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Frequency and Antibiotics Resistance of Extended-Spectrum Beta-Lactamase (ESBLs) Producing *Escherichia coli* and *Klebsiella pneumoniae* Isolated from Patients in Gaza Strip, Palestine

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ABSTRACT

Introduction: Extended-Spectrum β-Lactamases (ESBLs) hydrolyze broad-spectrum cephalosporin, monobactam, and penicillin. This study investigated ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* bacteria in the Gaza strip and explored their susceptibility to various antimicrobials to provide a reference for physicians in managing the hospital infection. **Methods:** Ninety-six isolates, comprising 69 *E. coli* and 27 *K. pneumoniae* were obtained from urine, wound, blood, and ear discharge samples from April-June 2013 in Gaza hospitals. The ESBL-producing isolates were screened using the double-disc diffusion test. Antibiotics susceptibility test was determined by the disc diffusion method on Mueller-Hinton agar, and PCR identified β-lactamases genes. **Results:** Our results revealed high rates of ESBL-producing *K. pneumoniae* (59.3%) and *E. coli* (39.1%) among isolates. About 65.1% of ESBL-producing isolates were susceptible to imipenem while exhibited 100% resistance to cefotaxime and ampicillin and 74.4% to sulfamethoxazole/trimethoprim. Except for imipenem, higher antibiotic resistance rates were observed among ESBL producers than non-ESBL producers. This study showed that the antimicrobial resistance and ESBLs were higher in *K. pneumoniae* isolates than *E. coli* isolates, and most *K. pneumoniae* isolates harbored simultaneously two or three β-lactamases-encoding genes. **Conclusion:** High ESBL-producing rates among *K. pneumoniae* and *E. coli* isolates and higher resistance rates to antibiotics among ESBL compared to non-ESBL producing isolates necessitate antimicrobial resistance surveillance and molecular characterization of ESBLs-producing bacteria to achieve a specific treatment.

INTRODUCTION

Extended-Spectrum β-Lactamases (ESBLs) hydrolyze broad-spectrum cephalosporin, monobactam, and penicillin; these enzymes are sensitive to inhibitors of beta-lactamases, such as clavulanic acid [1]. In addition, ESBLs are plasmid-mediated; many ESBL producing bacteria are also resistant to other antimicrobial agents, such as trimethoprim, tetracyclines, fluoroquinolones, chloramphenicol, and sulfonamides [2], limiting the treatment options. The significance of such ESBL-mediated infections is increasing worldwide [3]. Enterobacteriaceae members are the primary ESBL producers. The ESBLs mainly produced by *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* have also been identified in other Enterobacteriaceae members and other Gram-negative bacteria such as *Pseudomonas aeruginosa* (4). In recent years, the emergence of ESBL-producing *K. pneumoniae* and *E. coli* has become a severe problem in hospitalized patients worldwide and, causing various infectious diseases in hospitals and community settings [4].

Most ESBLs genes are carried via plasmids and can be horizontally transferred among bacteria of different

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genera, complicating the prevention and treatment of nosocomial infections [3].

Therefore, delay in identifying and reporting ESBL-producers results in extended hospitalizations, increased health care costs, morbidity, and mortality [1]. These enzymes are commonly detected among the Enterobacteriaceae members, such as *K. pneumoniae* and *E. coli.* According to a World Health Organization (WHO) report, among the significant threats to public health are ESBL-producing *E. coli* and *K. pneumoniae* listed in the preference first pathogens for developing new antibiotics [5]. Therefore, to control the threat of ESBL-producing bacteria in clinical settings, more insight is needed concerning their isolation and screening [6]. The infections caused by ESBL producing bacteria pose a therapeutic problem and infection control challenge in hospitals. Several reports of high occurrence rates and outbreaks of ESBL-positive bacteria are available, which confirm the importance of identifying their prevalence in hospitals to decrease the risk of these pathogens [7].

In Palestine, few studies have determined the prevalence of ESBL-producing isolates in hospitals. The ESBL rate was 37.5% among Gram-negative bacteria isolated from burn patients, 3.3% in *E. coli* isolates from urinary tract infections, and 32.7% in clinical *E. coli* isolates [8-10]. In many parts of the middle east, the prevalence of ESBL-producing *K. pneumoniae* isolates has been reported, e.g., United Arab Emirates (36%) [11], Syria (67.5%) [12], and Jordan (70%) [13]. Data from some countries showed that the prevalence of ESBL-producing *E. coli* was 16.8% in Lebanon [14], 22.9% in Jordan [15], 42.3% in Egypt [16], and 52% in Syria [17].

