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RESEARCH ARTICLE

The Antibiotic Susceptibility Patterns of Uropathogens among Adults with Recurrent Urinary Tract Infection in Mosul, Iraq

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ABSTRACT

The emergence of bacteria resistant to antimicrobial treatments can lead to prolonged hospitalization, increased financial costs, and even mortality. One of the most common bacterial infections, both in hospital and community settings, is recurrent urinary tract infections (UTIs). This study aimed to investigate the antibiotic resistance patterns of the most commonly used antibiotics and identify the causative uropathogenic bacteria isolated from the urine of patients suffering from recurrent UTIs. The study recruited 77 patients diagnosed with recurrent UTIs who had not received antibiotic therapy in the last 14 days, and collected urine samples for analysis. Using the disk diffusion method per the Clinical and Laboratory Standards Institute's guidelines, the study found that Escherichia coli was the most common uropathogens identified in all patients (51.94%), followed by Staphylococcus aureus (20.77%), K. pneumoniae (9.09%), Proteus spp. (7.79%), Enterobacter (6.49%), and P. aeruginosa (3.89%). Alarmingly, all of the isolated bacterial uropathogens were found to be resistant to at least five of the tested antibiotics. The findings of this study have important implications for the treatment of recurrent UTIs, as they provide valuable information on antibiotic resistance patterns and uropathogenic bacteria that can inform the development of more effective antibiotic regimens. This knowledge will empower physicians with the information they need to make informed decisions when treating recurrent UTIs.

1. Introduction

Antibiotics are one of the most effective treatments for bacterial illnesses, including urinary tract infections, however bacteria can rapidly acquire resistance to them. Antimicrobial resistance is becoming a major public health concern. Bacteria resistant to antimicrobial drugs have a dynamic nature that can cause prolonged disease, considerable economic burden, and even death. Infectious pathogens that develop multidrug resistance (MDR) have a higher rate of morbidity and mortality[1].

Recurrent urinary tract infections (UTIs) are the most common bacterial infections both in hospital and community settings[2]. Recurrent UTIs are a major cause of hospitalizations and are directly connected with high economic costs, morbidity, and mortality[3,4]. Globally, UTIs are reported to influence about 150 million humans per year, costing the world's economy, 2002 USD, as much as 6 billion[5]. Recurrent UTIs occur in both genders and in all age groups, however, their occurrence rises with age and the annual incidence of UTIs in the older people ranges from 10% in the community to 30% of the hospitalized patients[3]. Also, recurrent UTIs are more frequent in females than males. It is estimated that 50–60% of females experiencing at least one UTI in their lifetime[4].

The majority of Recurrent UTIs are caused by Enterobacteriaceae and the most prevalent pathogen is E. coli and nearly 90% of all UTI cases are due to the Uropathogenic Escherichia coli (UPEC). Other bacteria, such as Klebsiella pneumoniae, S. aureus and group B streptococci (GBS), are also responsible for UTIs[6]. Treatment of UTIs cases is often done empirically. The rationale for empiric treatment is rooted from the predictable and limited range of causative bacterial species and their patterns of antimicrobial resistance. Unfortunately, the spectrum and prevalence of antimicrobial-resistant pathogens has risen dramatically in recent years[1]. Interestingly, the antibiotic sensitivity patterns of bacteria differ according the geographical location and time. Therefore, routine surveillance of antibiotic resistance is required and necessary to enhance the recommendations for empiric antibiotic therapy and to promote appropriate use of antibiotics. Hence, detection of shifting pattern in the resistance of the uropathogens against the frequently prescribed antibiotics is a viable approach for empirical therapy[7].

The aim of the current research is to identify the most common uropathogens isolated from the urine of patients suffering from recurrent UTIs, and to determine the resistance patterns of these uropathogens to the most commonly used antibiotics. We assumed that the results will highlight an updated prospective upon the antibiotic resistance tragedy facing UTI treatment. This could be critical in providing health professionals with the knowledge they need to effectively manage and treat patients with recurrent UTIs.

2. Materials and methods

2.1. Study design

The research followed the Declaration of Helsinki and was approved by the Collegiate Committee for Medical Research Ethics in University of Mosul (APPROVAL NUMBER: CCMRE PhA 22 1). Participants' Verbal informed consent was obtained from all subjects before enrollment. This study was conducted from June 2018 to January 2021. Urine samples were collected from 77 patients suspected of recurrent UTI, who had not received antibiotics within the previous 14 days, and referred to the private laboratories for urine culture test. Two months was determined as the cutoff point to determine if the patient has a recurrent UTI or not. All patients were from Nineveh province, Mosul city, north of Iraq.

