Egypt. J. Bot. **Vol. 63**, No. 1, pp. 295-303 (2023)

Egyptian Journal of Botany
http://ejbo.journals.ekb.eg/

Prevalence of Drug-Resistant Strains of *Escherichia coli* and *Klebsiella pneumoniae* Isolated from Women with Urinary Tract Infections in Karbala City, Iraq

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URINARY tract infections (UTIs) are becoming more common among women worldwide and it usually caused by bacteria that are highly resistant to antibiotics. This study identifies the prevalence of multi-drug resistant and extensively drug resistant of *Klebsiella pneumoniae* and *Escherichia coli* that have been isolated from women with UTIs. It also identifies an effective antibiotic to use in the treatment of UTI infections. Bacterial strains were identified and recognized by standard laboratory protocols and tested to antibiotic susceptibility test for 11 antibiotics using standard disk diffusion technique. 63(42%) *E. coli*, and 30(20%) *K. pneumoniae* clinical strains were isolated from 150 women with "UTIs" over a period of seven months. The antibiotic sensitivity assays showed that all strains exhibited high resistance rate against Beta-lactam (Amoxicillin-clavulanic acid), and cephalosporin's antibiotics in all strains which were 95.2% for Amoxicillin-clavulanic acid , and from 71.4 to 90.5% to cephalosporin's antibiotics for *E. coli*, but 100%, and 90 to 100% relatively for *K. pneumoniae*. However, the antimicrobial agent imipenem was found to retain their antimicrobial properties against both bacteria, which were 100 and 90% respectively. Also nitrofurantoin exhibited activity only against *E. coli* strains. Out of 93 uropathogens 45(71.42%), and 27(90%) of *E. coli* and *K. pneumoniae* strains were found to be MDR respectively. Our study demonstrates that a significant frequency of multidrug-resistant *K. pneumoniae* and, *E. coli* . In addition, Imipenem was appropriate drug to treat infections caused by these uropathogens. These findings may aid physicians in the management of UTI infections.

Keywords: *Escherichia coli,* Extensively drug- resistance, *Klebsiellae pneumoniae,* Multidrug-Resistance, Urinary tract infections.

Introduction

The most frequent bacterial infections in humans are urinary tract infections (UTIs) (Bischoff et al., 2018). Each year, 150–250 million cases are reported across the world (Zowawi et al., 2015). In their lifetimes, 40 percent of women and 12 percent of males are predicted to have at least one symptomatic UTI. In addition, between 27 to 48% of affected women have recurrent UTIs (Brumbaugh et al., 2013; Micali et al., 2014). UTIs account for around 40–50% of all bacterial infections acquired in hospitals, contributing to higher morbidity and extended hospitalization (Karam et al., 2019; Kot, 2019). UTIs are also a financial issue, as around 150 million individuals globally are treated for UTIs each year, costing more than $6 billion (Semwal et al., 2017).

E. coli is the primary cause of UTIs, accounting for 70 to 95 % of cases (Kot et al., 2016). A further 7% of UTIs are caused by

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Received 10/08/2022; Accepted 01/12/2022
DOI: 10.21608/ejbo.2022.155164.2089
Edited by: Dr. Mahmoud S.M. Mohamed, Faculty of Science, Cairo University, Giza, Egypt.

Klebsiella pneumoniae, 5% by *Proteus mirabilis*, and the remainder by *Staphylococcus aureus, S. saprophyticus, and Enterococcus faecalis* (Mann et al., 2017).

UTIs affect everyone, however some characteristics enhance uropathogen exposure while others increase the probability of developing symptoms following colonization. The presence of urinary catheters and vaginal intercourse enhance uropathogen exposure; factors of human susceptibility to the illness include age; and the existence of other urinary tract conditions like as diabetes, pregnancy, or an enlarged prostate. Bacterial characteristics enhance the agent's ability to spread, induce infection, and cause diseases. Recurrent infections are frequent, and they can cause irreversible kidney damage, leading to renal hypertension and, in extreme cases, renal failure (Foxman & Brown, 2003).