Due to the limitation of data from Palestinian hospitals regarding the prevalence of ESBL- producing bacteria, we were promoted to investigate the frequency of ESBL-producing *K. pneumoniae*, and *E. coli* isolates in different clinical specimens collected from in- and outpatients in the Gaza strip. We also determined the susceptibility of ESBL-producing isolates to common antimicrobials agents used in our hospitals.

MATERIALS AND METHODS

Sample and data collection. This study was conducted for three months, from April-June 2013, at three Palestinian hospitals in Gaza (Military Balsam Hospital, Al- Shifa Hospital, and AL-Remal Martyrs' health center). Ninety-six clinical samples were collected from patients admitted to various wards during the study period. The origins of the isolates were urine (n=73), wound (n=19), blood (n=3), and ear discharges (n=1). The collected samples were transferred to a laboratory to examine microbial pathogens, and standard microbiologic methods were used to isolate and identify bacteria [18].

The local Helsinki Committee for Human Rights confirmed this research study in the Gaza strip, and consent was taken from patients to participate willingly in this study.

Antimicrobial susceptibility testing. The susceptibility testing of the isolates to antimicrobial agents was performed using the Kirby-Bauer disk diffusion method according to guidelines Clinical & Laboratory Standards Institute (CLSI) recommendations [19]. Antibiotic disks purchased from Bio-Rad, were as follows (µg/disk): ampicillin (10), cefoxitin (30), ceftazidime (30), cefotaxime (30), gentamicin (10), amikacin (30), tobramycin (10), amoxicillin-clavulanic acid (20/10), nalidixic acid (30), ciprofloxacin (5), imipenem (10), kanamycin (30), trimethoprim-sulfamethoxazole (1.25 /23.75), tetracycline (30), and chloramphenicol (30).

Detection of ESBL-producing isolates. The method for detection of ESBLs used in this study was the double-disk synergy test. Briefly, after spread plating bacterial inoculums on a Mueller-Hinton agar plate, an amoxicillin/clavulanic acid impregnated disc was placed in the middle of the plate. In contrast, ceftazidime and cefotaxime were placed 30 mm apart (center to center) around the amoxicillin/clavulanic acid. After overnight incubation, the enhanced inhibition zone of any cephalosporin discs on the side facing amoxicillin + clavulanic acid was considered ESBL producer [20].

Detection of β-lactamase genes. The encoding beta-lactamases genes, bla_{TEM}, $bla_{\text{CTX-M}}$, $bla_{\text{OXA-1}}$, and bla_{SHV}, in the ESBL-producing isolates, were detected by PCR [21] using the primers previously published by others (Table 1).

Data analysis. The data for antimicrobial susceptibility results in non-ESBL and ESBLs of *E. coli* and *K. pneumoniae* isolates were tabulated, encoded, and statistically analyzed using the Statistical Package for the Social Sciences (SPSS) software version 18.0 (IBM Corporation, Somers, NY). Data comparison was achieved via an analysis of Pearson's Chi-square results. The level of statistical significance was set at $P< 0.05$.

RESULTS

Ninety-six clinical samples were obtained from Balsam Hospital, Al-Shifa Hospital, and Al-Remal health centers. Among the patients, 51 (53.1%) were females, and 45 (46.9%) were males. Of 96 isolates, 69 (71.9%) were *E. coli*, and 27 (28.1%) *K. pneumoniae*.

ESBL-producing isolates and antimicrobial susceptibility. Among 69 *E. coli* and 27 *K. pneumoniae* isolates, 27 (39.1%) and 16 (59.3%) were ESBL-producing isolates. According to the disk diffusion test, all ESBL-producers were resistant to the broad-spectrum cephalosporin (cefotaxime) and /or ceftazidime. Of 43 ESBL-producing isolates, 62.8% were *E. coli*, and 37.2 % K. *pneumoniae*. Most of these isolates (72.1%) were