2.2. Microbiological methods

For bacterial culture, midstream urine samples were taken. Bacteria detection was conducted with the traditional methods in urine cultures, in which substantial replication was identified by incubation at 37 °C for 18–24 hrs. Among the analyzed urine culture results, that of ≥100,000 CFU/ml and single bacterial growth were recognized as a positive result. The in-vitro susceptibility tests against 21 selected antibiotics, which are commonly used for UTI treatment, were performed via the disk diffusion method. The disk diffusion method was car-

ried out in compliance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI)[8]. Basically, a sterile swab was dipped in urine samples and then applied over a Mueller-Hintone Agar plate by streaking the swab over the surface of agar. The process was repeated two times to uniformly cover the whole agar surface. The plates were then allowed to dry for 5-10 minutes. A sterile forceps was used to place antibiotics discs over the agar surface (11 antibiotic disks per 150 mm plate) leaving a fare distance from the edge of plate (15 mm). plates were then incubated for 18-24 hours at 37 °C after which, the inhibition zone were measured per each disk. Five replicates of each set of antibiotics were measured and the mean was taken.

2.3. Exclusion criteria

In the evaluated cases, 283 out of the total 421 patients were initially excluded from the study because they were cultured negative for bacterial growth, refused to give verbal consent, or their age was less than 18 years. Whereas, the results of the urine culture sensitivity tests for the remaining 138 patients were evaluated. Only 77 patients were classified as having recurrent UTI at the time of evaluation.

2.4. Statistical analysis

Descriptive statistical analysis has been carried out, including mean and standard deviation, and findings are reported as frequencies and mean percentages using Microsoft Excel® 2016.

3. Results

3.1. Demographics of Study Population

A total of 77 urine samples were collected from patients with recurrent UTIs during this study period. Among these samples, 42 (54.5%) belonged to female with recurrent UTIs whereas 35 (45.4%) belonged to male patients; as shown in figure 1.

3.2. The isolated uropathogens

The isolated bacterial uropathogens were Escherichia coli (51.94%) was identified as the most common uropathogens in all patients, Klebsiella pneumoniae (9.09%), Pseudomonas aeruginosa (3.89%), Proteus spp. (7.79%), Enterobacter (6.49%). Whereas, surprisingly, (20.77%) of the isolated uropathogens were Staphylococcus aureus; as shown in figure 2.

All isolated bacterial uropathogens were resistant to as a minimum five of the tested antibiotics. Generally, the highest rate of antibiotic resistance was recorded with the K. pneumoniae (92.98% ± 6.8), followed by Enterobacter (87.5% ± 6.7), E. coli (72.61% ±4.4), S. aureus (71.95% ± 3), and Proteus (70.63% ± 4.4). As shown in figure 3.

3.3 The antibiotic resistance patterns

The lowest antimicrobial resistance rates among all isolated uropathogens were to amikacin (23.68%), followed by doxycycline (31.58%), and levofloxacin (36.78%). Whereas the highest resistance rate among all isolated uropathogens were towards amoxicillin (98.53%), ampicillin (97.06 %) and cefixime (93.90%). The general resistance and sensitivity of all the tested antibiotics are shown in figure 4.

3.3.1 The resistance patterns among aminoglycoside antibiotics

The overall sensitivities of the isolated uropathogens against streptomycin, gentamycin, and amikacin were 21.05%, 23.68%, and 76.32%, respectively. As shown in figure 4 and figure 5. Amikacin showed a good antibacterial efficacy against the five uropathogens. Whereas, most of the isolated uropathogens were resistant to both of streptomycin and gentamycin, as shown in figure 5.

3.3.2 The resistance patterns among the cephalosporin antibiotics

The overall sensitivities of the isolated uropathogens against cefixime, ceftriaxone, cephalexin, and cefotaxime were 6.10%, 19.51%, 30.49%, and 42.68%, respectively. As shown in figure 6. Cefixime showed a

weak antibacterial efficacy against all of the five uropathogens. Whereas, the rest of the cephalosporins showed modest to moderate against the isolated uropathogens, as shown below in figure 6.

