

Coronavirus Pandemic

COVID-19 pandemic impact on antibiotics sensitivity of *E. coli* and *K. pneumoniae* from urine specimens: a retrospective study

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Abstract

Introduction: *Escherichia coli* and *Klebsiella pneumoniae* are common organisms associated with urinary tract infections. The COVID-19 pandemic has had a negative impact on antibiotics misuse globally. This study analyzed the antibiotic susceptibility for these two pathogens isolated from urine samples during the period of 18 months before and after the COVID-19 pandemic.

Methodology: This retrospective study was conducted in Al-Karak government referral and teaching hospital in Jordan. The study included two groups; group A included urine samples from September 2018 to March 11, 2020, while group B from March 12, 2020 to August 2021. Samples were analyzed using the automated VITEK 2 system and the analysis of results was done using the WHONET version 5.6.

Results: A total of 642 *E. coli* and 113 *K. pneumoniae* were isolated and analyzed. The antibiogram showed a significant overall increase in antibiotic susceptibility of both bacteria during the pandemic period (group B). The sensitivity has significantly increased by 75% (15/20) and 50% (10/20) for all antibiotics used for *E. coli* and *K. pneumoniae* respectively. On the other hand, *E. coli* showed a significant increase in resistance to ceftriaxone (13.4%) and gentamicin (6.4%). A similar trend of an increase in resistance to gentamicin (17.4%) was also noticed among *K. pneumoniae* isolates.

Conclusions: The antimicrobial susceptibility pattern for urine isolates showed an increased overall sensitivity and an increased resistance to ceftriaxone and gentamicin during the pandemic period. Our results highlight the need for revising and updating the antimicrobial stewardship programs post-COVID pandemic utilizing local data.

Key words: Antibiotic; resistance; COVID-19; *E. coli*, *K. pneumoniae*.

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Introduction

Urinary tract infections (UTIs) are among the most common types of bacterial infections with a high healthcare cost burden worldwide [1]. In addition to the significant deaths caused by UTIs among different age groups, patients with UTIs are at risk of serious complications including recurrence, sepsis, pyelonephritis, and high levels of antibiotic resistance due to misuse of antibiotics [2-4]. Both Gram-positive and Gram-negative bacteria can cause UTIs [2-4]. Among the Gram-negative bacteria, the most common causative agent of UTIs is the uropathogenic *Escherichia coli*. Other common Gram-negative organisms causing UTIs are *Klebsiella* spp., *Enterobacter* spp., and *Proteus* species. The Gram-positive bacteria associated with UTIs include *Enterococcus* spp. and *Staphylococcus* spp. [2,3,5,6].

The most significant threat to the global public health regarding infections caused by Gram-negative bacteria is the emergence and dissemination of antimicrobial resistance (AMR). Bacterial antimicrobial resistance occurs when antibiotics become less effective to treat infections because of certain changes in the bacteria. This is largely due to the inappropriate use of antibiotics [7]. Understanding the burden of bacterial AMR has been considered a real challenge particularly in developing countries, where data and surveillance are scarce [8]. Therefore, valid data on bacterial AMR burden and distribution is an essential step to tackle the growing incidence of AMR and preventing the spread of lethal bacterial isolates in the future [8]. In 2021, the World Health Organization (WHO) declared AMR as one of the ten major threats to public health globally and urged for a multisectoral effort to achieve sustainable

development goals in fighting AMR [9]. According to the WHO, the rate of resistance to many infections, including UTIs commonly caused by *E. coli* and *Klebsiella pneumoniae*, has increased significantly which made many antibiotics less effective for the treatment of such infections causing increased mortality and morbidity [9]. Another potential adverse outcome of AMR is the projected 10 million deaths and estimated 100 trillion USD cost by the year 2050 [7]. The inappropriate use of antibiotics in clinical settings has been aggravated by the COVID-19 pandemic [10]. COVID-19 was first noticed after an acute atypical respiratory disease occurred in Wuhan, China which was then diagnosed as a novel strain of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) that was initially named 2019-nCoV due its 80% genetic similarity with SARS-CoV [11]. Later on, in March 2020, the WHO declared it as a pandemic [12,13]. COVID-19 is associated with lower respiratory tract infection causing fever, dry cough, dyspnea, in addition to dizziness, weakness, diarrhea, vomiting, and can eventually cause acute respiratory distress syndrome [14]. Regardless of different precautions on antibiotics misuse or abuse during the pandemic, there was a general trend of overuse of antibiotics leading to an increase in AMR. This is largely because COVID-19 infections presented with symptoms similar to community acquired pneumonia or because many physicians were worried about the presence of secondary bacterial infections in COVID patients, particularly in those with underlying comorbidities [10]. It has been shown that 75% of adults with COVID-19 infection who received an antimicrobial prescription were negative for bacterial infections and that antibiotics were inappropriately used in more than one third of cases [15].

