Carbapenem resistance among clinical and environmental Gram-negative isolates recovered from hospitals in Gaza strip, Palestine

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Abstract

Background **The world is threatened by the ongoing emergence of carbapenem resistant organisms, which are contributing to increasing morbidity and mortality rates. The main objective of this study was to highlight carbapenem resistance among clinical and environmental Gram-negative bacteria (GNB) isolates.**

Methods **A cross-sectional study wherein 210 clinical isolates, 150 environmental swabs, and 110 air samples were collected from three major hospitals in Gaza strip: Al-Shifa, AlNaser and the European Gaza hospitals. The study lasted for seven months (September 2016 to March 2017). All isolates/samples were cultured and identified using conventional bacteriological methods. All GNB isolates were tested for their antimicrobial susceptibility using the disk diffusion method. Modified Hodge Test (MHT) was performed to investigate carbapenemases production.**

Results **The overall percentage of carbapenem resistance among GNB was (30/247) 12.1%. Resistance to imipenem was (20/247) 8.1% while resistance to ertapenem and meropenem was (8/226) 3.5% and (2/247) 0.8%, respectively. The intensive care units exhibited the highest resistance rate 9/17 (52.9%). Carbapenem resistance among Enterobacteriaceae was (30/226) 13.2% while in *Pseudomonas* it was (0/21) 0%. *Klebsiella* spp. was the most resistant to carbapenems 13/90 (14.4%), followed by *E. coli* (9/91) 9.8%. Seven isolates out of 30 (23.3%) were positive for MHT. All Enterobacteriaceae isolates had a multiple antibiotic resistance (MAR) index higher than 0.2, while those of *Pseudomonas* had an average of 0.2. GNB were isolated from 19/110 (17.2%) and 21/150 (14%) of air and environmental samples, respectively.**

Conclusion **The resistance found, after a recent introduction of carbapenem use in Gaza, shows the need for policies to prevent misuse and overuse of carbapenems, the need for infection control procedures and screening policies for carbapenem resistance on a routine basis.**

Keywords **Carbapenem resistant Enterobacteriaceae (CRE), carbapenemases, Modified Hodge Test (MHT), Multiple Antibiotic Resistance (MAR) index.**

Introduction

Carbapenems, which were developed in the 1980s, are a β-lactam group of drugs that are considered as last resort antibiotics for treating serious infections with multidrug-resistant (MDR) Gram-negative bacteria (GNB). The broad-spectrum antimicrobial activity of carbapenems includes *Pseudomonas aeruginosa*, which is part of the reason why they were considered as appropriate therapy for the treatment of healthcare-associated infections. Back then, almost all Enterobacteriaceae were sensitive to carbapenems,[1] but this is not the case anymore. The change of the scenario is attributed to the

Received: 31 July 2018; revised: 29 August 2018; accepted: 30 August 2018.

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Published September 2018

ISSN 2248 – 2997
ISSN – L = 2248 – 2997

emergence of carbapenem resistance (CR) in non-fermenter GNB (*Acinetobacter baumannii* and *P. aeruginosa*) as well as in fermenter GNB (Enterobacteriaceae) over the past few years.[2]

Various mechanisms are involved in CR; these include carbapenemases production, decreased permeability caused by porin mutations, efflux pump overexpression, and changes in penicillin-binding proteins (PBPs).[3] The emergence of CR is a public health concern. The most notable genera that can develop CR are *E. coli* and *K. pneumoniae*. However, CR has also been reported in *Pseudomonas*. CRE bacteria have high levels of resistance to other antibiotics. Infections caused by these bugs are life-threatening. One report cites they can contribute to death in up to 50% of patients who become infected.[4]

The World Health Organization (WHO)'s global report issued in April 2014 had some disturbing conclusions. Surveillance of antimicrobial resistance revealed the world is on the verge of entering a post-antibiotic era. At present, the full extent of how this problem is affecting people, and more expansively in a global scenario, is unclear and needs to be quantified. Dependable data that is predictable and up to date is urgently needed to determine the extent of this potential dilemma.[5]

Gaza strip has been witnessing an escalation of antibiotic resistance. The studies conducted concerning this have yielded scary results which are sounding the alarm for urgent action.[6,7] Carbapenems are one of the few therapeutic agents we have left. But now, with the scarcity in data concerning the prevalence of CR among clinical and environmental GNB isolates in the region, things are getting out of hand and efforts must be targeted to finding urgent solutions. The main objective of this study was to screen clinical and environmental Gram-negative isolates for CR.