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from Al-Shifa Hospital, followed by Balsam Hospital (20.9%) and Al-Remal Martyrs Clinic (7.0%) (Table 2). In all patients, urine (56%) was the primary source of the ESBL-producing isolates, followed by wounds (37%) and blood (7.0%) (Fig. 1). The resistance rate to cephalosporins was almost high among ESBL-producing *K. pneumoniae* and *E. coli* isolates, i.e., 100% to cefotaxime and 67.4% to ceftazidime. However, the isolates showed lower resistance to cefoxitin, i.e., a susceptibility rate of 58.1%. Among all isolates, the resistance rate to ampicillin, sulfamethoxazole/trimethoprim, kanamycin, and nalidixic acid was 100%, 74.4%, 65.1%, and 65.1%, respectively. Imipenem was the most effective antibiotic against ESBL positive isolates, i.e., 65.1% of isolates was susceptible to imipenem (Table 3). Sensitivity to gentamicin, chloramphenicol, and tobramycin was 53.5%, 48.8%, and 41.8 %, respectively.

Table 1. Primers of β-lactamase encoding genes

Target gene	Sequence (5'to 3')	Amplicon size	References
bla_{CTX-M}	F: GTTACAATGTGTGAGAAGCAG R: CCGTTTCCGCTATTACAAAC	1049 bp	[21]
bla_{SHV}	F: CACTCAAGGATGTATTGTG R: TTAGCGTTGCCAGTGCTCG	885 bp	[21]
bla_{TEM}	F: ATTCTTGAAGACGAAAGGGC R: ACGCTCAGTGGAACGAAAAC	1150 bp	[21]
bla_{OXA-1}	F: ACACAATACATATCAACTTCGC R: AGTGTGTTTAGAATGGTGATC	813 bp	[21]

Table 2. The rate of ESBL-producing bacteria from Gaza Strip Hospitals, Palestine

Place of Sample Collection	No. of ESBL producing Bacteria	Percentage (%)
Al- Shifa Hospital	31	72.1**%**
Balsam Hospital	9	20.9**%**
AL-Remal martyrs health center	3	7.0**%**
Total	43	100**%**

Table 3. Antimicrobial resistance of ESBL-producing *E. coli* and *K. pneumoniae* isolates

Antibiotics	Susceptible (%)	Intermediate (%)	Resistant (%)
Amoxycillin–clavulanic acid	16 (37.2%)	11(25.6%)	16(37.2%)
Ceftazidime	6(14.0%)	8(18.6%)	29(67.4%)
Cefotaxime	0	0	43(100.0%)
Gentamicin	23(53.5%)	1(2.3%)	19(44.2%)
Ampicillin	0	0	43(100.0%)
Imipenem	28(65.1%)	6(14.0%)	9(20.9%)
Kanamycin	8(18.6%)	16.3	28(65.1%)
Nalidixic acid	7(16.3%)	8(18.6%)	28(65.1%)
Amikacin	13(30.2%)	13(30.2%)	17(39.6%)
Sulfamethoxazole/trimethoprim	9(20.9%)	2(4.7%)	32(74.4%)
Cefoxitin	25(58.1%)	4(9.3%)	14(32.6%)
Tobramycin	18(41.8%)	2(4.7%)	23(53.5%)
Chloramphenicol	21(48.8%)	3(7.0%)	19(44.2%)
Ciprofloxacin	39.5	4.7	55.8

β-Lactamase Genes. All ESBL-producing *E. coli* isolates had the $bla_{\text{CTX-M}}$ gene. The bla_{TEM} was amplified in 8 isolates (29.6%), whereas bla_{SHV} and bla_{OXA} genes were detected. Among *K. pneumoniae* isolates, $bla_{\text{CTX-M}}$ was detected in 16 (100%), bla_{SHV} in 12 (75%), bla_{TEM} in 7 (43.75%), and bla_{OXA} in 1 (6.25%).

ESBL production and antimicrobial resistance. The frequency of ESBL-producing isolates was higher in *K. pneumoniae* than in *E. coli*. Both ESBL-producing *E. coli* and *K. pneumoniae* isolates were more resistant to cefotaxime and ampicillin. The resistance rate to aminoglycosides, amoxicillin-clavulanic acid, and imipenem was significantly higher in ESBL-producing *K. pneumoniae* than ESBL-producing *E. coli* (P=0.001). However, the difference in resistance to ceftazidime, nalidixic acid, sulfamethoxazole/trimethoprim, cefoxitin, chloramphenicol, and ciprofloxacin was not statistically significant ($P > 0.05$). (Table 4, Fig. 2).

