ORIGINAL ARTICLE

Co-occurrence of *blaNDM-1* and *blaOXA-48* among carbapenem resistant *Enterobacteriaceae* isolates causing bloodstream infections in Alexandria, Egypt.

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ABSTRACT

Background: *Bloodstream infections are serious ailments, that require prompt appropriate treatment. This is challenging with the growing number of multi-drug resistant organisms.* ***Objective:*** *The aim of this study was to genotypically characterize the carbapenem resistance among cephalosporin resistant Enterobacteriaceae isolates causing bloodstream infections.* ***Methodology:*** *Twenty-eight enterobacterial isolates resistant to ceftazidime and cefepime causing bloodstream infections were collected. Their identification was confirmed using Vitek-2 system (Biomerieux, France), and their susceptibility pattern was assessed using disk diffusion method. They were genotypically tested for the presence of blaSHV, blaCTX-M as well as blaTEM. Furthermore, carbapenem resistant isolates were genotypically examined to detect blaKPC, blaIMP, blaNDM-1, blaVIM and blaOXA-48 genes.* ***Results:*** *The enterobacterial isolates were identified as Klebsiella pneumoniae and Escherichia coli. Of these, (85.71%) were carbapenem resistant. Genotypically blaCTX-M, blaSHV and blaTEM were detected in (85.71%), (89.29%) and (64.29%) of the twenty-eight isolates, respectively. Moreover, (66.67%) and (62.50%) of the carbapenem resistant isolates possessed blaOXA-48 and blaNDM-1, respectively. Only one harbored blaVIM. Moreover, blaIMP and blaKPC were not detected among these isolates. Ten (35.71%) of the isolates harbored beta-lactamases genes belonging to three beta-lactamases classes (A, B and D).* ***Conclusion:*** *The co-occurrence of different beta-lactamases belonging to diverse classes and the co-existence of blaOXA-48 and blaNDM-1 among isolates causing bloodstream infections is quite alarming and necessitates prompt action.*

INTRODUCTION

Bloodstream infections are known to be a major cause of morbidities and mortalities worldwide. Not only are they life threatening, but also therapeutically challenging, especially with rising antimicrobial resistance and a plethora of causative organisms.[1, 2] According to SENTRY program, *Staphylococcus aureus* as well as *Escherichia coli* were the predominant pathogens causing bloodstream infections, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.[3]

Antimicrobial resistance is a growing global challenge, in which beta-lactamases play a significant role. Beta-lactamases are categorized into four major classes using Ambler classification. These classes are named (A, B, C as well as D). Class A comprises the greater share of the extended-spectrum beta-lactamases (ESBLs). TEM, SHV as well as CTX-M are examples of ESBLs which belong to this class. ESBL producing *Enterobacteriaceae* isolates are frequent causes of bloodstream infections in developing countries in addition to the developed ones.[4, 5] ESBL-producing bacteria have spread extensively worldwide, which resulted in the widespread usage of carbapenems. This expanded use, contributed to a rise in resistance among various bacteria. Carbapenemases are enzymes which inactivate carbapenems, they are included within different Ambler classes. For instance, OXA-48 one of class D beta-lactamases and KPC one of class A beta-lactamases, are among the notable serine carbapenemases. Additionally, VIM, IMP and NDM are metallo-beta-lactamases which belong to class B beta-lactamases.[6, 7] Carbapenem resistance among ESBL-producing enterobacterial isolates is a profound source of concern.[8] Therefore, the aim of this study was to genotypically characterize the carbapenem resistance among cephalosporin resistant *Enterobacteriaceae* isolates causing bloodstream infections.

METHODOLOGY

Isolates collection and identification:

Gram-negative isolates belonging to *Enterobacteriaceae* family, resistant to both ceftazidime as well as cefepime were collected from positive blood cultures from the microbiology laboratory of different hospitals in Alexandria, Egypt. Ethical approval was obtained from the Ethics Committee, Faculty of Pharmacy, Pharos University in Alexandria. Identification of the collected isolates was confirmed using Vitek-2 system (Biomerieux, France).

Susceptibility testing:

Antimicrobial susceptibility testing was carried out by disk diffusion method, according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[9] The antibiotics used were ceftazidime (CAZ) and cefepime (FEP), in addition to imipenem (IPM), meropenem (MEM), levofloxacin (LEV), amikacin (AK) and gentamycin (CN).

Investigation of the different resistance genes:

All isolates were genotypically tested to detect ESBL genes (*blaTEM*, *blaSHV* and *blaCTX-M)* belonging to class A beta-lactamases. Moreover, isolates resistant to IPM and MEM, were genotypically investigated to detect carbapenemases-encoding genes which included *blaVIM*, *blaIMP* and *blaNDM-1* belonging to class B beta-lactamases, *blaOXA-48* belonging to class D beta-lacatamases and *blaKPC* belonging to class A beta-lactamases.