A significant public health problem is antibiotic resistance with serious implications for infection treatment. Infection with multidrug-resistant microbes have become more common during the last decade (MDROs). Both social and economic development are impacted as a result of this. Multidrug resistance "MDR", which has risen globally and is regarded as a hazard to public health, These raise the necessity for regular use of antimicrobial susceptibility testing to choose the preferred antibiotic as well as the requirement to screen for new "MDR" strains (Abolghait et al., 2019; Algammal, et al., 2020; Makharita et al., 2020). When compared to infections brought on by non-MDR bacteria, MDR infections have a higher death rate. Misuse of antibiotics, which leads to selected pressures that encourage the creation of resistant strains, is responsible for the issue (Prestinaci et al., 2015). Therefore, the aim of this study was to detect the frequency of uropathogens such us *E. coli* and *K. pneumoniae* responsible for UTIs in hospitalized patients and the prevalence of the most commonly-found MDR, XDR, and PDR *E.coli* and *Klebsiellae pneumoniae* in women with UTIs from Karbala city, Iraq in order to define the empirical antibiotic treatment for hospitalized patients

Materials and Methods

Urine collection

One hundred fifty urine samples were collected aseptically from Patients with UTI who were hospitalized to Al-Hussein General Teaching Hospital in Karbala city, Iraq, between July 2021 and February 2022 and brought to the Laboratory of Microbiology at the College of Pharmacy at Al-Zahraa University for Women in Iraq. the patients were asked to clean their external genitalia with liquid soap. 10mL of freshly midstream urine was collected from women aged 20 to 45 years old in sterile bottles and closed tightly. Included and excluded criteria: a high fever, vomiting, and abdominal discomfort. The collected urine specimens were transported with the temperature of 4-8º C with coolant pack to the laboratory. All urine specimens brought to the microbiology laboratory were examined at once (Ghanghro & Laghari, 2010; Woldemariam et al., 2019).

Isolation and identification of bacteria

Bacterial strains were isolated from urine specimens using differential and selective media including MacConkey agar "MAC", blood agar "BA", and Eosin methylen blue agar "EMB" plates. Urine was inoculated on MAC agar, BA, and EMB agar and incubated at 37°C for 24h. The isolates then were identified by the morphology of colonies, pigmentation, Gram staining, and biochemical tests characteristics. The following biochemical assays were used in this study: Oxidase, catalase, urease indole production, Methyle red, Voges-Proskauer (VP), Citrate test (Forbes et al., 2007).

Antibiotic susceptibility test

In accordance with the recommendations of the "Clinical and Laboratory Standards Institute" (CLSI), the disk diffusion method was used to assess the antibiotic sensitivity profile of the bacterial isolates. By using 11 different antimicrobial impregnated discs, including: Norfloxacin (NOR 10mcg), cefotaxime (CTX 30mcg), ceftriaxone (CRO 30mcg), gentamicin (GN 10mcg), amikacin (AK 30mcg), and amoxicillin-clavulanic acid (AMC 30mcg), nitrofurantoin (F 300mcg), Imipenem (IPM 10mcg), cefoperazone (CFP 75 mcg), cefixime (CFM 10mcg), and azithromycin (AZM 15mcg).

Uropathogenic isolates were freshly grown overnight, a "0.5 McFarland" suspension of each isolate was heavily streaked on a whole plate surface Mueller–Hinton (MH) agar (in triplicate) aseptically by streaking the cotton swab in forth and back motions. Then, MH

agar plates were covered with 4 mm antibiotic paper discs, which were commercially available (Bioanalyse®, Turkey), and incubated for 24h at 37ºC. Following that, the bacterial lawn's zone of inhibition was measured and noted. The zones of inhibition's sizes were then categorized as resistant or sensitive using the CLSI's standard diameters (CLSI, 2020).

Statistical analysis

Chi-square test was used to significant compare between percentage (0.05 and 0.01 probability) in this study. P≤0.05 was considered significant, P≤0.01 was considered highly significant (SAS, 2018).

Based on the criteria listed in, the non-susceptible strains were categorized as "MDR", and "XDR" ,Strains that are resistant to one antimicrobial agent "≥1" are called non-susceptible "Non-MDR; those that are resistant to three "≥3" antimicrobial categories are termed MDR; and those that are not susceptible to one agent "≥1" in all except two antimicrobial categories "≤2" are considered XDR (Mohapatra, et al., 2018).