ß-lactamase genes among K. pneumoniae and E. coli isolates. According to ß-lactamase-encoding genes, *K. pneumoniae*, and *E. coli*, ESBL-producing isolates were grouped into three classes, harboring three, two, or one gene (Table 5). The majority (n=13) of ESBL-producing *K. pneumoniae* isolates (81.25%) harbored more than one ß-lactamase encoding gene, nine (56.25%) three genes, and 4 (25%) two genes. However,

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only 8 (29.60%) ESBL-positive *E. coli* isolates harbored two ß-lactamase encoding genes. The majority (n=19, 70.40%) of the ESBL-producing *E. coli* isolates harbored only bla_{CTX-M} alone, whereas only 3 (18.75%) of *K. pneumoniae* isolates carried one of the detected ß-lactamase encoding genes (Table 5 and Fig. 3).

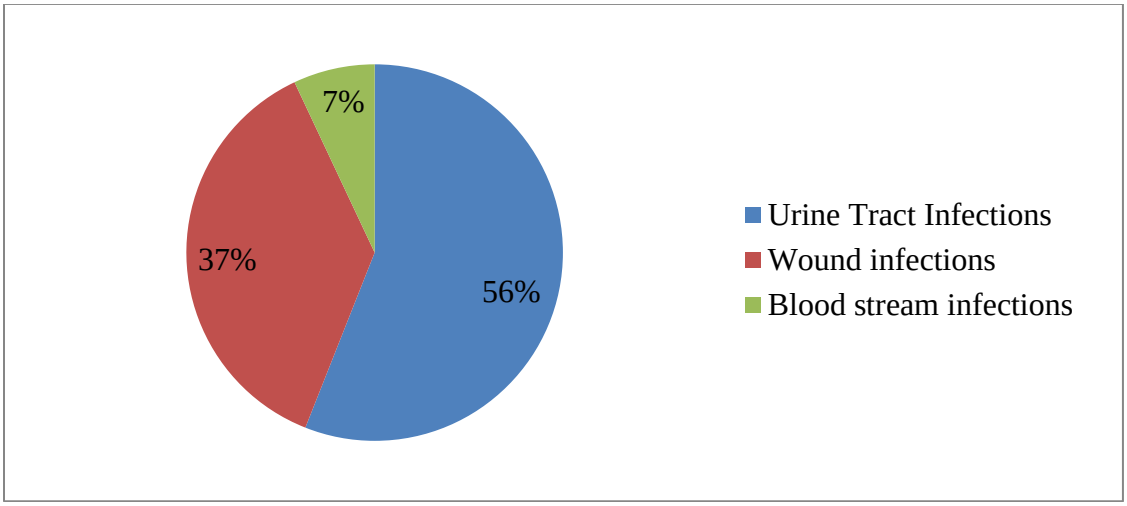

Fig. 1. Samples distribution of isolated ESBL.

Antibiotics resistance among ESBL and non-ESBL-producing isolates. Both ESBL and non -ESBL producing *E. coli* and *K. pneumoniae* isolates exhibited a low resistance to imipenem. However, resistance to other antibiotics was significantly higher in both bacterial groups ($P \leq 0.001$) (Table 6, Fig. 4).

Table 4. Comparison of frequency of antibiotics resistance among ESBL producing isolates of *E. coli* and *K. pneumoniae.*