Boiling method was used for the DNA extraction, as previously described.[10] Amplification of the afore mentioned genes, was achieved using PCR, which was performed on BioRad T100™ Thermal Cycler (Biorad, CA, USA). The details of the PCR amplification scheme were: 5 minutes activation at 95 °C, followed by 40 cycles of denaturation, annealing and extension, then final extension step for 7 minutes at 72 °C. Denaturation was performed for 30 seconds at 95 °C and extension was performed for 1 minute at 72 °C, while annealing temperatures varied according to each set of primers as presented in (**Table 1**). The amplicons were, then, separated using gel electrophoresis on BioRad PowerPac Basic (BioRad, CA, USA), using (2%) agarose gel containing ethidium bromide (0.5 µg/ml). The different primers used in this study are demonstrated in (**Table 1**), and they were all purchased from Invitrogen. (ThermoFischer, CA, USA).

Table 1: Primers used in this study

Primer	Nucleotide Sequence (5'–3')	Annealing temperature in °C	Reference
blaSHV (F)	GCAAAACGCCGGGTTATTC	50 °C	[11]
blaSHV (R)	GGTTAGCGTTGCCAGTGCT		
blaTEM (F)	ATGAGTATTCAACATTTCCG	46 °C	[12]
blaTEM (R)	TTAATCAGTGAGGCACCTAT		
blaCTX-M (F)	CGCTTTGCGATGTGCAG	50 °C	[11]
blaCTX-M (R)	ACCGCGATATCGTTGGT		
blaKPC	TGTCACTGTATCGCCGTC	52 °C	[13]
blaKPC	CTCAGTGCTCTACAGAAAACC		
blaVIM (F)	AGTGGTGAGTATCCGACAG	50 °C	[11]
blaVIM (R)	ATGAAAGTGCGTGGAGAC		
blaIMP (F)	CATGGTTTGGTGGTTCTTGT	50 °C	[11]
blaIMP (R)	ATAATTTGGCGGACTTTGGC		
blaNDM-1 (F)	GGTTTGGCGATCTGGTTTTC	52 °C	[14]
blaNDM-1 (R)	CGGAATGGCTCATCACGATC		
blaOXA-48 (F)	AAATCACAGGGCGTAGTTGTG	52 °C	[11]
blaOXA-48 (R)	GACCCACCAGCCAATCTTAG		

RESULTS

Twenty-eight *Enterobacteriaceae* isolates (resistant to both CAZ and FEP) were collected form bloodstream infections. They were identified as *K. pneumoniae* as well as *E. coli*. Twenty-four of the 28 isolates (85.71%) were *K. pneumoniae* and four (14.29%) *E. coli*, this is shown in (**Figure 1**).

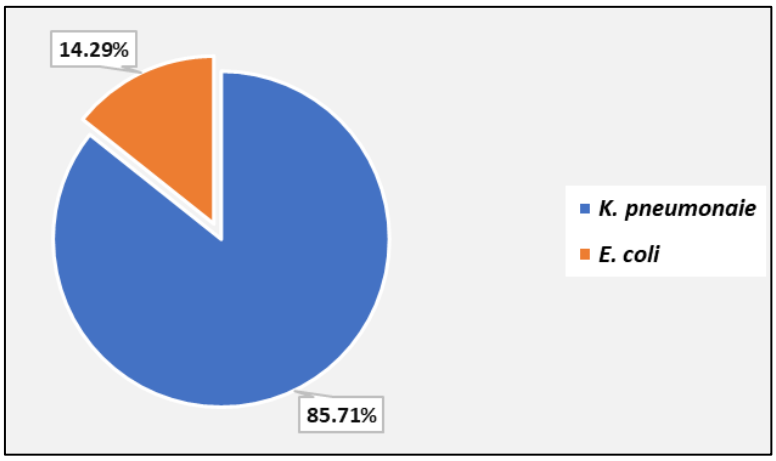

Fig. 1: The different *Enterobacteriaceae* isolates

Antibiotic susceptibility testing:

Twenty-four (85.71%) of the isolates were resistant to IPM and MEM. Moreover, 17 (60.71%) of the collected isolates were found resistant to CIP. The collective susceptibility patterns for all isolates are detailed in (**Table 2**).