Methods

Permissions and ethical considerations

Prior the initiation of the research work, approval (PHCR/HC/138/16) was obtained from the Helsinki Committee on 01 August 2016. In addition, permissions were obtained from the Ministry of Health for collection of samples and obtaining clinical isolates.

Setting and duration of the study

This cross-sectional study was performed at the three major Gaza Strip hospitals; Al-Shifa hospital, the European Gaza hospital and AlNaser hospital. The study lasted from September 2016 to March 2017.

Sampling

A total of 140 clinical isolates (from the Microbiology laboratory), 150 environmental swabs, and 110 air samples were collected from the Al-Shifa and the European Gaza hospitals. In addition, 70 clinical isolates were collected from Al-Naser hospital (from the Microbiology laboratory). Air samples and environmental swabs were obtained from the following departments: intensive care units (ICUs), pediatric ICU (PICU), neonatal ICU (NICU), and surgery departments. Environmental surfaces including bed rails, bed sheets, tables, door handles, sinks, soaps and floors were sampled using pre-moistened sterile swabs. These swabs were used to swab an area of 3×3 cm with the aid of sterile plastic windows. For air samples collection, 150 liters of air were aspirated for each sample from different sites of the investigated departments using an air sampler. The 150 liters were distributed as 50 liters for each culture media that was used. MacConkey agar plates were used to grow GNB, whereas nutrient agar (NA) and Sabouraud dextrose agar (SDA) (HiMedia, Mumbai, India) plates were used for total plate count and yeast and molds (fungi) count, respectively. All isolates/air and environmental swab samples were collected during the same period distributed over multiple seasons (fall, winter, and spring), and at different times of the day (before and after 12 pm).

Microbiological investigation

The isolates were identified based on colony color and morphology in addition to conventional biochemical tests (e.g., oxidase, indole, methyl red, Voges-Proskauer, citrate, and

urease tests). Ambiguous results were confirmed using API 20 E kit (bioMérieux, Marcy-l'Etoile, France) according to the manufacturer instructions. Microbial counts (total bacterial and fungal counts) were expressed in terms of colony forming units (CFU) per cubic m.

Antimicrobial susceptibility testing

The susceptibilities of the isolates to carbapenems and other antibiotics including amikacin, amoxicillin, ampicillin, aztreonam, ceftazidime, ceftriaxone, cefuroxime, chloramphenicol, ciprofloxacin, gentamicin, piperacillin, tetracycline and trimethoprim/sulfamethoxazole were determined using the disk diffusion (modified Kirby-Bauer) method according to the methods and interpretation criteria of the Clinical and Laboratory Standards Institute (CLSI).[8]

The multiple antibiotic resistance (MAR) index and MDR

The MAR index was calculated for each isolate by dividing the number of antibiotics for which each isolate was resistant by the number of antibiotics for which each isolate was tested. Isolates were determined as MDR by their resistance to one or more antibiotics from each of at least three different families.

Modified Hodge test

Isolates that showed resistance to at least one of the tested carbapenems (imipenem, meropenem, ertapenem) were further investigated for carbapenemases production by MHT according to CLSI guidelines.[8] A lawn of pre-tested carbapenem-sensitive *E. coli* was streaked onto Mueller Hinton agar plates and left for a while to dry. Then a 10 µg carbapenem disk was placed in the center of the test area; ertapenem disk was used for the isolates that were resistant to ertapenem, and imipenem disk was used for the isolates that showed resistance to imipenem, while meropenem disk was used for the isolates that were resistant to meropenem. Test organisms were then streaked from the edge of the disk to the edge of the plate. After incubation, the plates were examined for an inward distortion of zone of inhibition (clover leaves appearance).

Data analysis

Collected data were summarized, tabulated and analyzed using Statistical Package for Social Sciences (SPSS) program version 24 (IBM Corp, Armonk, NY, USA). Chi square test was used to detect significant differences among hospitals and/or samples. A p-value <0.05 was considered statistically significant.

