Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 1, 2022, pp. 419-426.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

DETECTION OF CARBAPENEM RESISTANCE AMONG *ESCHERICHIA COLI AND KLEBSIELLA PNEUMONIAE* IN CHEST INTENSIVE CARE UNIT AT ASSIUT UNIVERSITY HOSPITALS, EGYPT

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This study aimed to determine antimicrobial susceptibility pattern, percentage of carbapenem resistance and presence of blaNDM1, blaVIM1, blaIMP, blaKPC genes among Escherichia coli (E.coli) and Klebsiella pneumonia (K. pneumonia) isolated from chest intensive care unit (ICU) at Assiut University Hospitals, Egypt. Antibacterial susceptibility was detected by disc diffusion method. Genotypic detection of carbapenem resistant genes (IMP, NDM, VIM, and KPC) was done by PCR. From totally 200 patient clinical samples, 100 isolates (50%) were identified to be E.coli and K. pneumonia. Various percentages of resistance were reported for oxacillin (80 and 60%), ciprofloxacin (46 and 52%), amikacin (66 and 86%) amoxicillin & clavulanic acid (60 and 90%) lomefloxacin (22 and 18%) gentamicin (70 and 54%) chloramphenicol (54.4 and 66.7%), imipenem (90 and 84%), meropenem (80 and 72%) for E.coli and Klebsiella. The prevalence of KPC, NDM1, IMP, VIM genes was 74, 56, 30, 26 % for E.coli and NDM1,KPC, VIM1, IMP was 66, 64, 54, 50 % For K. pneumoniae. In conclusion, carbapenemases have essential role in antibiotic resistance of E. coli and K. pneumonia.

Keywords: *carbapenem resistance; blaNDM1, blaVIM1, blaIMP, blaKPC; E.coli; K. pneumoniae*

INTRODUCTION

Because of the rapid emergence and spread of antibiotic resistance, it is critical to track antibiotic use and establish treatment options in order to reduce antibiotic misus[1-5].

As a result, it's critical to keep looking into the genes that cause bacteria to become resistant to various antibiotics. Multidrug resistant Gram-negative bacteria is a growing concern across the Middle East due to several risk factors for acquisition, and treatment failure due to patient's compliance and duration of treatment[6].

β-lactam antibiotics are a class of antibiotic which have a broad spectrum of antibacterial activity, including important Gram-positive and Gram-negative pathogens and are the most broadly used antibiotics worldwide[7].

So, an increasing incidence of resistance to these drugs is a public health concern. β-lactam antibiotics act by inhibiting a set of transpeptidase enzymes called penicillin binding proteins (PBPs), that are crucial for cell wall peptidoglycan synthesis, leading to death of the growing bacteria[8&9].

Carbapenems are class of antibiotics of last refuge used for treatment of several infections due to Gram-negative bacilli, as extended spectrum *β*-lactamase- (ESBL-) producing bacteria**.** Several clinically relevant

Received in 4/12/2021 & Accepted in 1/3/2022

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bacteria induce resistance to these life-saving drugs bacteria**.** Carbapenemases are responsible for those resistance to carbapenems and mediated by several types of those enzyme such as metallo-*β*-lactamases (MBLs) of Imipenemase (IMP), NDM and VIM types, and serine carbapenemases of *K. pneumoniae* (KPC) type[10]**.**

Prevalence of infections due to carbapenem resistant enterobacteriaceae (CRE) has been increased during the last decade**.** Infections due to these isolates are significantly have morbidity and mortality rate. Several risk factors can associate with those infection that included antibiotic exposure, intensive care unit (ICU) stay, and poor functional status[11].

Various strains of *E.coli* have different antibiotic sensitivities. Many drugs that are effective against Gram-Positive bacteria are ineffective against *E.coli*. Antibiotic resistance is on the rise. Some of this is due to human abuse of antibiotics, but much of it is likely owing to antibiotics being used as growth promoters in animal feeds[12]. Due to widespread β-lactam antimicrobial use, bacterial resistance has been increasing and now represents a serious threat to the continued use of antibiotic therapy[13&14].

In this study we aimed to determine the prevalence of *E.coli and K. Pneumoniae* in chest intensive care units causing pneumonia, the percentage of carbapenem resistance among *E.Coli* and *K. Pneumoniae* isolates. Also to determine the presence of *blaIMP, blaNDM1, blaVIM1, blaKPC* genes by PCR.