The differences in antibiotic use and prevalence of AMR before and during the COVID-19 pandemic have been demonstrated in several studies and reviews [16-18]. The impact of COVID-19 on AMR varies between countries, depending on the health care policies [18]. Studies on the change in antibiotic consumption, susceptibility and resistance patterns, and the emergence of new AMR organisms are essential in establishing new strategies to overcome AMR. This will assist in updating the antimicrobial stewardship programs based on local data and in prevention of the spread of microbial isolates, which can be fatal in the future [8,19]. In this study, it was aimed to investigate the probable change in antibiotic sensitivity of bacteria associated with UTIs among Jordanian patients before and during the COVID-19 pandemic.

Methodology

Specimens

Urine samples were received in the microbiology laboratory of Al-Karak governmental hospital, a referral hospital in the southern part of Jordan, which provides services to the surrounding hospitals in the area. The samples that were included in this study were collected before the COVID-19 pandemic between September 2018 to March 11, 2020 and after the COVID-19 pandemic between March 12, 2020 to August 2021. The total number of urine samples that were received in the laboratory before and after COVID-19 were 1300 and 900 respectively. The study was approved by the ethics committee in the Faculty of Medicine at Mutah University (approval number 012023).

Cultures and antibiotic susceptibility tests

Cultures and antibiotic susceptibility tests were performed according to the Clinical and Laboratory Standard Institute [20]. Microorganism identification and antibiotic susceptibility were determined using the VITEK 2 system (bioMérieux, Marcy l'Etoile, France). After data extraction from the VITEK 2 system, the antibiotics susceptibility data was analyzed using WHONET Version 5.6 program.

Antibiotics

Our laboratory used 20 antibiotics for *E. coli* and 19 for *K. pneumoniae* according to CLSI 2018, which includes the following panels: ampicillin (AMP: 30 µg), amoxicillin/clavulanic acid (AMC: 30 µg), ampicillin/sulbactam (SAM: 10/10 µg), piperacillin/tazobactam (Pip/Tzp: 110 µg), cefazolin (CZO: 30 µg), ceftazidime (CAZ: 30 µg), ceftriaxone (CRO: 30 µg), cefotaxime (CTX: 30 µg), cefepime (FEP: 30 µg), aztreonam (ATM: 30 µg), ertapenem (ETP: 10 µg), imipenem (IPM: 10 µg), meropenem (MEM: 10 µg), amikacin (AMK: 30 µg), gentamicin (GEN: 10 µg), ciprofloxacin (CIP: 10 µg), levofloxacin (LVX: 10 µg), trimethoprim/sulfamethoxazole (Tpm/Smz: 1.25/23.75), fosfomycin (FOS: 50 µg), and nitrofurantoin (NIT: 100 µg).

Statistical analysis

Data analysis was done using the Statistical Package for Social Science (SPSS) version 24. Data were expressed as means and standard deviation for continuous variables and as a percentage for categorical variables. Categorical variables were compared using

the Chi-square test and a *p* value less than 0.05 was considered statistically significant.

Results

The extended spectrum beta lactamases (ESBLs) number and change in susceptibility pattern for *E. coli* and *K. pneumoniae* are shown in Tables 1 and 2 respectively. The results represent a period of 18

months before (group A) and after pandemic declaration (group B).

The tables show the results for a total of 642 *E. coli* and 113 *K. pneumoniae* isolated during that period. The results revealed that there was no significant change in the number of ESBLs. However, a significant increase (*p* < 0.05) in sensitivity was noticed in group B for 75% (15/20) and 50% (10/20) of all antibiotics used for *E.*

Table 1. Number of ESBLs and susceptibility profile for *E. coli* 18 months before and post-pandemic declaration.

	No. of susceptible <i>E. coli</i> isolates in group A (%) n = 148	No. of susceptible <i>E. coli</i> isolates in group B (%) n = 494	Chi square	p value
ESBL	115 (59.0)	296 (59.9)	0.0518	0.8199
AMP	41 (21.0)	453 (91.7)	465.4	< 0.0000001
AMC	161 (82.6)	487 (98.6)	64.1	< 0.0000001
SAM	135 (69.2)	309 (62.6)	2.723	0.09895
Pip/Tzp	160 (82.1)	466 (94.3)	17.12	0.00003506
CZO	110 (56.4)	201(40.7)	0.4848	0.4863
CAZ	149 (76.4)	370 (74.9)	0.1719	0.6785
CRO	132 (67.7)	268 (54.3)	10.37	0.001279
CTX	109 (55.9)	314 (63.6)	21.74	0.000003117
FEP	176 (90.3)	429 (86.8)	1.522	0.2177
ATM	130 (66.7)	423 (85.6)	31.73	< 0.0000001
ETP	194 (99.5)	493 (99.8)	0.4654	0.4951
IPM	191 (97.9)	494 (100.0)	10.04	0.001534
MEM	180 (92.3)	494 (100.0)	38.85	< 0.0000001
GEN	177 (90.8)	417 (84.4)	4.752	0.02926
CIP	124 (63.6)	389 (78.7)	16.88	0.00003974
LVX	122 (62.6)	370 (74.9)	10.42	0.001248
NOR	152 (77.9)	428 (86.6)	7.93	0.004863
Tmp/Smz	93 (47.7)	275 (55.7)	3.574	0.05869
FOS	182 (93.3)	494 (100.0)	33.57	< 0.0000001
NIT	186 (95.4)	494 (100.0)	23.1	0.00001536