Antibiotics	*E. coli* (n = 27)%		*K. pneumonia* (n = 16) %		
	Susceptible (%)	Resistant (%)	Susceptible (%)	Resistant (%)	*P-value
Amoxycillin–clavulanic acid	15(55.6%)	7(25.9%)	1(6.3%)	9(56.3%)	0.002
Ceftazidime	6(22.2%)	14(51.9%)	0	15(93.8%)	0.020
Cefotaxime	0	27(100.0%)	0	16(100.0%)	0.436
Gentamicin	20(74.1%)	7(25.9%)	3(18.8%)	12(75.0%)	0.001
Ampicillin	0	27(100.0%)	0	16(100.0%)	0.436
Imipenem	24(88.9%)	2(7.4%)	4(25%)	7(43.8%)	0.001
Kanamycin	7(25.9%)	14(51.9%)	1(6.3%)	14(87.5%)	0.058
Nalidixic acid	5(18.5%)	20(74.1%)	2(12.5%)	8(50%)	1.000
Amikacin	12(44.4%)	5(18.5%)	1(6.3%)	12(75.0%)	0.001
Sulfamethoxazole/trimethoprim	5(18.5%)	21(77.8%)	4(25%)	11(68.8%)	0.580
Cefoxitin	19(70.4%)	7(25.9%)	6(37.5%)	7(43.75%)	0.098
Tobramycin	16(59.3%)	10(37.0%)	1(6.3%)	13(81.3%)	0.001
Chloramphenicol	15(55.6%)	10(37.0%)	6(37.5%)	9(56.3%)	0.220
Ciprofloxacin	9(33.3%)	16(59.3%)	8(50%)	8(50%)	0.375

**P*-value of Pearson's Chi-square

Table 5. Multiplicity of ß-lactamase encoding genes in *K. pneumoniae* and *E. coli* isolates

Bacterial Strains	Three ß-lactamase genes		Two ß-lactamase genes		One ß-lactamase gene
	bla_{CTX-M} + bla_{SHV}+ bla_{TEM}	bla_{CTX-M} + bla_{SHV} + bla_{OXA}	bla_{CTX-M} + bla_{SHV}	bla_{CTX-M} + bla_{TEM}	bla_{CTX-M}
K. pneumoniae	6 (37.50%)	3 (18.75%)	3 (18.75%)	1 (6.25%)	3 (18.75%)
E. coli	0	0	0	8 (29.60%)	19 (70.40%)

DISCUSSION

Antimicrobial resistance is an increasingly emerging problem worldwide. Knowledge of the drug resistance pattern of pathogens in hospitals is the key to the successful treatment of patients [22]. The ESBLs are among the most alarming groups of β-lactamases in pathogens isolated from clinical isolates; many reports indicated increased mortality by infections caused by ESBLs- producing bacteria [23]. The increasing incidence of ESBLs among Enterobacteriaceae is a growing problem. In this study, we described the antibiotics resistance and the emergence of ESBLs

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among *E. coli*, and *K. pneumoniae* isolates in patients from Balsam Hospital, Al-Shifa Hospital, and Al-Remal martyrs' health center in Gaza, Palestine.

Our study showed ESBLs phenotype in 39.1% and 59.3% of *E. coli* and *K. pneumoniae* isolates, respectively. These rates are much higher than 3.3% ESBL-producing *E. coli* isolates reported 16 years ago in the Gaza strip [9]; however, not much higher than reports indicating ESBL production in 9% *E. coli* and 35.5% *K. pneumoniae* isolates12 years ago [24]. There is limited data from Palestinian hospitals regarding the prevalence of ESBLs producers in clinical isolates; the last report in 2008 depended only on phenotypic methods to detect ESBLs. Studies from the West Bank hospitals reported that the prevalence of ESBL producers among *E. coli* clinical isolates were 32.7% and 47.7% [10, 25].

Table 6. Comparison of frequency of antibiotics resistance among ESBL and non-ESBL *E. coli* and *K. pneumoniae*

Antibiotics	ESBL **(n = 43)%**		Non- ESBL **(n = 53) %**		
	Susceptible (%)	**Resistant (%)**	**Susceptible (%)**	**Resistant (%)**	*P*-value
Amoxycillin–clavulanic acid	16 (37.2%)	16 (37.2%)	41(77.4%)	2(3.8%)	0.001
Ceftazidime	6(13.9%)	29(67.4%)	48(90.6%)	4(7.5%)	0.001
Cefotaxime	0(0.0%)	43 (100%)	40(75.5%)	4(7.5%)	0.001
Gentamicin	23(53.5%)	19(44.2%)	48(90.6%)	4(7.5%)	0.001
Ampicillin	0(0.0%)	43 (100%)	18(33.9%)	31(58.5%)	0.001
Imipenem	28(65.1%)	9(20.9%)	44(83.0%)	3(5.7%)	0.020
Kanamycin	8(18.6%)	28(65.1%)	22(41.5%)	9(17%)	0.001
Nalidixic acid	7(16.3%)	28(65.1%)	41(77.4%)	7(13.2%)	0.001
Amikacin	13(30.2%)	17(39.5%)	40(75.5%)	4(7.5%)	0.001
Sulfamethoxazole/trimethoprim	9(20.9%)	32(74.4%)	36(67.9%)	17(32.1%)	0.001
Cefoxitin	25(58.1%)	14(32.6%)	47(88.7%)	1(1.9%)	0.001
Tobramycin	17(39.5%)	23(53.5%)	41(77.4%)	5(9.4%)	0.001
Chloramphenicol	21(48.8%)	19(44.2%)	47(88.7%)	5(9.4%)	0.001
Ciprofloxacin	17(39.5%)	24(55.8%)	47(88.7%)	6(11.3%)	0.001