Table 2: Collective susceptibility pattern of the isolates

	Antimicrobial agent	Resistant	Intermediate	Susceptible
K. pneumonaie **(n=24)**	**CAZ**	24 (100%)	0 (0%)	0 (0%)
	FEP	24 (100%)	0 (0%)	0 (0%)
	IPM	23 (95.83%)	0 (0%)	1 (4.17%)
	MEM	23 (95.83%)	0 (0%)	1 (4.17%)
	GN	13 (54.17%)	2 (8.33%)	9 (37.50%)
	AK	16 (66.67%)	2 (8.33%)	6 (25%)
	CIP	15 (62.50%)	5 (20.83%)	4 (16.67%)
E. coli **(n=4)**	**CAZ**	4 (100%)	0 (0%)	0 (0%)
	FEP	4 (100%)	0 (0%)	0 (0%)
	IPM	1 (25%)	0 (0%)	3 (75%)
	MEM	1 (25%)	0 (0%)	3 (75%)
	GN	2 (50%)	0 (0%)	2 (50%)
	AK	0 (0%)	0 (0%)	4 (100%)
	CIP	2 (50%)	1 (25%)	1 (25%)

Genotypic investigation of antimicrobial resistance:

ESBL genes belonging to class A beta-lactamses:

Genotypically *blaSHV*, *blaCTX-M*, and *blaTEM* were identified in (89.29%), (85.71%), and (64.29%), respectively. These results are demonstrated in (**Table 3**).

Carbapenemases genes belonging to various beta-lactamases classes:

Concerning class B beta-lactamases, fifteen (62.5%) of the 24 carbapenem resistant isolates harbored *blaNDM-1*. On the other hand, *blaVIM* was detected in only one isolate. Additionally, *blaIMP* was not detected in any of the isolates. Concerning class D beta-lactamases 16 (66.67%) of the 24 isolates harbored *blaOXA-48* gene. However, *blaKPC*, which belongs to class A beta-lactamases was not detected among the isolates. The details are demonstrated in (**Table 4**), and the pattern in which genes were distributed throughout the isolates is listed in (**Table 5**).

Table 3: Distribution of ESBL genes belonging to class A beta-lactamases among the 28 isolates

	Class A beta-lactamases		
	blaSHV	***blaTEM***	***blaCTX-M***
Positive	25 (89.29%)	18 (64.29%)	24 (85.71%)
Negative	3 (10.71%)	10 (35.71%)	4 (14.29%)

Table 4: Distribution of carbapenem resistance genes among the 24 isolates resistant to carbapenems

	Class A	Class B			Class D
	blaKPC	***blaIMP***	***blaVIM***	***blaNDM-1***	***blaOXA-48***
Positive	0 (0%)	0 (0%)	1 (4.17%)	15 (62.5%)	16 (66.67%)
Negative	24 (100%)	24 (100%)	23 (95.83%)	9 (37.5%)	8 (33.33%)

Table 5: Distribution of the different genes throughout the isolates

Organism	Number of isolates	Resistance	Different Genes	Beta-lactamases Classes
K. pneumonaie (n=24)	**1**	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaCTX-M+blaOXA-48+blaVIM+blaNDM-1***	**A+B+D**
	3	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaCTX-M+blaOXA-48+blaNDM-1***	**A+B+D**
	3	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaCTX-M+blaOXA-48+blaNDM-1***	**A+B+D**
	2	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaOXA-48+blaNDM-1***	**A+B+D**
	3	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaCTX-M+blaOXA-48***	**A+D**
	2	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaCTX-M+blaNDM-1***	**A+B**
	3	**CAZ+FEP+ IPM+MEM**	***blaSHV+ blaCTX-M+blaOXA-48***	**A+D**
	2	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaNDM-1***	**A+B**
	1	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaCTX-M+blaNDM-1***	**A+B**
	2	**CAZ+FEP+ IPM+MEM**	***blaSHV+blaTEM+blaCTX-M***	**A**
	1	**CAZ+FEP+ IPM+MEM**	***blaSHV+ blaCTX-M***	**A**
	1	**CAZ+FEP**	***blaSHV+ blaCTX-M***	**A**
E. coli (n=4)	**1**	**CAZ+FEP+IPM+MEM**	***blaSHV+blaTEM+blaCTX-M+blaOXA-48+blaVIM+blaNDM-1***	**A+B+D**
	1	**CAZ+FEP**	***blaTEM+blaCTX-M***	**A**
	2	**CAZ+FEP**	***blaCTX-M***	**A**

DISCUSSION

Bloodstream infections and sepsis are, indeed, critical ailments and the determination of the causative pathogen together with its susceptibility pattern is essential to properly manage them.[15] The aim of this study was to genotypically characterize the carbapenem resistance among cephalosporin resistant *Enterobacteriaceae* isolates causing bloodstream infections. Here, twenty-eight *Enterobacteriaceae* isolates (resistant to CAZ and FEP) causing bloodstream infections were collected. Most of the collected isolates 24 (85.71%) were identified as *K. pneumoniae*, and only 4 (14.29%) were identified as *E. coli*. Similarly, Abdulall et al.,[16] revealed that the most frequent isolate among all their collected isolates, was indeed *K. pneumoniae*. Conversely, Elseady et al,[17] stated that the most frequently collected organism from blood cultures was *E. coli* (27.8%), followed by *K. pneumoniae* (12.2%).