3.3.3 The resistance patterns among the penicillin antibiotics

The overall sensitivity of the isolated uropathogens against amoxicillin is only (1.47%). Whereas, the sensitivity of the isolated uropathogens against ampicillin, and ampicillin-cloxacillin gentamycin is (2.94%). As shown in figure 7.

3.3.4 The resistance patterns among the quinolone antibiotics

The overall sensitivities of the isolated uropathogens against the nalidixic acid, norfloxacin, ciprofloxacin, and levofloxacin were 8.05%, 14.94%, 29.89%, and 63.22, respectively. As shown in figure 8. Levofloxacin showed a strong antibacterial activity against E. coli. Whereas, the norfloxacin only had a trivial antibacterial efficacy against all of the five uropathogens, as shown below in figure 8.

3.3.5 The resistance patterns among the miscellaneous antibiotics

Doxycycline and nitrofurantoin showed a good activity against the E. coli. In addition, both of doxycycline and rifampicin showed good antibacterial activity against the Proteus spp. In contrast, tetracycline and trimethoprim-sulfamethoxazole showed a trivial antibacterial efficacy against all of the isolated uropathogens, as shown in figure 9.

4. Discussion

Recurrent UTIs are common tragedy among population worldwide[5]. The recurrent infection is mainly attributed to improper antibiotic regimen, which may be a source for the evolution of resistant bacterial strains[9,10]. Eventually, the outcome is only partial eradication of the uropathogens with the recurrence of illness and emergence of symptoms followed in a couple of months[11]. The situation may become even worse when the same treatment protocol is followed in the event of a recurrent illness[12]. As such, resistance of the uropathogens is aggravated since more resistant bacterial strains may evolve that will overwhelm the proposed antibiotic treatment[6]. These strains are now the source of a more severe UTI progressively invading the upper urinary system. With the persistence of these recurrent uropathogens, a more sever threat manifested by bacteremia may drive the patient into an emergency or even fatal state[13,14].

In the current work, the isolated bacterial strains from urine culture reflect a spectrum of uropathogens, commonly encountered in high percentage of UTIs among several age groups[15]. Escherichia coli was the most abundant strain followed by Staphylococcus aureus and Klebsiella pneumoniae. These findings are in accordance with some studies stating that E.coli being the highest percentages of bacterial isolates from urine that may reach over 90 % in some cases[16,17]. The results are also in agreement with previous studies such as Bi Xue-Cheng et al and Tessema Belay et al in finding that S. aureus was the 2nd high percentage urine isolate after E.coli[18,19]. However, the results are contrary with Abdulrahman Bazaid et. al, and Muhammad A et al who showed that the 2nd most prevalent uropathogens was Klebsiella pneumoniae next to E. Coli rather than S. aureus[11,20]. The high percentage of S. aureus strains recognized, as shown in the current results, could probably related to contaminated samples because of inaccurate sample collection made by patients or health professionals. The challenging prospective of clean catch, midstream, urine collection has been confirmed according to certain literatures with S. aureus being recognized as evidence of contamination in some cases[21,22]. This can be explained by failure to catch the midstream (avoid catching the first part) urine flow while collecting urine sample. The result is high prevalence of bacterial strains that mostly inhabited the outer urethra such as staph aureus[23,24].

The other bacterial isolates, obtained in the present study, involve a plethora of uropathogens with variable percentages such as Pseudomonas aeruginosa, Proteus spp., and Enterobacter. These findings are