**P*-value of Pearson's Chi-square

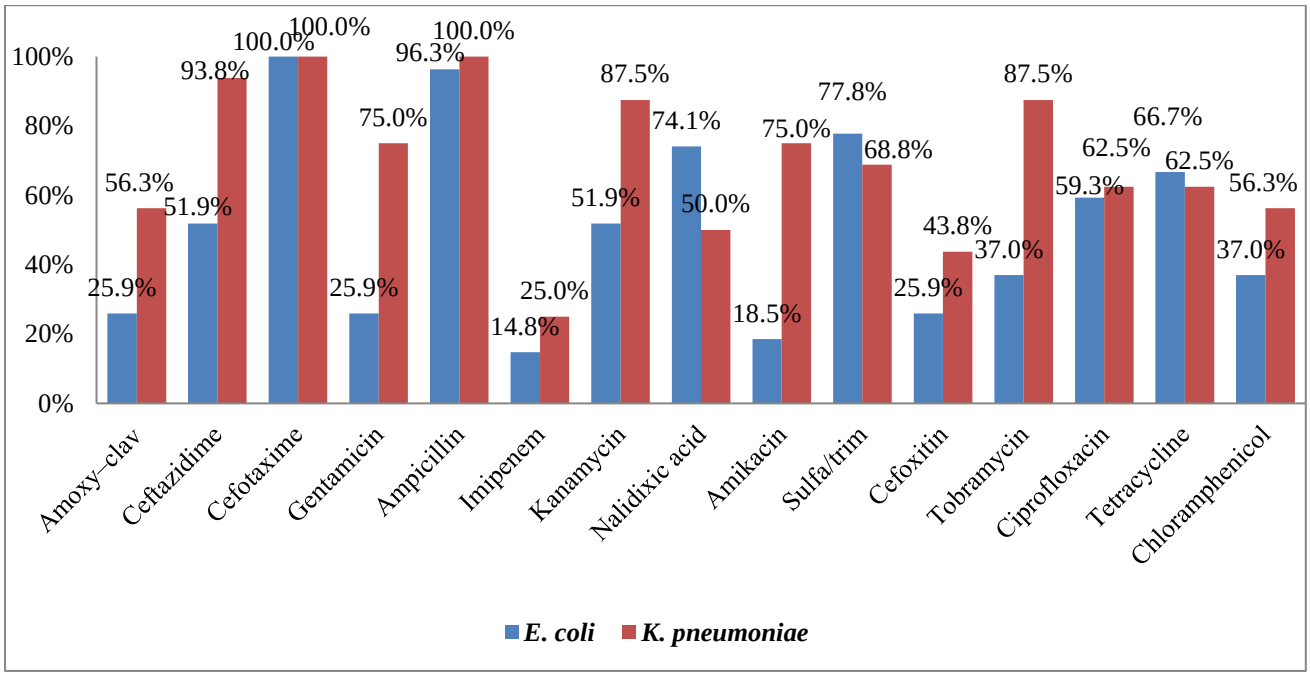

Fig. 2. Comparison of antibiotics resistance among isolates of *K. pneumoniae*and *E. coli*.

In the present study, the overall prevalence rate of ESBL-producing *E. coli* isolates was 39.1%. Similar studies have shown 16.8% in Lebanon [14], 22.9% in Jordan [15], 42.3% in Egypt [16], and 52% in Syria [17]. We observed that 59.3% (n=16) of the *K. pneumoniae* isolates were ESBL producers in the present study. Reports from different parts of the world showed high ESBL-producing rates among *K. pneumoniae* isolates, e.g., 23.5% in Kuwait [26], 36% in the United Arab Emirates [11], 67.5% in Syria [12], and 70% in Jordan [13]. Our findings of ESBL production in *E. coli* and *K. pneumoniae* isolates agree with the results from developing countries, particularly the Middle Eastern countries.