Concerning carbapenem resistance, many of the collected isolates 24 (85.71%) were carbapenem resistant. Moreover, the majority of *K. pneumoniae* (95.83%) were carbapenem resistant. Similarly,

Abdulall et al.,[16] reported that more than (70%) of their *K. pneumoniae* were resistant to carbapenems. Using Magiorakos et al.,[18] criteria to define multi-drug resistant (MDR) organisms, 22 (78.58%) of the twenty-eight isolates were MDR organisms. A high percentage was also revealed in another study, where (68.6%) of their isolates causing bloodstream infections were MDR organisms.[19]

ESBLs confer resistance to monobactams and oxyimino-cephalosporins including CAZ and FEP, however, they do not affect carbapenems.[20] Here, *blaSHV*, *blaCTX-M*, and *blaTEM* were detected genotypically in (89.29%), (85.71%), and (64.29%), respectively. Additionally, the twenty-eight isolates harbored at least one ESBL gene belonging to class A beta-lactamases. Tohamy et al.,[19] found that *blaSHV*, *blaCTX-M*, and *blaTEM* were present in (44.3%), (55.7%) and (31.4%) of their isolates causing bloodstream infection, respectively. Another study, reported that *blaCTX-M* prevalence among Gram-negative bloodstream isolates was (11%), and that they were most common among their *E. coli* isolates.[21] Son et al.,[22] stated that *blaCTX-M* was the most ESBL gene detected among their *E. coli* isolates causing bloodstream infections.

Carbapenemases genes were investigated among the 24 carbapenem resistant isolates. *blaOXA-48* was detected in 16 (66.67%), followed by *blaNDM-1* in 15 (62.5%). However, *blaIMP* and *blaKPC* were not found at all among the 24 isolates and *blaVIM* was detected in only one isolate. Balkan et al.,[23] revealed that almost all their isolates harbored *blaOXA-48*. Villegas et al.,[24] and Abdulall et al.,[16] did not detect *blaOXA-48* gene among their isolates causing bloodstream infections. Moreover, Cayci et al.,[25] stated that only (1.3%) of their enterobacterial isolates harbored *blaNDM* gene.

In this study, fifteen (65.22%) of the 23 *K. pneumoniae* that were resistant to carbapenems carried *blaOXA-48* gene, fourteen (60.87%) harbored *blaNDM-1*, however none of them harbored *blaKPC*. Ghaith et al.,[26] demonstrated that *blaOXA-48* was detected in (60.8%) of their carbapenem resistant *K. pneumoniae*. In a previous study conducted in Alexandria, *blaOXA-48* was detected in (96.67%) of the carbapenem resistant *K. pneumoniae* isolates.[27] Two other studies conducted by Abdulall et al.,[16] and Ghaith et al,[26] reported the occurrence of *blaNDM* in (28.6%) and (52.2%) of their carbapenem resistant *K. pneumoniae*, respectively. However, Ghaith et al.,[26] did not find *blaKPC* among their isolates, while another study in Egypt reported that *blaKPC* was present in 33.3% of their *K. pneumoniae* isolates.[16]

In this work, fifteen (62.5%) of the 24 isolates co-harbored *blaNDM-1* together with different ESBL genes. Also, 16 (66.67%) of the 24 isolates co-harbored *blaOXA-48* together with different ESBL genes. Balkan et al.,[23] reported that all their isolates except two carried both *blaCTX-M* gene and *blaOXA-48*.

Here, nine (39.13%) of the 23 *K. pneumoniae* resistant to carbapenems co-harbored *blaOXA-48* and *blaNDM*-1. Ghaith et al.,[26] also reported the co-existence of both genes together in 52.2% of their isolates.

In this study, ten (35.71%) of the isolates harbored beta-lactamases genes belonging to various Ambler classes (A, B and D), while six (21.43%) isolates harbored genes belonging to both class A and class D, and five (17.86%) isolates harbored genes belonging to classes A and B and all the isolates had at least one ESBL gene.

CONCLUSION

The co-occurrence of different beta-lactamases belonging to various classes and the co-existence of *blaOXA-48* (serine carbapenemase) together with *blaNDM-1* (metallo-beta-lactamase) among isolates causing bloodstream infections is quite alarming and necessitates prompt action.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

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