Results

Patients and clinical isolates

Among 150 urine samples collected from women with a mean age of 35 years, 34 (23%) belonged to other bacteria, and 23 (15%) showed negative result, while 93 (62%) urine samples were culture-positive for uropathogenic bacteria, of which 63 (42%) were *E. coli* and 30 (20%) were *K. pneumoniae* as shown in (Fig. 1).

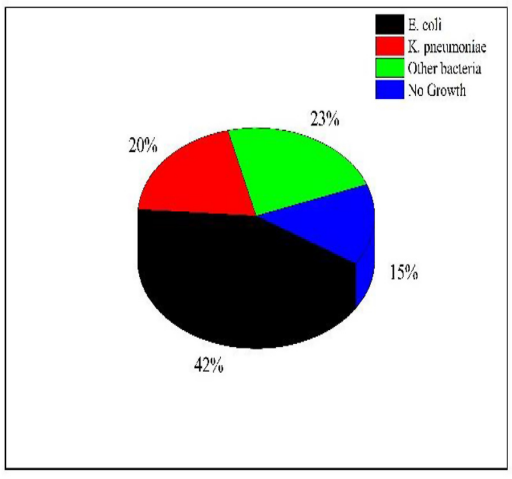

Fig.1. The percentage of isolates among urine samples

Uropathogenic strains' characterization

Ninety three different *K. pneumoniae* and *E. coli* strains were isolated and named. According to biochemical tests, bacteria in both groups were Gram (-ve), negative for oxidase activity, and positive for catalase activity. *E.coli* shows positive in methyl red (MR), indole production, and negative to urease. The biochemical tests for *K. pneumoniae* are negative to indole, positive to urease, variable to MR, positive to VP, positive to citrate test. As shown in (Table 1).

Pink, opaque, or slightly deeper color colonies on MacConkey agar were identified as *E. coli*, whereas large mucoid, opaque, pink in color colonies are *K. pneumoniae.* The *E. coli* bacteria appeared as colonies with a metallic sheen on EMB agar. Colonies that were chosen were then picked, purified, and stored at the freezer at -20°C until additional analysis.

Antibiotic susceptibility

Analysis of the antimicrobial susceptibility profile of the isolates showed that most of *E. coli* isolates (100%) were susceptible to carbapeneme antibiotics (imipenem) followed by nitroforantion 81.9%. This isolate showed resistance to other tested antibiotics. Of 63 isolates, 95.2% of the isolates were resistant to B-lactam antibiotics (amoxicillin-clavulanic acid) and cephalosporins (cefixime, ceftriaxone, cefotaxim, cefoperazon) which was (90.5, 76.2, 71.4 and 66.7%), respectively, as shown in Table 2.

The highest sensitivity rate was shown to carbapeneme antibiotics (imipenem) that was 90%, followed by aminoglycoside antibiotics (amikacin) that was 60%. But The highest degree of antibiotic resistance among *K. pneumoniae* isolates was observed in B-lactam antibiotics (amoxicillin-clavulanic acid) 100%, and cephalosporins (cefixim, cefoperazone, ceftriaxone, cefotaxime) that was (100, 100, 90,and 90%), respectively followed by (nitroforantion) 70%, as shown in Table 3.

Antibiotic resistance phenotype

The estimated of MDR, XDR, and non-MDR are reported in Table 4. Out of 63 *E. coli*, 45 (71.42%) were found to be multidrug drug-resistant (MDR), but 18 (28.57%) isolates were non-MDR., whereas 27(90%) of *K. pneumoniae* isolates were MDR, and 3 (10%) were XDR.

TABLE 1. Characterization test of the uropathogenic bacterial strains identified in patients with UTIs

Characterization test	*E. coli* (*n*= 63)	*K. pneumoniae* (*n*= 30)
Gram staining	Gram-negative	Gram-negative
Catalase test	+	+
Oxidase test	–	–
Urease test	–	+
Indol production	+	–
Methyl red test	+	–
Voges-Proskauer test	–	+
Citrate utilization test	–	+

TABLE 2. Antibiotic susceptibility of *E. coli* strains.