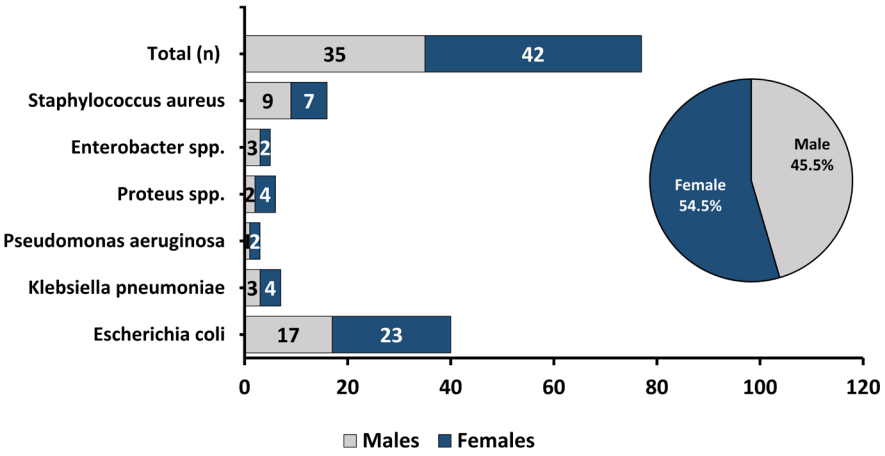

Figure 1: *Distribution frequency and the overall percentage of the uropathogens with regard to gender. Stacked bars represent the number (n) of males versus females and the number of each bacterial strain isolated in males (light color) and females (dark colour). Pie chart indicates the percentage of males to females included in the study.*

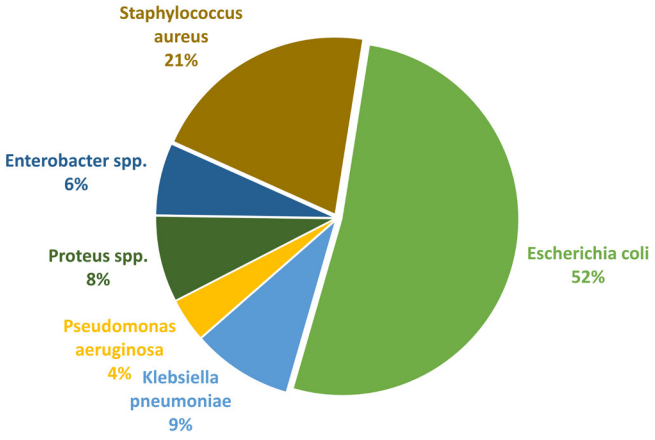

Figure 2: *Percentages of the isolated bacterial uropathogens. Pie chart illustrate the variations in the percentages of the isolated uropathogens from urine samples.*

in agreement with previous studies in reflecting the common types and percentages of the isolated uropathogens from urine samples of patients with or suspected UTI[25,26].

Although various percentages of isolated bacteria were revealed, the prevalence rates are mostly within the same range for the common strains such as E. coli. These variations may be the consequence of regional and geographical differences across the globe[27].

In view of the present results, the isolated strains showed high resistance rate to the commonly used antibiotics. Although the highest percentage of the isolated uropathogens was for the E. coli spp., the maximum bacterial resistance granted for the K.

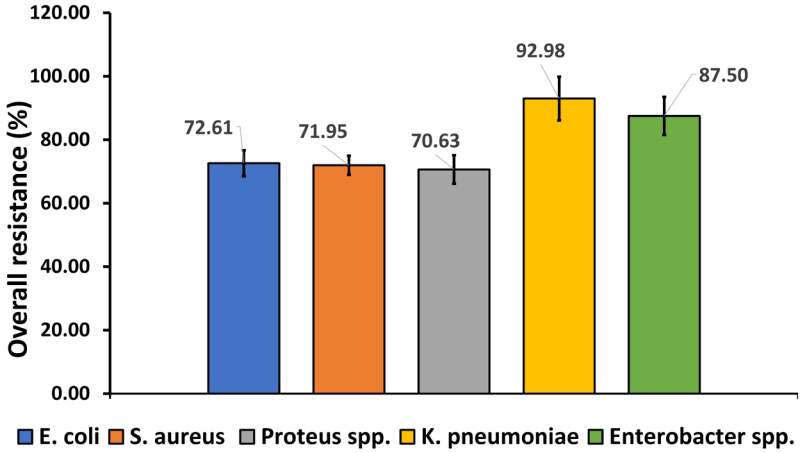

Figure 3: *Overall resistance of all isolated uropathogens against the tested antibiotics. Figure bars represent the mean percentage of each resistant pathogens Error bars indicate ±SD, n=5.*