MATERIALS AND METHODS

Sample collection and isolation

All clinical samples were collected from chest intensive care unit (ICU) at Assiut University Hospitals for microbiological diagnosis in Microbiology and Immunology Department throughout the period of November 2018 to November 2019. They were 200 samples, *E.coli and K. pneumoniae* caused 100 of them. Patients were with a mean age of 47±15years (SD). They included 45 males (45%) and 55 females (55%). The sputum samples were collected from patients with lower respiratory tract infection.

Culture characteristics

On MacConkey medium, *E. coli* and *K. pneumoniae* colonies are pink due to lactose fermentation, but *K. pneumoniae* colonies are large and mucoid dark pink due to slime layer. On Eosin Methylene Blue (EMB), *K. pneumonia*e showed large mucoid pink or purple colonies, *E.coli* showed a characteristic green metallic sheen[5].

Antimicrobial susceptibility testing of isolated bacteria

Antimicrobial susceptibility patterns were determined by disk diffusion method on Muller-Hinton agar. The following antimicrobial disks were used; gentamicin (30 µg), cefatriaxone (30 µg), imipenem (10 µg), chloramphenicol (30 µg), cefotaxime (30 µg), meropenem (10 µg),oxacillin(1 µg), cefepime (30 µg), ciprofloxacin (5 µg) , norfloxacin (10 µg) , oxytetracycline(30µg), penicillin(10 µg) , amoxicillin- clavulanic acid (20/10 µg), amikacin (30 µg), lomefloxacin (10 µg) .

Genotypic detection of carbapenem resistant genes (bla_{IMP}, bla_{NDM1}, bla_{VIM1} and bla_{KPC}) by Polymerase chain reaction.

Extraction of DNA from bacterial Colonies

Total cellular DNA was prepared as follows: culture grown overnight on Tryptic Soy Broth (TSB) was transferred to a 250 µl Eppendorf vial, and then centrifuged at 10000 rpm for 10 min. The supernatant was discarded and 250 µl of distilled water was added to the pellet and resulting solution was heated for 15 min at 100˚C and centrifuged at 10000 rpm for 10 min. The supernatant was transferred to a new microtube and stored at -20 ˚C.

PCR amplification

PCR in a 50-µl reaction mixture was performed on 2 µl of extracted DNA. The PCR mixture consisted of 1× PCR buffer (10 mM Tris-HCl [pH 8.3], 50 mM KCl), 1.5 mM MgCl2, 0.125 mM each dNTP, 0.1 µM each primer as shown in table (1), and 2 U of AmpliTaq Gold polymerase (Roche, Meylan, France). The PCR amplification thermal cycling conditions were as follows; 10 min at 94°C; 36 cycles of amplification consisting of 30 s at 94°C, 40 s at 52°C, and 50 s at 72°C; and 5 min at 72°C for the final extension.

Table 1: Primer sequences and product size for bla_{IMP} , blaNDM1, blaVIM1 and bla_{KPC} genes.

GENE	Primer		Product size (bp)
	Forward	Reverse	
bla$_{IMP}$	GCGTTTATGTTCATACTTCGTTT	TCTATTCCGCCCGTGCTGT	587
blaNDM1	CAACTGGATCAAGCAGGAGA	TCGATCCCAACGGTGATATT	621
blaVIM1	GACCGCGTCTGTCATGG	GGCGACTGAGCGATTTTT	748
bla$_{KPC}$	CGTTGACGCCCAATCC	ACCGCTGGCAGCTGG	700

RESULTS AND DISCUSSION

Results

From totally 200 patient clinical samples, 100 isolates were identified to be *E.coli and K. pneumonia* (50%) according to culture characters and biochemical reaction results.

Isolation and identification of *bacterial* isolates

Primary identification of the isolates was conducted by Gram stain.

Isolates were a Gram-negative bacillus arranged in pairs and/or short chains.

Cultivation of the isolates on MacConkey (selective media) showed red colonies due to lactose fermentation, but *K. pneumoniae* colonies are large and mucoid dark pink due to slime layer.

On Eosin Methylene Blue (EMB), *K. pneumonia*e showed large mucoid pink or purple colonies, *E.coli* showed a characteristic green sheen.

Antimicrobial susceptibility profile for isolated *E.coli* and *K. pneumoniae*

As shown in table 2, all isolates were resistant to penicillin, ampicillin, Various percentages of resistance were reported for oxacillin (80 and 60%), ciprofloxacin (46 and 52%), amikacin (66 and 86%), amoxicillin & clavulanic acid (60 and 90%), lomefloxacin (22 and 18%), gentamicin (70 and 54%), chloramphenicol (54.4 and 66.7%), oxytetracycline (20 and 16%), norfloxacin (26 and 36%), cefotaxime (80 and 90%), cefepime (201 and 0%), imipenem (90 and 84%), meropenem (80 and 72%) for *E.coli* and *Klebsiella* respectively.