ESBL: extended-spectrum β-lactamases; ampicillin (AMP: 30 µg); amoxicillin/clavulanic acid (AMC: 30 µg); ampicillin/sulbactam (SAM: 10/10 µg); piperacillin/tazobactam (Pip/Tzp: 110 µg); cefazolin (CZO: 30 µg); ceftazidime (CAZ: 30 µg); ceftriaxone (CRO: 30 µg); cefotaxime (CTX: 30 µg); cefepime (FEP: 30 µg); aztreonam (ATM: 30 µg); ertapenem (ETP: 10 µg); imipenem (IPM: 10 µg); meropenem (MEM: 10 µg); gentamicin (GEN: 10 µg); ciprofloxacin (CIP: 10 µg); levofloxacin (LVX: 10 µg); trimethoprim/sulfamethoxazole (Tmp/Smz: 1.25/23.75); fosfomycin (FOS: 50 µg); nitrofurantoin (NIT: 100 µg).

Table 2. Number of ESBLs and susceptibility profile for *K. pneumoniae* 18 months before and post pandemic declaration.

	No. of <i>K. pneumoniae</i> isolates in group A (%) n = 52	No. of <i>K. pneumoniae</i> isolates in group B (%) n = 61	Chi Square	p value
ESBL	23 (44.2)	24 (39.3)	0.2759	0.5994
AMP	2 (3.8)	52 (85.2)	74.54	< 0.0000001
PIP	52 (100.0)	61 (100.0)	0.013	0.9092
AMC	43 (82.7)	55 (90.2)	1.361	0.244
SAM	35 (67.3)	61 (100.0)	23.47	0.00001266
Pip/Tzp	39 (75.0)	61 (100.0)	17.23	0.00003307
CZO	26 (50.0)	39 (63.9)	2.231	0.1354
CAZ	27 (51.9)	54 (88.5)	18.53	0.00001676
CRO	33 (63.5)	61 (100.0)	0.5696	0.4504
CTX	21 (40.4)	44 (72.1)	11.58	0.0006672
FEP	35 (67.3)	56 (91.8)	12.39	0.0004327
ETP	52 (100.0)	61 (100.0)	0.013	0.9092
IPM	52 (100.0)	61 (100.0)	0.013	0.9092
MEM	52 (100.0)	61 (100.0)	0.013	0.9092
AMK	49 (94.2)	61 (100.0)	1.443	0.2302
GEN	44 (84.6)	41 (67.2)	4.561	0.03271
CIP	36 (69.2)	52 (85.2)	4.179	0.04093
NOR	48 (92.3)	61 (100.0)	4.865	0.02742
LVX	35 (67.3)	61 (100.0)	23.47	0.00001266
Tmp/Smz	16 (30.8)	26 (42.6)	1.689	0.194

ESBL, extended-spectrum β-lactamases; ampicillin (AMP: 30 µg); piperacillin (Pip: 100 µg); amoxicillin/clavulanic acid (AMC: 30 µg); ampicillin/sulbactam (SAM: 10/10 µg); piperacillin/tazobactam (Pip/Tzp: 110 µg); cefazolin (CZO: 30 µg); ceftazidime (CAZ: 30 µg); ceftriaxone (CRO: 30 µg); cefotaxime (CTX: 30 µg); cefepime (FEP: 30 µg); aztreonam (ATM: 30 µg); ertapenem (ETP: 10 µg); imipenem (IPM: 10 µg); meropenem (MEM: 10 µg); amikacin (AMK: 30 µg); gentamicin (GEN: 10 µg); ciprofloxacin (CIP: 10 µg); levofloxacin (LVX: 10 µg); trimethoprim/sulfamethoxazole (Tmp/Smz: 1.25/23.75); fosfomycin (FOS: 50 µg); nitrofurantoin (NIT: 100 µg).

coli (Table 1) and *K. pneumoniae* (Table 2) respectively. On the other hand, *E. coli* showed a significant increase (more than 5%) in resistance to cefazolin (15.7%), ceftriaxone (13.4%), cefataxime (7.7%), ampicillin/sulbactam (606%), and gentamicin (6.4%). An increase in resistance to gentamicin (17.4%) was also noticed among *K. pneumoniae* isolates.