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The high rates of ESBL production among *E. coli* and *K. pneumoniae* isolates in Al-Shifa Hospital should alert the physicians about the uncontrolled prescription of cephalosporins, e.g., cefotaxime. The infections by ESBL-producing isolates have shown co-resistance to quinolones, aminoglycosides, and sulfamethoxazole/trimethoprim.

The ESBL-producing isolates in our study were resistant to the most commonly prescribed antibiotics in Gaza hospitals. The high level of resistance (>50%) to sulfamethoxazole/trimethoprim, nalidixic acid, ciprofloxacin, ceftazidime, cefotaxime, ampicillin, kanamycin, and tobramycin could be due to overuse or misuse of these antimicrobial agents in the Gaza Strip, i.e., easy availability of these antibiotics and lack of an antibiotic policy in Palestine. In a similar study in a Palestinian hospital, most *K. pneumoniae* and *E. coli* isolates were resistant to most tested antibiotics [24].

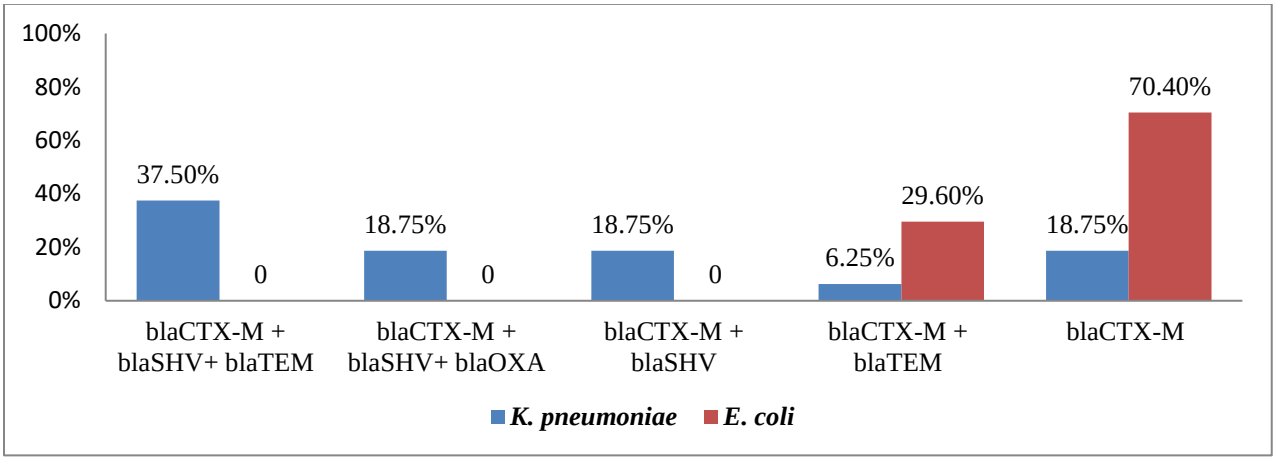

Fig. 3. Multiplicity of ß-lactamase encoding genes in *K. pneumoniae* and *E. coli* isolates.