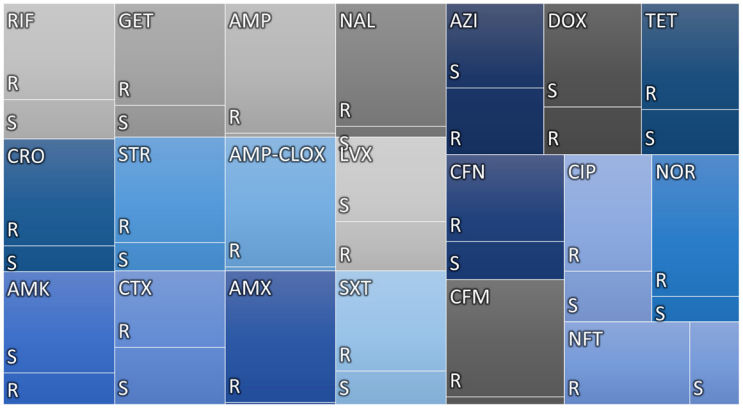

Figure 4: *Overall resistance and sensitivity of all the tested antibiotics.*
R: Resistant; S: Sensitive; AMK: Amikacin; GET: Gentamycin; STR: Streptomycin; CFN: Cephalexin; CFM: Cefixime ; CRO: Ceftriaxone; CTX: Cefotaxime; AMP: Ampicillin; AMP-CLOX: Ampicillin-Cloxacillin; AMX: Amoxicillin; NAL: Nalidixic Acid; NOR: Norfloxacin; CIP: Ciprofloxacin; LVX: Levofloxacin; SXT: Trimethoprim-Sulfamethoxazole; AZI: Azithromycin; DOX: Doxycycline; TET: Tetracycline; NFT: Nitrofurantoin; RIF: Rifampicin

pneumonia spp. and Enterobacter spp. followed by the E. Coli. Such resistance pattern has been reported in literature[28]. However, other studies have indicated E. coli. as having the highest percentage of resistance[26,29].

The emergence of resistance among isolated uropathogens towards selected set of antibiotics is basically correlated with the poor knowledge and practice of correct antibiotic dosage and use among population[10,30]. Poor compliance and improper antibiotic regimen are a recognized and growing issue among the population of Iraq and Nineveh province. Combined with the uncontrolled over the counter dispensing of antibiotics, has contributed widely to the flash of antibiotic resistance theme in this region[28,29].

According to the present study, the isolated strains

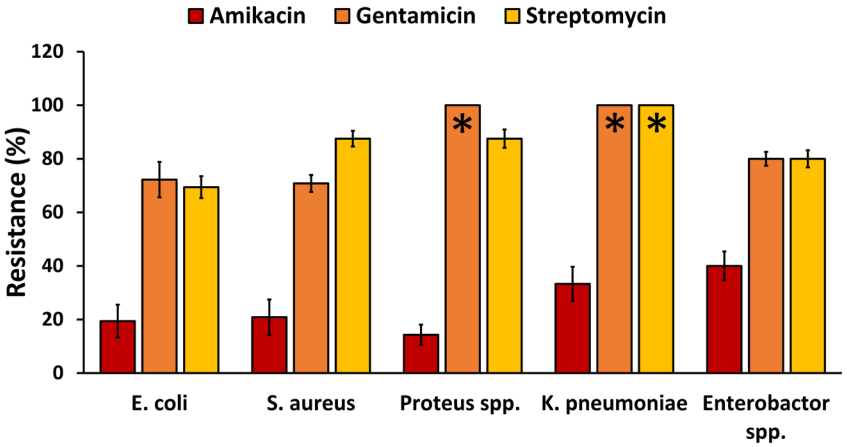

Figure 5: *The resistance patterns of the isolated uropathogens against the aminoglycoside antibiotics. Bars represent the mean percentages of the resistant uropathogens. Astricks indicate a 100 % mean resistance of uropathogens. Error bars indicate ±SD, n=5.*

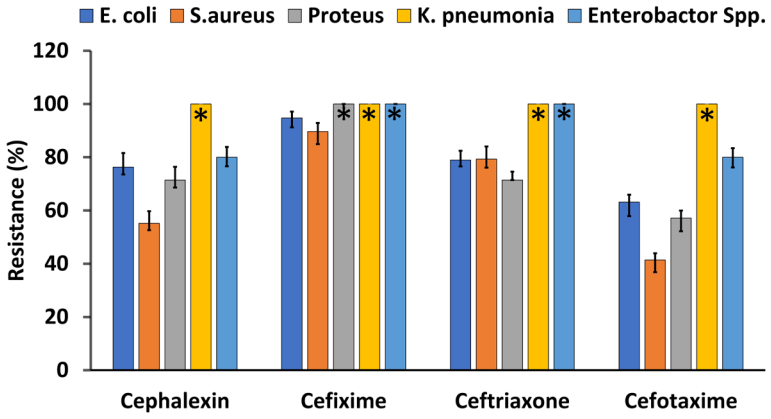

Figure 6: *The resistance patterns of the isolated uropathogens against the cephalosporin antibiotics. Bars represent the mean percentages of resistant uropathogens. Astricks indicate a 100 % mean resistance of uropathogens. Error bars indicate ±SD, n=5.*

