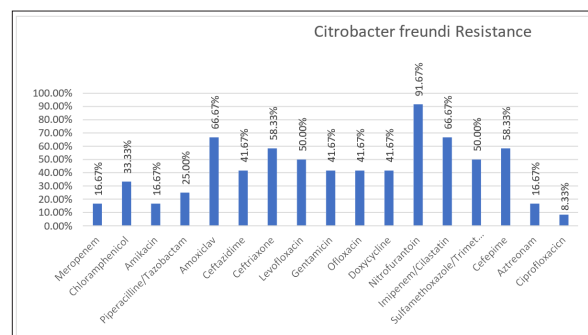


Figure 11: *Citrobacter freundii* Resistance Patterns

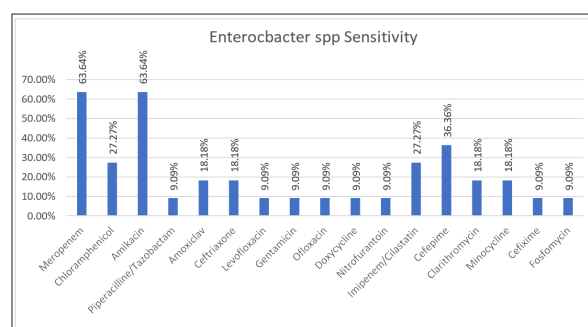


Figure 12: *Enterobacter spp* Sensitivity Patterns

Other Causative Agents of UTI

Isolated cases of the 203 cases of UTI considered in this research were due to *Pseudomonas aeruginosa*, *Yersinia spp*, *Providencia spp*, *Moraxella catarrhalis*, *Enterococcus*, *Staphylococcus saprophyticus*, *Micrococcus spp*, *Serratia marcescens*, *Proteus vulgaris*, *Acinetobacter baumannii*, Non-haemolytic Streptococci, *Morganella morganii*, *Shigella spp*, *Streptococcus spp* and possible faecal contaminants *Salmonella paratyphi*, with sensitivity and resistance patterns similar to those exhibited by the five leading causes of UTIs.

Trends in Susceptibility Patterns

Overall, the identified causative agents of UTIs exhibited minimal sensitivity and massive resistance patterns to all orally active antibiotics. With Chloramphenicol, resistance was at 56.92% and sensitivity was at 36.92% for all cases tested. With the β -Lactam antibiotics, it was observed that Amoxicillin/Clavulanic Acid, tested in 154 of all the isolates, resistance rate was 64.94%, Oxacillin was 100% resistant, and Cloxacillin at 79.17%. Cefixime, a third-generation Cephalosporin was 90.55% resistant. Regarding the fluoroquinolones, Levofloxacin had resistance rate of 60.43%, Ofloxacin 66.67%, Norfloxacin 71.43%, Ciprofloxacin 79.59% and Nitrofurantoin 57%. The tetracycline doxycycline was resistant to 62% of the microbes, while Minocycline was 41.48%; TMP-SMX resistant to 96.23% of all isolates. For the macrolides, Clarithromycin had 70.59% resistance, Erythromycin had 100% and Azithromycin 97.18%. Resistance to Clindamycin was 56.00%.

Discussion

Amoxicillin/Clavulanic Acid is a reliable oral antibiotic for most infections and not recommended in most literature for the

empirical treatment of simple UTIs due to its broad spectrum but recommended for severe infections including UTIs [4]. It was tested in 154 of the 203 Isolates. Of these, only 48 cases of the various isolates (27.27%) were sensitive to it, 7.79% intermediate, and 64.94% of all isolates were resistant. Most literature do not recommend it for empirical therapy of any infection [5], due to its broad spectrum.

Similarly, Levofloxacin is an orally active third generation fluoroquinolone recommended by the European Association of Urologists [4]. in severe UTI treatment. It has documented activity against Extended Spectrum Beta Lactamases (ESBL) producing enterobacteriales [6]. Strangely, Levofloxacin was tested in 139 of all the 203 isolates considered. Of these, only 30.22% were sensitive, 5.05% intermediate and 60.43% were resistant to Levofloxacin. This massive resistance limits therapeutic choices in UTIs known to be caused by ESBL, and may require parenteral, more expensive options with the Carbapenems (Meropemem, Imipenem/Cilastatin or Ertapenem) which all have significant documented activity against ESBL [4]. Available literature, however, recommends that whenever possible, Carbapenem-sparing strategies with non-carbapenem β -Lactams (with a β -Lactamase inhibitor) and non- β -Lactams like fosfomycin should be employed [5].

From the results, we observe that most UTIs are caused by *E. coli*. However, there is an observed shift in the preponderance of *E. coli* associated UTI compared to most literature. Recording up to 90% of all cases of UTI in some settings, we observed that *E. coli* accounted to just 33% of all UTIs [5-7]. We thus observe that *E. coli* is the leading aetiologic agent for UTI, but less prevalent. Up to five organisms (*E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Citrobacter freundii* and *Enterococcus* spp are responsible for 73.7% of all UTIs. These other associated causative organisms are in line with those identified by Christiano [6] as other commonly implicated organisms in UTI [6].

From the findings, one rare organism, *Citrobacter freundii*, was equally identified to be implicated in a minority of UTIs, which Ranjan & Ranjan, and Jabeen, Islam, Hassan, Tasnim, & Shuvo, as a growing and emerging threat in healthcare associated UTI because of its high degree of virulence and the spectrum of Anti-microbial Resistance (AMR), even to apparently reserved and reliable molecules like fluoroquinolones, carbapenems, and colistin [8,9].