Frequency of some carbapenem resistance genes in the bacterial isolates.

Virulence genes including (*$bla_{IMP,}$ $bla_{NDM1,}$ bla_{VIM1}* and *bla_{KPC}*) of fifty isolates of *E.coli* and *K. pneumoniae* were amplified by PCR.

For *E.coli*, the prevalence of *blaKPC*, *blaNDM1*, *blaIMP*, *blaVIM1* genes were 74%, 56%, 30%, 26% respectively. For *K. pneumoniae,* the frequency of *blaNDM1*, *blaKPC*, *blaVIM1*, *blaIMP* was 66%, 64%, 54%, 50 % respectively as shown in table 3. Some strains were carrying one and others were carrying more than one carbapenem resistance genes as shown in table 4.

Table 2: Antimicrobial susceptibility profile for isolated *E.coli* and *K. pneumoniae*.

Antibiotics	*E. coli*	*K. pneumoniae*
Penicillin	50(100%)	50(100%)
Oxacillin	40(80%)	30(60%)
Amoxicillin/ clavulanic acid	30(60%)	45(90%)
Gentamicin	35(70%)	27(54%)
Amikacin	33(66%)	43(86%)
Ciprofloxacin	23(46%)	26(52%)
Norfloxacin	13(26%)	18(36%)
Lomefloxacin	11(22%)	9(18%)
Oxytetracycline	10(20%)	8(16%)
Chloramphenicol	6(54.5%)	6(66.7%)
Cefotaxime	40(80%)	45(90%)
Cefepime	10(20%)	5(10%)
Imipenem	45(90%)	42(84%)
Meropenem	40(80%)	43(86%)

Table 3: Frequency of some carbapenem resistance genes in the isolated *E.coli* and *K. pneumoniae.*

Isolates	N	bla_{IMP}		*blaNDM1*		*blaVIM1*		bla_{KPC}	
		N	%	N	%	N	%	N	%
E.coli	50	15	30%	28	56%	13	26%	37	74%
K. pneumoniae	50	25	50%	33	66%	27	54%	32	64%

Table 4: Frequency of one or more than one carbapenem resistance genes in the isolated *E.coli* and *K. pneumoniae*

Gene(s) in each isolate	*E. coli*		*K. pneumoniae*	
	N	%	N	%
One gene	17	34 %	6	12%
Two gene	20	40%	15	30%
Three gene	9	18 %	15	30%
Four gene	2	4 %	9	18%
No gene	2	4 %	5	10%
Total	50	100	50	100

Discussion

In this study, we reported nosocomial infections to be 33.3% (200/600). *E.coli* and *K. pneumoniae* caused 100 (50%) of these nosocomial infections. Our result was much higher than a study by Amazian, K. et al who reported that prevalence of nosocomial infections was 10.5%; this was higher in non-teaching centers and moderate-sized hospitals[14]. In Amazian, K. et al study, the most commonly isolated organisms were: *E.coli* [17.2%], *Staph. aureus* [12.5%], *P. aeruginosa* and *K. pneumoniae* [9.2% each]. This difference might be different sample size, different region and infection control policies. The factors associated with acquisition of CRE were often complex.

In this study, the factors associated with acquisition of CRE were recorded. It was found that diabetes, malnutrition, immunodeficiency, peripheral I.V Catheter, artificial feeding, assisted ventilation, previous antibiotic Administration are the major risk factors significantly associated with CR *E.coli*. In contrast, diabetes, obesity, surgery, peripheral, I.V catheter, artificial feeding, endotracheal intubation, previous antibiotic administration are the major risk factors significantly associated with CRKP. In agreement with this study, several studies reported that hospital environment due to failure of adequate cleaning and disinfection, diabetes, organ/stem cell transplantation, mechanical ventilation, exposure to antimicrobials, and overall longer length of stay in hospitals are major risk factors for acquiring CRE infections[15&16] .