are highly resistant to the frequently prescribed oral broad-spectrum penicillin antibiotics. This was observed at the highest level with amoxicillin then by ampicillin and ampicillin-cloxacillin. Analogous resistance is found for cefixime, the third-generation oral cephalosporin. These findings may indicate the diminishing value of these antibiotics which may limit their future therapeutic choices. Studies from around the world have demonstrated similar outcomes regarding the increased resistance of common uropathogens against these oral broad spectrum antibiotics mainly penicillins and cephalosporins[26,28,31]. Thus,

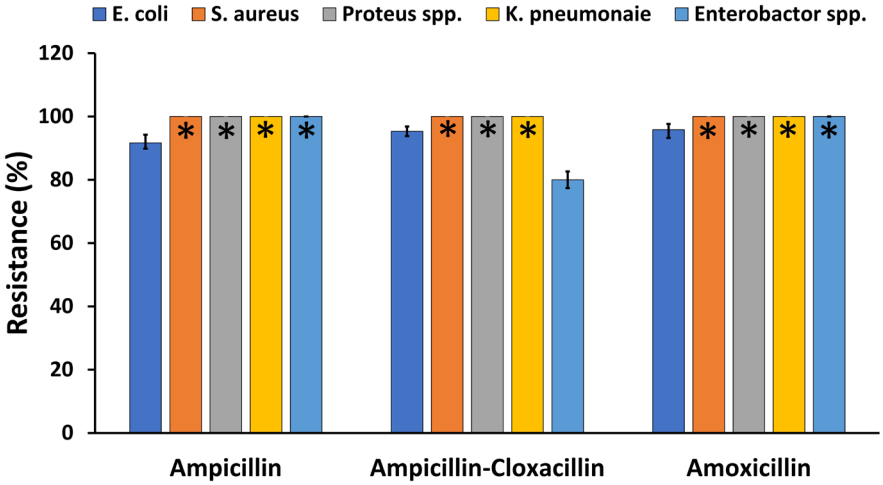

Figure 7: *The resistance patterns of the isolated uropathogens against the penicillin antibiotics. Bars represent the mean percentages of resistant uropathogens. Astricks indicate a 100 % mean resistance of uropathogens. Error bars indicate ±SD, n=5.*

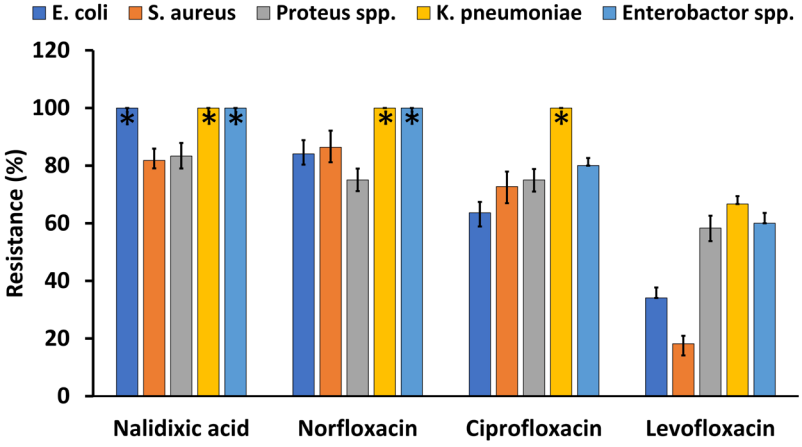

Figure 8: *The resistance patterns of the isolated uropathogens against the quinolone antibiotics. Bars represent the mean percentages of resistant uropathogens. Astricks indicate a 100 % mean resistance of uropathogens. Error bars indicate ±SD, n=5.*

they raise the questioning of the validity of these widely dependable antibiotics as a recommended line of therapy in UTI at all.