Antimicrobial drug symbols	Resistance pattern (n= 63)						P value
	Sensitivity		Resistance		Intermediate		
	No.	%	No.	%	No.	%	
CRO	6	9.5	48	76.2	9	14.3	0.0001 **
CFP	3	4.8	42	66.7	18	28.6	0.0001 **
CFM	0	0	57	90.5	6	9.5	0.0001 **
CTX	12	19	45	71.4	6	9.5	0.0001 **
GM	24	38.1	21	33.2	18	28.8	0.381 NS
AK	21	33.3	24	38.1	18	28.6	0.177 NS
IPM	63	100	0	0	0	0	0.0001 **
NB	0	0	42	66.7	21	33.3	0.0001 **
F	51	81.9	6	9.5	6	9.5	0.0001 **
AMC	3	4.8	60	95.2	0	0	0.0001 **
AZM	18	28.6	18	28.6	27	42.9	0.0419 *
P value	---	0.0001 **	---	0.0001 **	---	0.0001 **	---

Abbreviations: CRO: Ceftriaxone; CFP: Cefoperazone; CFM: Cefixime; CTX: Cefotaxime; GM: Gentamicin; AK: Amikacin; IPM: Imipenem; NB: Norfloxacin; F: Nitrofurantoin; AMC: Amoxicillin-clavulanic acid; AZM : Azithromycin.
Notes**:** * (P≤0.05): Significant, ** (P≤0.01): Highly Significant, NS: Non-Significant.

TABLE 3. Antibiotic susceptibility of *K. pneumoniae* strains.

Antimicrobial drug symbols	Resistance pattern (*n*= 30)						P value
	Sensitivity		Resistance		Intermediate		
	No.	%	No.	%	No.	%	
CRO	0	0	27	90	3	10	0.0001 **
CFP	0	0	30	100	0	0	0.0001 **
CFM	0	0	30	100	0	0	0.0001 **
CTX	0	0	27	90	3	10	0.0001 **
GM	12	40	9	30	9	30	0.272 NS
AK	18	60	3	10	9	30	0.0001 **
IPM	27	90	3	10	0	0	0.0001 **
NB	15	50	12	40	3	10	0.0001 **
F	0	0	21	70	9	30	0.0001 **
AMC	0	0	30	100	0	0	0.0001 **
AZM	0	0	15	50	15	50	0.0001 **
P value	---	0.0001 **	---	0.0001 **	---	0.0001 **	---

Abbreviations: CRO: Ceftriaxone; CFP: Cefoperazone; CFM: Cefixime; CTX: Cefotaxime; GM: Gentamicin; AK: Amikacin; IPM: Imipenem; NB: Norfloxacin; F: Nitrofurantoin; AMC: Amoxicillin-clavulanic acid; AZM : Azithromycin.
Notes**:** ** (P≤0.01): Highly Significant, NS: Non-Significant.

TABLE 4. Incidence of MDR, and XDR strains of each species of *E. coli* and *K. pneumoniae* strains (*n*= 93)

Strains	Antibiotic resistance phenotype						P value
	MDR[a] strains		XDR[b] strains		Non-MDR[c] strains		
	No.	%	No.	%	No.	%	
E. coli	45	71.42	0	0	18	28.57	0.0001 **
K. pneumoniae	27	90	3	10	0	0	0.0001 **
P value	---	0.0089 **	---	0.317 NS	---	0.0052 **	---

Abbreviations: a. multi-drug resistant, b. extremely- drug resistant, and c. non multi-drug resistant.
Notes**:** ** (P≤0.01): Highly Significant, NS: Non-Significant.

Discussion

Antibiotic use in livestock, self-medication, the availability of too many antibiotics, the distribution of antibiotics without valid prescriptions, patient non-compliance with an antibiotic regimen, and indiscriminate antibiotic use may all be contributing factors for the emergence of such high bacterial antibiotic resistance in community acquired urinary tract infections. A very major public health problem is how these drug-resistant bacteria contribute to the emergence of community-acquired diseases. As a result, steps should be made right once to handle the issue.