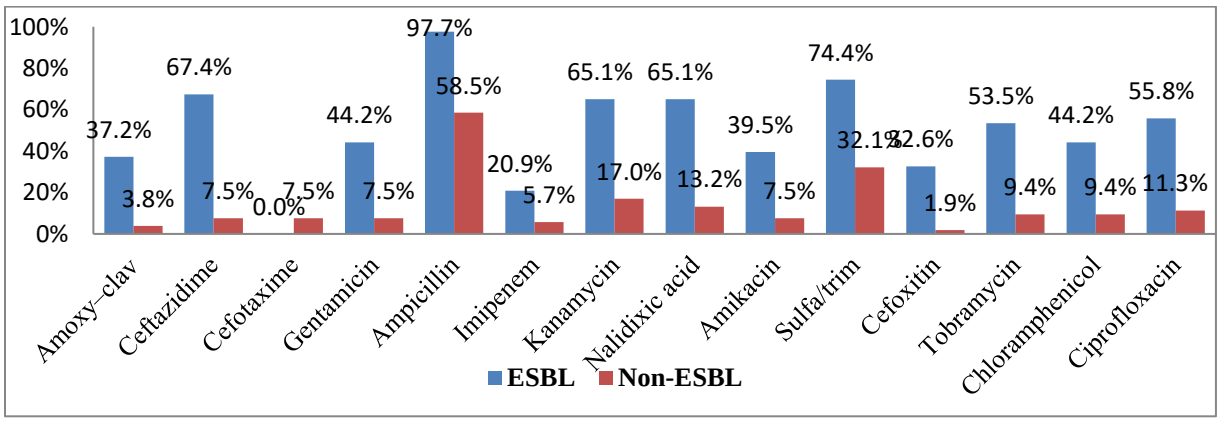

Fig. 4. Comparison of antibiotics resistance among ESBL and non-ESBL producers of *E. coli* and *K. pneumoniae.*

One of the significant findings of this study is the sensitivity of both pathogenic agents to imipenem. The resistance rate to imipenem was about 20.9%, and *E. coli* was more sensitive than *K. pneumoniae*. Therefore, imipenem remains an effective treatment option for *E. coli* and *K. pneumoniae* in Gaza Strip hospitals. A recent survey in Palestine showed a 20% imipenem-resistant rate among *K. pneumoniae* and *E. coli* isolates [24]. In Iran, the resistance rate to imipenem was 8.5% to 20% [22], which agrees with our findings; however, in Turkey, the rate was much higher (79.2%) [27].

Our findings showed apparent susceptibility pattern variations between the 43 ESBL-producers *K. pneumoniae* and *E. coli* isolates regarding quinolones, aminoglycosides, amoxicillin-clavulanic acid, chloramphenicol, and ceftazidime. The resistance to aminoglycosides, amoxicillin-clavulanic acid, and imipenem in *K. pneumoniae* isolates was higher than in *E. coli*. Other studies reported susceptibility patterns similar to our findings for some antimicrobials; however, none of the reports have provided the same susceptibility patterns [28, 29].

Regarding the ß-lactamase encoding genes, $bla_{\text{CTX-M}}$ was detected in 70.4% of *E. coli* isolates. Our results agree with other studies in Palestine and United Arab Emirates [30, 31]. The $bla_{\text{CTX-M}}$ and $bla_{\text{TEM-1}}$ genes were identified in 29.6% of *E. coli* isolates; others have previously reported this association [30, 32]. The present study found that most CTX-M-producing *K. pneumoniae*

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isolates harbor more than one ß-lactamase encoding gene. Our results revealed that > 50% of *K. pneumoniae* isolates harbor three ß-lactamase encoding genes and 25% two genes, similar to findings in previously reported studies [33-35].

K. pneumoniae isolates had a higher ESBL producer rate than *E. coli*. This finding correlates with other studies in the USA [36] and Turkey [37]. However, some reports indicated higher ESBL-producing rates in *E. coli* than *K. pneumoniae* in some countries, e.g., Saudi Arabia [38] and Bangladesh [29]. Most *K. pneumoniae* harbored two or three β-lactamases-encoding genes, limiting the antibiotic choice for the treatment.

We observed that resistance to antibiotics was higher among ESBL producers than non-ESBL producers, which indicates the need for a screening strategy in our laboratories to identify the ESBL- associated infections in patients and prescribe specific and suitable antibiotics.

In our study, ESBL and non-ESBL producers isolates were 91% and 97% sensitive to imipenem, respectively. Similar studies have reported 100% and 96.8% sensitivity to imipenem among ESBL and non-ESBL *E. coli* isolates [20, 39], inconsistent with our findings.

In conclusion, our findings depict a complicated resistance problem with limited antimicrobial choices for *K. pneumoniae* infections. Therefore, continuous monitoring of ESBLs-producing isolates is required to reduce their frequency and prevent any possible outbreak of these superbugs. According to the results of this study, there are limited treatment options available for these pathogens; imipenem, a carbapenem member, can be suggested as a drug of choice. The development of ESBL-producing pathogens can be decreased by restricting third-generation cephalosporins, increasing imipenem use, and implementing infection control measures in hospitals to avoid the dissentation of resistance bacteria such as hand hygiene, use of personal protective equipment (e.g., gloves, masks, eyewear) and clean and disinfected environmental surfaces.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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