Considering the other cephalosporin antibiotics, included in the present study, cephalexin was moderately effective against the tested uropathogens, specifically against S. aureus and Proteus spp. compared to cefixime. According to a review by Nguyen H.M et al, cephalexin is recommended for uncomplicated lower UTI due to its pharmacokinetic properties manifested by high concentration of active drug in urine, and lower margin of side effects[32]. These findings may repre-

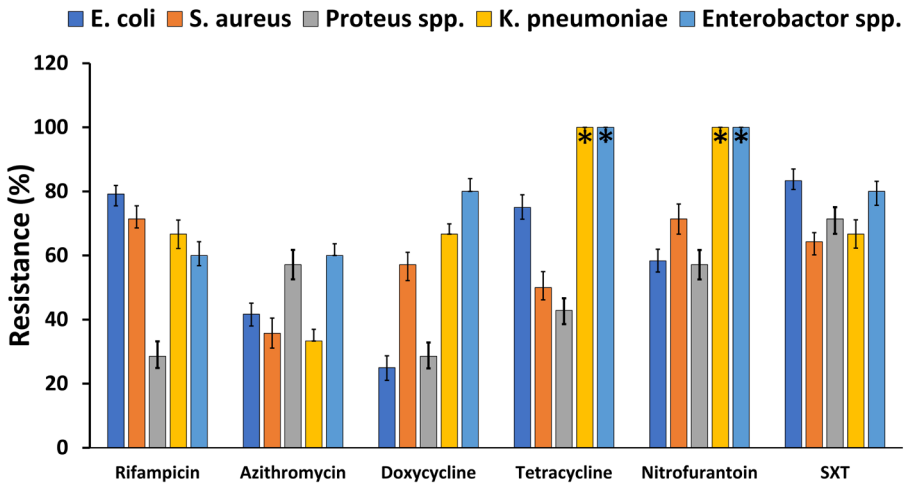

Figure 9: *The resistance patterns of the isolated uropathogens against miscellaneous antibiotics. Bars represent the mean percentages of resistant uropathogens. Astricks indicate a 100 % mean resistance of uropathogens. Error bars indicate ±SD, n=5.*

sent a drawback for cefixime as a priority option in UTI. On the other hand the findings by Rodríguez-Gascón H. et al,[33] showed that cefixime proved a better antibiotic choice for empirical treatment, but with moderate efficiency, among other oral third generation cephalosporines. However, this was only applicable when using 400mg twice daily dosage, which is not eligible option according to FDA.

Amikacin, according to the current results, clearly revealed remarkable antibacterial strength against the isolated uropathogens. This was specifically evidenced with E. coli and S. aureus strains showing the lowest bacterial resistance whereas other isolated strains were moderately sensitive to amikacin.

All the isolated uropathogens were highly resistant to both gentamicin and streptomycin with resistance rate ranging from about 70% up to 100% mostly seen with K. pneumonia spp. The isolated strains also showed high sensitivity to levofloxacin which again was superior with E. coli and S. aureus but only moderate with the rest of uropathogens. The above antibiotics involve some very popular medications that are frequently prescribed for UTI in Iraq such as gentamicin and ciprofloxacin, whether in hospital wards or outpatient clinics[34,35]. This frequent use may contribute to such a high percentage of resistance encountered in the present study.

In regard to other miscellaneous antibiotics, the isolated strains showed various rate of resistance. For instance, proteus spp. was notably less resistant to both doxycycline and rifampicin while moderate to high resistance rate was obvious with the rest of this group of antibiotics. Another observation with doxycycline was the low resistance rate of E. coli. Moreover, a reasonable sensitivity of E. coli, S. aureus, and K. pneumonia were obtained with azithromycin. These findings may enhance the usefulness of these antibiotics as empirical treatment options in UTI based on specified age and diagnosed symptoms[36].

5. Conclusion

In light of the above findings, the isolated uropathogens, such as E. coli, K. pneumonia, Enterobacter, and proteus are the most common isolated uropathogens from patients with recurrent UTI. These bacterial strains showed reasonable sensitivities to only few groups among the tested antibiotics. The high

level of resistance was noticed amid the widely and repeatedly prescribed antibiotics. As such, antibiotics such as ampicillin, amoxicillin, or cefixime may no longer be considered as a choice for empirical therapy in any recurrent UTI. Perhaps, old antibiotics, such as first-generation oral cephalosporin, cephalexin, may now be considered as a line of therapy based on the current findings. □

Ethics approval and consent to participate

This study was approved by the Collegiate Committee for Medical Research Ethics in University of Mosul (APPROVAL NUMBER: CCMRE-PhA-22-1).

Declaration of competing interest

The authors declare that there is no conflict of interest to publish this article.

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