Results

Out of 110 air samples, only 19 exhibited growth for GNB (17.3%). Although the European Gaza hospital showed the highest positive rate, no statistically significant difference was found (Chi-square=0.448, p=0.339). The highest incidence 11/42 (26.2%) of GNB was in the ICUs, while the surgery departments' air samples showed the least 3/38 (7.9%) (Chi-square=4.788, p=0.188). The greatest percentage 16/59 (27.1%) of GNB was isolated in fall while the lowest 1/37 (2.7%) was in winter (Chi-square=9.587, p=0.008). *Citrobacter* and *Enterobacter* spp. were the most frequently isolated bacteria. The average levels of bacteria obtained from air samples were (7.8×10^2 CFU/m^3) and of fungi were (5.2×10^2 CFU/m^3). Levels of fungi were the highest 13/37 (35.1%) during winter (Chi-square=25.233, p<0.001). A total of 21 out of 150 (14%) environmental swabs were positive for GNB with a significant difference between the two hospitals as well as between the departments. With respect to hospitals, the European Gaza hospital had the highest positivity rate 15/68 (22.1%) (Chi-square=6.7097, p=0.009). Regarding departments, PICU exhibited the highest positivity rate 9/22 (40.9%) (Chi-square=15.588, p=0.001). A higher percentage 15/81 (18.5%) of GNB was recovered from samples collected in the morning than from samples collected at noontime 6/69 (8.7%) (Chi-square=2.986, p=0.083). *Klebsiella* spp. was the most commonly isolated bacteria.

The isolates showed 100% resistance to ampicillin (226/226), amoxicillin (226/226),

and aztreonam (247/247). Resistance to chloramphenicol was (95/226) 42%, trimethoprim/sulfamethoxazole (200/226) 88.5%, cefuroxime (219/226) 96.9%, gentamicin (2/247) 0.8%, amikacin (3/247) 1.2%, tetracycline (141/226) 62.4%, piperacillin (245/247) 99.1%, ceftriaxone (10/21) 47.6%, ciprofloxacin (35/247) 14.1%, and ceftazidime (96/226) 42.5%. All Enterobacteriaceae isolates had a MAR index higher than 0.2, while those of *Pseudomonas* had an average of 0.2. All Enterobacteriaceae isolates were 100% MDR, while those of *Pseudomonas* were 47.6% MDR. Antibiotic resistance profiles of the isolated organisms are presented in Table 1.

The overall percentage of CR among GNB was (30/247) 12.1%. CR among Enterobacteriaceae was (30/226) 13.2% and (0/21) 0% in *Pseudomonas*. With respect to CR among hospitals, AlNaser hospital had the highest resistance rate 12/70 (17.1%), followed by European Gaza hospital 8/62 (12.9%), while that of Al-Shifa hospital was (10/115) 8.6% (Chi-square=2.954, p=0.228). Resistance to imipenem, ertapenem and meropenem is presented in Table 2. CR among air samples, environmental swabs and clinical isolates is illustrated in Table 3. CR in *Klebsiella* spp. was (13/90) 14.4% and in *E. coli* (9/91) 9.8%, while in other Enterobacteriaceae it was (8/45) 17.7% (Chi-square=1.805, p=0.405). The ICUs exhibited the highest CR rate, 9/17 (52.9%), followed by surgery departments 3/8 (37.5%), and PICU 4/12 (33.3%). Outpatient clinics had a rate of 3/49 (6.1%), while other departments had a CR percentage of 11/19 (57.8%) (Chi-square=25.498, p<0.001).

Among 30 isolates that were resistant to at least one of the tested carbapenems, seven were positive (23.3%) for MHT. Inward distortion of zone of inhibition was an indicator of carbapenemases production. Out of 7 MHT positive isolates, the frequency of *Klebsiella* spp. was (4/7) 57.1% and that of *Citrobacter* spp. was (3/7) 42.9%.

Discussion

Carbapenems were officially introduced in clinical practice at Gaza Strip hospitals in 2007. The main carbapenems in use are meropenem and imipenem. In Gaza Strip, carbapenems are only restricted to be used in hospitals. The overall percentage of CR among GNB was (30/247) 12.1%. This is comparable to the prevalence rate (13.8%) obtained from Germany,[9] a little higher than that of Jordan 5.6%,[10] Nepal 7.4%[11] and Colombia 8.8%,[12] but much lower than that obtained from Egypt, 50.8%.[13] Our study found a CRE rate of (30/226) 13.2%, which is close to that of India, 12.26%,[14] and lower than that of Saudi Arabia (53% showed resistance to meropenem and 36% to imipenem).[15] However, other studies have reported lower rates compared to Gaza. A rate of 4.2% was observed in the USA,[16] 6% in Qatar,[15] 6% in Pakistan,[15] 2.5% and 7.84% in Lebanon,[15] and 9.1% in Iran.[15] These proportional variances could be attributed to the restrictions imposed on antibiotic use and the time each country started using carbapenems. Antimicrobial therapeutic protocols and practices vary from one hospital/city/country to another, making comparisons and interpretations of prevalence of CRE variations a difficult task. Sample size, sample sources, the time when the study took place, laboratory techniques used and other factors may contribute to variable prevalence rates.