In our study, we reported that all isolates were resistant to penicillin, ampicillin, Various percentages of resistance were reported for oxacillin (80 and 60%), ciprofloxacin (46 and 52%), amikacin (66 and 86%), amoxicillin & clavulanic acid (60 and 90%), lomefloxacin (22 and 18%), gentamicin (70 and 54%), chloramphenicol (54.4 and 66.7%), oxytetracycline (20 and 16%), norfloxacin (26 and 36%), cefotaxime (80 and 90%), cefepime (201 and 0%), imipenem (90 and 84%), meropenem (80 and 72%) for *E.coli* and *K.* respectively. Our results came in agreement with this study those of Kotsoanas et al., (2013) who reported that 85–100% of the isolates were Ampicillin resistant , (66.7–100%) were resistant to Piperacillin, Ceftazidime, Cefotaxime and Aztreonam. (90%) of the isolates were resistant to Amoxicillin, Piperacillin and Cephalothin[17]. In our study the resistance rate was much higher than one study, reported that high antibiotic resistance patterns were detected among *E. coli* and *K. pneumoniae* isolates[18].

Also, other study, stated that, Ceftriaxone resistance is increased in *E. coli* (from 48% to 70.5%) and in *K. pneumoniae* up to 81%, whereas Ciprofloxacin resistance in both organisms is in the range of 60-70%. Carbapenem resistance is also started increasing for both organisms[19].

In this study, the prevalence of *blaKPC*, *blaNDM1*, *blaIMP*, *blaVIM1* genes 74,

56,30,26 % respectively for *E.coli.* and *blaNDM1*, *blaKPC*, *blaVIM1*, *blaIMP* 66,64,54,50 respectively For *K. pneumoniae*. Our findings were much higher than several studies included Egyptian where reported that the most prevalent gene was *blaVIM* (21,10.7%), followed by *blaOXA-48* (19, 9.7%), *blaIMP* (12, 6.1%), *blaKPC* (10,%) and *bla*NDM-1 (5, 2.6%). Also, carbapenemases genes, 62.1 % were *blaKPC* positive, 20.7 % were *blaVIM*-positive, 3.4 % were *blaNDM*-positive, 13.8 % were blaOXA-48-positive and none was *blaIMP*-positive. In addition, the most prevalent gene was *blaKPC* 47.8% followed by blaVIM-1 21.7%, *blaIMP* 15.2%, *blaOXA*-48-like 10.9% and blaNDM-1 4.3%[20,21].This difference might be due to different strains, geographical area, sample size and different antibiotics used in treatment of infections[22-26].

The rapid emergence and spread of antibiotic resistance makes it vital to keep track of antibiotic use and develop therapeutic solutions to decrease antibiotic misuse[27-32]. As a result, it's vital to continue researching the genes that drive bacteria to become antibiotic-resistant[33-40].

Conclusion

Our results revealed a high level of antimicrobial resistance among the studied clinical isolates of *E. Coli and K. Pneumoniae*. The prevalence of carbapenemases producing isolates and their isolation from life threatening infections is increasing at an alarming rate worldwide. *IMP, NDM1, VIM1, KPC* play a vital role in the generation of this antimicrobial resistance phenotypically and genotypically. So, clinicians should understand the drug resistance of *E.coli and K. Pneumoniae* in order to control further propagation of these severely resistant bacterial strains in community and hospital settings.

Acknowledgments

The authors would like to thank the Medical Research Center at the Faculty of Medicine, Assiut University for providing the research equipment.

Conflicts of Interest

The authors declare no conflict of interest.

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Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 1, 2022, pp419-426.

نشرة العلوم الصيدلية
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الكشف عن مقاومة الكاربابينيم بين الإشريكية القولونية والكلبسيلا الرئوية في وحدة العناية المركزة للصدر بمستشفيات جامعة أسيوط بمصر

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في هذه الدراسه ، تم تجميع ٢٠٠ عينه اكلينيكيه من مرضي العنايه المركزه الصدريه . تم عزل ١٠٠ عتره ايشريشيا كولاي وكليبسيلا رئويه من ١٠٠ مريض يعانون من عدوي المستشفيات المكتسبه. تبين أن العديد من عوامل الخطر يمكن أن تشارك في اكتساب العدوى. فيما يتعلق بمقاومة المضادات الحيوية كانت الإيشريشيا كولاي والكليبسيلا الرئوية مقاومة بالكامل لمعظم المضادات الحيوية التي تم اختبارها .تم عمل فحص الجينات المسئولة عن المقاومة لمجموعة كاربابينيم (blaIMP ، blaNDM1 ، blaVIM1 ، blaKPC) من خمسين عزلة من كل من الإيشريشيا كولاي والكليبسيلا الرئوية بواسطة PCR ، كان blaKPC أعلى نسبة في الإيشريشيا الكولاي بينما كان blaNDM1 أعلى نسبة في الكليبسيلا الرئوية.