The results of the current study indicated that strains of the two bacterial species under investigation were more resistant to cephalosporins, amoxicillin-clavulanic acid, and B-lactam antibiotics. Recently, Al-Hasnawy et al. (2019) reported a rising prevalence in resistance rate to amoxicillin-clavulanic acid in *E. coli* up to 100% in 2019 in Babylon province, Iraq. Vazouras et al. (2020) revealed that resistance rates for amoxicillin-clavulanic acid was 12.2%, nitrofurantoin 2.3%, cephalosporins 1.7%, and amikacin 0.9%, which were much lower than those discovered in our investigation. Although Iqbal et al. (2021) reported 80% of the *E. coli* were resistant to ceftriaxone and, cefotaxime with cefixime having the greatest level of resistance 93% and cefuroxime having the second-highest level of resistance 90% respectively. This variance may be the result of regional variations in the ease and frequency of antibiotic availability due to local disparities in antibiotic use (Prestinaci et al., 2015). The effectiveness of these agents is limited as a result of increased expression of bacterial β-lactamases that inactivate these antibiotics and production of β-lactamase resistant to inhibitors (Epand et al., 2016). Multiple β-lactamases produced by some bacteria may impair the effectiveness of β-lactam/-lactamase inhibitor combinations (Paterson & Bonomo, 2005). In the current study, Imipenem was found to be effective against both strains and the resistance rate was low (0% for *E. coli* and 10% for *K. pneumoniae*). These results were reasonably equivalent to those of Al-Hilali (2015), who discovered that 9.6% of uropathogenic *E. coli* strains were imipenem resistant. On the other hand, Pirko et al. (2017) revealed that only 6% of *E. coli* exhibit imipenem resistance. Because it is commonly suggested for the treatment of complex cystitis in patients, quinolone resistance is of interest in addition to resistance to other antibiotics. Due to the advantages of quinolones over co-amoxiclav, notably in terms of its pharmacokinetic features, these antibiotics are also widely employed as a first choice for the treatment of UTIs (McCormick et al., 2008; Okonko et al., 2009). In the present study results revealed 10% of *E. coli* strain also showed low resistance rate to nitroforantion but *K. pneumoniae* showed low resistance rate to amikacin (10%). *E. coli* has a 44.8 % nitrofurantoin resistance rate according to frequencies in Mexico (Paniagua-Contreras et al., 2017). Nitrofurantoin would be a wonderful option for UTI therapy while awaiting the results of culture and sensitivity tests because a higher percentage of the UTI isolates in this research were sensitive to it. Additionally, the recent decreased use of nitrofurantoin in hospitals may have resulted in a decline in nitrofurantoin resistance.

In recent years, several research with a range of results have been undertaken about the spread of "MDR *E. coli* and *K. pneumoniae* "in various regions of the world (Rezaee et al., 2011). The frequency of multi-drug resistance (MDR) was 90 % among *K. pneumoniae* isolates and 71.42%

among *E. coli* isolates in this study. Iqbal et al. (2021) reported the low MDR for both strains that was 7.5 and 24.3% respectively, but XDR for both strains was 92.06 and 75.7% respectively. Fallah et al. (2018) in Iran found that 51.9 and 28.5% of *E. coli* and *K. pneumoniae* strains, were MDR, while 3.3 and 14.2% of the previous strains were found to be XDR. Addis et al. (2021) reported that 59 and 77% of *E. coli* strains *K. pneumoniae* strains were MDR, but 18 and 41% of the previous strains were found to be XDR. While PDR were 24 and 0% respectively. The usage of antibiotics improperly may be the reason why the MDR rates in the earlier trials were significantly lower than ours. also commensal bacteria shared their β-lactamase enzymes widely, which has facilitated the emergence of MDR strains (Tiwari et al., 2020). Additionally, infections with β-lactamase-producing microorganisms are brought on by prolonged hospital stays (Dayan et al., 2013). The emergence of MDR in uropathogens and their plasmid carrying MDR genes may possibly be caused by an inevitable genetic response to the strong discriminating power imposed by antibiotic treatment (Chakraborty et al., 2011), Therefore, a change to Karbala's present antimicrobial stewardship policy is required to increase the effectiveness of CA-UTIs therapy.