It is obvious from these findings that the level of resistance in uropathogenic *E. coli* (UPEC) as well as other Urinary Pathogens is alarming, with varied trends of resistance. This is similar to the varied trend in different settings and countries, thus frustrating any attempt on empirical therapy.

The first line antibiotics that were originally recommended for the treatment of *E. coli* associated UTIs as well as UTI associated with other uropathogens are gradually becoming unresponsive and obsolete. The varied trends in sensitivity and resistance is obvious and results in a varied choice of antibiotics used to test for sensitivity in different settings [10]. Kot highlighted Fosfomycin and Nitrofurantoin as first line treatment options for UPEC in Poland, but this choice seems to be setting dependent as evidenced by the massive resistance to Nitrofurantoin and

Fosfomycin in this research.

The rate at which resistance to antibiotics develops warrants a regular review of the Standard Treatment Guidelines (STGs) for each setting, since empirical therapy is most often the first therapeutic approach to UTI treatment. Alkhawaldeh, Farha, Hammour, & Alefishat, in their study found out that 87.6% of the study participants received empirical antiobiotherapy, yet only 13.4% of these patients were successfully treated empirically [11]. Besides this, Islam, et al. found significant resistance of *E. coli* to penicillin, macrolides, third generation cephalosporins, fluoroquinolones and carbapenems [12]. In this study, the varied trend in resistance patterns implies that empirical therapy is not more an option but must give way to the gold standard of Culture and Sensitivity before therapy.

The massive resistance observed in this study with *E. coli* and *Klebsiella pneumoniae* to the Penicillins, Cephalosporins and the Carbapenems is in congruence with the patterns documented by the CDC [13]. This is most probably because these Enterobacteria produce the ESBLs enzyme and thus result in MDR Enterobacteria associated UTI.

Most UTIs are simple infections and need to be treated on out-patient basis with oral antibiotics. The observed resistance to antibiotics, especially with oral antibiotics means that clinicians will soon run out of therapeutic options for simple UTIs and will be compelled to use systemic treatment options only after culture and sensitivity. This may warrant a reclassification of UTIs and pose the question whether there truly exists anything again called "simple UTI".

Salmonella paratyphi was identified in four out of the 203 samples. The observation that all four samples were women, indicate a possible contamination of the urine sample from stool originating from the perineal area due to inappropriately collected urinary sample. Generally, if clear instructions are not given, especially to the elderly female patients, they can produce contaminated samples that will result in wrongful diagnosis and overtreatment of UTIs. However, Altaf, Tunio, Tunio, Zafar, & Bajwa document a case of *Salmonella* UTI following Non-typhoidal *Salmonella* Gastroenteritis, and highlight structural abnormalities of the urinary tract, immunodeficiency and chronic illness as predisposing factors, which could not be rolled out in the present study since data collection was retrospective [14].

Recommendations and Conclusions

This research sought to identify the leading causes of UTI in a tertiary hospital in Douala II Cameroon, as well as the other associated pathogens commonly encountered. The research equally targeted elaborating the susceptibility patterns of uropathogens, highlight the common antibiotics used in the sensitivity testing, and recommend novel first line treatment regimens for empirical therapy, drawing from the findings, while identifying antibiotics that should never be considered in the treatment of UTI following the resistance patterns.

The study found out that the leading five causes of UTI in adults in Douala II Cameroon include *E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Citrobacter freundii*, and *Enterococcus* spp. Apart from *Staphylococcus aureus*, all the leading causes of

UTI are members of the Enterobacteriaceae family and potential producers of ESBL enzyme.

These uropathogens exhibit varied sensitivity and resistance patterns that make it extremely difficult to define a treatment guideline for empirical therapy in adult patients with a UTI. Much of the resistance was found to be linked to oral antibiotics that are usually prescribed on out-patient basis. This makes therapy for uncomplicated UTI very difficult and expensive for the patient as most of the patients will now have to be hospitalised before successful treatment.

Additionally, resistance to apparently very effective antibiotics is becoming alarming as identified in the research. Cefixime, a third-generation cephalosporin exhibited 90% resistance in all pathogens, clindamycin 56%, and Fosfomycin 77.8%. Cloxacillin resistance stood at 79%, Amoxicillin/Clavulanic Acid resistance stood at 64.9%, Piperacillin/Tazobactam at 56% among others.

From the above analysis, the researchers arrived at the following recommendations, which are not exhaustive, but will go a step further in solving the acute problem of AMR for Uropathogens and potentially other pathogens.

- Avoid Empirical Therapy on all patients with suspected UTI (even those perceived to be having simple UTIs) owing to the vast resistance highlighted in this research.
- Do urine culture and sensitivity on all patients with suspected UTI to determine the right antibiotics to prescribe following the susceptibility patterns. This option seems expensive but very cost-effective.
- Stop the use of TMP-SMX, Cefixime, Amoxicillin/Clavulanic Acid, and all other antibiotics that exhibited significant resistance until a culture result is obtained indicating susceptibility of the Uropathogen to the said antibiotics.
- Strengthen antimicrobial Stewardship at both local and National levels to combat the geometrically progressing threat of AMR to healthcare delivery.
- Employ combination therapy whenever possible to limit the emergence of resistant pathogens [15-18].

Conflict of Interest

The authors declare that they have no known competing interests that could have influenced the work reported in this paper.

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