Our finding that ICUs exhibited the highest CR rate, 9/17 (52.9%), comes in accordance with the outcome of a Turkish study done by Meric et al.[15] and an American study conducted by Guh et al.[16] This might be due to the weak health conditions of hospitalized patients in ICUs and their need for intensive use of antibiotics. However, outpatient clinics also showed a considerable CR rate, 3/49 (6.1%) which indicates that CR is not limited to hospitals but can also be acquired from the community. This happened irrespective of the recent introduction of carbapenem drugs, 11 years ago in Gaza Strip hospitals. Thus, infection control measures should be established not only for hospitals but should be promoted also in communities.

Table 1. Antibiotic resistance profiles of the isolated organisms from air samples, environmental swabs, in addition to clinical isolates

Antimicrobial		*Escherichia* spp.	*Klebsiella* spp.	*Enterobacter* spp.	*Citrobacter* spp.	Other E*	*Pseudomonas* spp.
Number of isolates		91	90	16	18	11	21
		Resistance %					
Ceftazidime	N	40	36	7	6	7	NT
	%	44	40	43.8	33.3	64	
Ciprofloxacin	N	18	13	1	0	3	0
	%	19.8	14.4	6.3	0	27.3	0
Chloramphenicol	N	43	37	4	6	5	NT
	%	47.3	41.1	25	33.3	45.5	
Piperacillin	N	91	90	15	18	10	21
	%	100	100	93.8	100	91	100
Tetracycline	N	61	56	9	9	6	NT
	%	67	62.2	56.3	50	54.5	
Ampicillin	N	91	90	16	18	11	NT
	%	100	100	100	100	100	
Amoxicillin	N	91	90	16	18	11	NT
	%	100	100	100	100	100	
Trimethoprim/ Sulfamethoxazole	N	84	81	14	13	8	NT
	%	92.3	90	87.5	72.2	72.7	
Aztreonam	N	91	90	16	18	11	21
	%	100	100	100	100	100	100
Cefuroxime	N	85	89	16	18	11	NT
	%	93.4	98.9	100	100	100	
Gentamicin	N	0	2	0	0	0	0
	%	0	2.2	0	0	0	0
Amikacin	N	1	2	0	0	0	0
	%	1.1	2.2	0	0	0	0
Ceftriaxone	N	NT	NT	NT	NT	NT	10
	%						47.6
Imipenem	N	7	7	0	4	2	0
	%	7.7	7.8	0	22.2	18.1	0
Ertapenem	N	1	5	0	1	1	NT
	%	1.1	5.6	0	5.6	1.1	
Meropenem	N	1	1	0	0	0	0
	%	1.09	1.1	0	0	0	0
		MAR index and MDR %					
MAR index		0.6	0.5	0.5	0.5	0.6	0.2
MDR %		100%	100%	100%	100%	100%	47.6%

E* – Enterobacteriaceae, **MAR** – multiple antibiotic resistance; **MDR** – multidrug resistant; **NT** – not tested.

Klebsiella spp. was found to be the most resistant to carbapenems 13/90 (14.4%), followed by *E. coli* 9/91 (9.8%). This is similar to the finding of many reports coming from countries in the Middle East,[15] but divergent from the outcome of other different studies in Asia and Middle East countries where *P. aeruginosa* and *A. baumannii* had the highest CR rates.[15] This could be attributed to different antimicrobial treatment protocols for the aforementioned bacteria.

Table 2. Antimicrobial susceptibility testing of carbapenems for isolated organisms from air samples, environmental swabs, in addition to clinical isolates

All tested isolates	Imipenem (n=247)		Ertapenem (n=226)		Meropenem (n=247)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Sensitive	153	61.9	165	73.0	218	88.3
Intermediate	74	30.0	53	23.5	27	10.9
Resistant	20	**8.1%**	8	**3.5%**	2	**0.8%**

Table 3. Resistance to carbapenems by source of isolate

Carbapenems		Air samples n=17			Environmental swabs n=20			Clinical isolates n=210			Chi-square	P-value
		S	I	R	S	I	R	S	I	R		
Ertapenem	N	6	7	2	7	12	1	152	34	5	Chi(4)= 29.409	<0.001
	%	40.0	46.7	13.3	35.0	60.0	5.0	79.6	17.8	2.6		
Imipenem	N	4	8	5	4	12	4	145	54	11	Chi(4)= 35.545	<0.001
	%	23.5	47.1	29.4	20.0	60.0	20.0	69.0	25.7	5.2		
Meropenem	N	9	7	1	17	3	0	192	17	1	Chi(4)= 24.593	<0.001
	%	52.9	41.2	5.9	85.0	15.0	0.0	91.4	8.1	0.5		

I – intermediate; **R** – resistant; **S** – sensitive.