Conclusion

Our data discovered a significant frequency of multidrug-resistant (MDR) uropathogenic *K. pneumoniae*, and *E. coli* isolated from urinary tract infections in Karbala city-Iraq and recommending that such antibiotic use be discontinued after thorough, long-term analyses. To stop the spread of drug resistance in both of these clinically significant bacterial species, self-medication and incorrect diagnosis must be prevented.

Acknowledgements: My great thanks to the medical staff in laboratory of Al-Hussein General Teaching Hospital in Karbala City for assistance in specimens' collection, I feel deeply in debt with thanks and gratitude to my friends and colleagues of Faculty of Pharmacy/ University of Al-Zahraa for women in Karbala city for their advice, sympathy, and care.

*Conflict of interests:*The authors declare no conflict of interest.

Authors' contributions: Zahraa A. Al-Khfaji: Investigation, sample collection, data curation, writing original draft. Sahbaa H. Sagban, Ali F. Al-Musawi: data curation, writing-review and editing, all the contributing authors have participated in the preparation of manuscript. All authors have read and agreed to the published version of the manuscript.

Ethical approval: The experimental work was approved by the Ethical Committees of the hospital and in compliance with recommendations of the Ethical Committees Committee; privacy was maintained regarding patient data.

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انتشار السلالات المقاومة للمضادات الحيوية من الإشريكية القولونية والكلبسيلا الرئوية المعزولة من النساء المصابات بعدوى المسالك البولية في كربلاء ، العراق

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أصبحت الاصابة بالتهابات المسالك البولية أكثر شيوعًا بين النساء في جميع أنحاء العالم، وعادة ما تسببها البكتيريا المقاومة للمضادات الحيوية. ترصد هذه الدراسة انتشار سلالات بكتيريا *Klebsiella pneumoni-ae* و *Escherichia coli* ذات المقاومة المتعددة والعالية للمضادات الحيوية والتي تم عزلها من النساء المصابات بعدوى المسالك البولية. كما أنها تحدد المضاد الحيوي الفعال لاستخدامه في علاج التهابات المسالك البولية. تم تحديد السلالات البكتيرية وتمييزها من خلال البروتوكولات المخبرية القياسية واختبار حساسيتها لـ 11 مضادًا حيويًا باستخدام التقنية القياسية للانتشار بالاقراص. تم عزل 63 (42٪) سلالة من الاشريكية القولونية و30(20٪) سلالة من بكتريا الكليبسيلا الرئوية من 150 امرأة مصابة بالتهاب المسالك البولية ولمدة سبعة اشهر. أظهرت فحوصات الحساسية للمضادات الحيوية أن سلالات النوعين أظهرت معدل مقاومة عاليًا ضد المضادات العائدة إلى مجموعة البيتا لاكتام (حمض أموكسيسلين - كلافولانيك)، والمضادات الحيوية من مجموعة السيفالوسبورين في سلالات كلا النوعين والتي كانت 95.2٪ لحمض أموكسيسلين- كلافولانيك، ومن 71.4 إلى 90.5٪ لمضادات السيفالوسبورين للإشريكية القولونية، وكانت 100٪ و من 90 إلى 100٪ على التوالي لبكتيريا الكليبسيلا الرئوية. ومع ذلك وجد أن المضاد الحيوي imipenem يحتفظ بخصائص مضادة للميكروبات ضد سلالات كلا النوعين، والتي كانت 100 و 90٪ على التوالي. كما أظهر النيتروفورانتوين نشاطًا فقط ضد سلالات الإشريكية القولونية. من بين 93 من البكتريا المسببة لامراض المسالك البولية 45 (71.42٪) و 27 (90٪) من الإشريكية القولونية و بكتريا الكليبسيلا الرئوية على التوالي كانت متعددة المقاومة للمضادات الحيوية. توضح دراستنا أن هناك ترددا كبيرًا للمقاومة المتعددة للأدوية في عزلات الإشريكية القولونية و الكليبسيلا الرئوية. بالإضافة إلى ذلك ، كان Imipenem دواءً مناسبًا لعلاج الالتهابات التي تسببها هذه المُمْرِضات البولية. قد تساعد هذه النتائج الأطباء في السيطرة على التهابات المسالك البولية.