Discussion

Several reports have highlighted that the COVID-19 pandemic has had a negative impact on antibiotics use worldwide. This effect depends on the health care environment and infection prevention policies of each country [21]. This study was the first local study from Jordan to assess the patterns of antibiotics susceptibility based on local data post-COVID-19 pandemic. The current study analyzed the antibiotic susceptibility pattern for uropathogenic *E. coli* and *K. pneumoniae* in urine samples. A significant increase ($p < 0.05$) in sensitivity was noticed in the post-pandemic samples for 75% (15/20) and 50% (10/20) of all antibiotics used on *E. coli* and *K. pneumoniae* respectively. A significant increase in resistance amongst *E. coli* isolates was observed against ceftriaxone (13.4%) and gentamicin (6.4%). Moreover, an increase in resistance to gentamicin (17.4%) was also observed among *K. pneumoniae* isolates.

Despite the fact that the WHO, Center for Disease Control (CDC) and other international organizations warned against the inappropriate use of (broad-spectrum) antibiotics in the management of COVID-19 [22], the use of broad spectrum antibiotics such as ceftriaxone and gentamicin has increased since the start of the pandemic. This is probably because COVID-19 infection presents with symptoms that mimic community-acquired bacterial pneumonia. This is in addition to physicians' worries of secondary infections and the presence of comorbidities amongst many COVID-19 patients [23-25]. Some studies revealed that around 72% of COVID-19 patients received antibiotics despite the fact that only 8% had superinfection [24,26]. A recent study from Jordan revealed that the consumption of third generation cephalosporins was increased by 19% in 2020 compared to 2019 [27].

Our results indicate that such wide use of irrelevant antibiotics may be a major factor that has led to the increased resistance to ceftriaxone and/or gentamicin among *E. coli* and *K. pneumoniae* isolates respectively. In the case of *K. pneumoniae*, the sensitivity to ceftriaxone has not changed significantly and this could be due to low number of the study isolates: 52 samples in the pre-pandemic and 61 samples during the

pandemic period. However, more studies are needed particularly in hospitals that were allocated as COVID-19 facility. There were two main reasons for the increase in antibiotic consumption among COVID-19 patients [28]. First, the cross similarities between COVID-19 symptoms and bacterial pneumonia which mandates the prescription of empiric antibiotics for hospitalized COVID-19 patients. Second, the possibility of COVID-19 patients of acquiring secondary co-infection [28].

On the other hand, there was a significant increase in sensitivity to ampicillin, amoxicillin/clavulanic acid, cefotaxime, carbapenems (imipenem and meropenem), fluoroquinolones and nitrofurantoin in the case of *E. coli*, and to ampicillin, cefotaxime, ceftazidime and fluoroquinolones in the case *K. pneumoniae*. This could be mainly due to the of reduction of total antibiotic consumption during the pandemic time due to curfews and the lockdowns. Lockdowns had restricted many patients from reaching healthcare facilities, which were either closed or overwhelmed because of the COVID-19 patients [29,30]. This hypothesis is supported by a study from Jordan which showed that the total antibiotic consumption in Jordan decreased in 2020 (26.8% defined daily dose) compared to 2019 (28.4%) [27]. Other explanations for our results could include the fact that some classes of antibiotics such as carbapenems were not frequently used because of unavailability or because they were expensive.

There was no significant change in the number of *K. pneumoniae* or *E. coli* ESBLs isolates. This finding is opposite to some studies that found either a decrease [31] or an increase [32,33] in the proportion of ESBLs in the pandemic period. This could be due to the small number of isolates in the case of *K. pneumoniae* in our study, where there were a total of 113 isolates identified in both groups. Further investigations, particularly in hospitals that were allocated for COVID-19 management during the pandemic are needed.

The mechanism behind differing antibiotic susceptibility among Enterobacterales is the β -lactam resistance including extended-spectrum β -lactamases (ESBL), AmpC, and carbapenemases, as in *Klebsiella pneumoniae* carbapenemase (KPC) or metallo- β -lactamase. Enterobacterales possessing β -lactam resistance often show resistance to other classes of antibiotics [34]. In addition to that, there was a difference in the number of isolates of *E. coli* compared to that of *K. pneumoniae*.

In conclusion, the impact of the COVID-19 pandemic on antibiotic resistance is still largely unknown and more studies are needed, particularly in

developing countries. Antibiotic susceptibility and resistance have changed in the post-pandemic period. Therefore, there is an urgent need to strengthen infection control measures and antimicrobial stewardship during the pandemic period depending on local data.

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