In this study, seven isolates out of 30 (23.3%) were positive for MHT. A higher rate (47.4%) was documented in Colombia.[12] Much higher rates were documented in Pakistan (69%), USA (76%), and India (62.5%).[17] This could mean that the MHT-negative isolates harbor different mechanisms for CR other than the production of carbapenemases (e.g., efflux pump or altered porins). It is worth mentioning that the class of carbapenemase cannot be determined by MHT and some isolates show a slight indentation but do not produce carbapenemase (producing false positive results). One of the limitations of this study is that the result was not verified with molecular techniques, as the main aim of the study was to present data on the carbapenem resistance among Gram negative bacteria.

In the present study, the average levels of bacteria obtained from air samples were (7.8×10^2 CFU/m^3) and of fungi (5.2×10^2 CFU/m^3). Our investigation showed a total bacterial load exceeding 7.5×10^2 CFU/m^3 which, according to de Aquino Neto FR and de Góes Siqueira LF is considered contaminated.[18] The study also exhibited a total fungal load exceeding 3×10^2 CFU/m^3 which, according to Cappitelli and colleagues is also considered contaminated.[19] This finding emphasizes the need for regular indoor air quality assessment. A study done in Thailand revealed similar average levels of bacteria (7.8×10^2 CFU/m^3).[20] A Korean study conducted reported comparable averages of bacteria (7.2×10^2 CFU/m^3) and fungi (5.5×10^2 CFU/m^3).[21] A study from Poland found lower averages of 2.5×10^2 - 4.4×10^2 CFU/m^3 for airborne bacteria,[22] while higher averages of (2.4×10^3 CFU/m^3) for airborne bacteria were reported in Iran.[23]

GNB were isolated from (19/110) 17.2% of air samples. A lower rate (3.05%) was documented in Turkey, while a higher rate (56.9%) was found in an Ethiopian study.[24] In our study, ICUs exhibited the highest positivity rate 11/42 (26.2%). Crowded conditions and insufficient ventilation may be contributing factors. The greatest percentage 16/59 (27.21) of GNB was isolated in fall (p=0.008) while the lowest 1/37 (2.7%) was in winter. Since most diseases peak and are likely to spread in summer

and fall, seasons might have contributed to this variation.

With respect to bacteria isolated from environmental swabs, 47.3% (71/150) were culture positive. That is lower than the finding (57.4%) of an Iranian study.[23] GNB accounted for 29.6% (21/71) of the total positive cultures. A much lower rate of (4.9%) was documented in a German study. In the present study, (15/81) 18.5% of GNB were recovered from samples collected in the morning, whereas (6/69) 8.7% were from samples collected at noontime. This finding is supported by the work of Lerner et al.,[25] giving an assumption that time period amongst cleaning and testing is a contributing factor, hence emphasizing the importance of regular cleaning. CR among GNB isolated from environmental swabs was (5/20) 25%. This is comparable to the finding (24%) of Lerner et al. (2013).[25] These findings about surfaces contaminated with CR bacteria may render increasingly difficult-to-treat nosocomial infections. Since these surfaces serve as cross-transmission reservoirs of infections, disinfectants, such as bleach, should be checked for quality and strength.

Our study has some limitations. First, it is worthwhile to mention that the clinical data of clinical isolates were not available for this study. Second, we performed this study for a moderate time in the three main referral hospitals in Gaza Strip. So, this may underestimate or overestimate the real prevalence of carbapenem resistance among clinical and environmental Gram-negative isolates. Third, molecular identification was not performed, such that the types of carbapenem resistance associated genes were not investigated and confirmed.

Conclusion

The results revealed that carbapenem resistance is becoming a serious problem in Gaza. Efforts need to be focused on promoting improved infection control and preventing overuse and misuse of antibiotics.

Authors' contributions statement: RHR performed the laboratory experiments, collected the data and performed the statistical analysis. NAL collected the data, interpreted the findings and drafted the manuscript. AAE designed the study, supervised the laboratory experiments and drafted the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to disclose.

Funding: None to declare.

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Please cite this article as:
Rida RH, Al Laham NA, Elmanama AA. Carbapenem resistance among clinical and environmental Gram-negative isolates recovered from hospitals in Gaza strip, Palestine. GERMS 2018;8(3):147-154. doi: 10.18683/germs.2018.1142.