Epidemiology and antibiotic susceptibility patterns of carbapenem-resistant Gram-negative bacteria isolated from two tertiary care hospitals in North Lebanon

Monzer Hamze[1], Marwan Osman[1,3],
Hassan Mallat[1,2,3], Sandy Nasr[1], Elie Bou Raad[3],
Marcel Achkar[2]

1 Laboratoire Microbiologie Santé et Environnement (LMSE), Doctoral School of Sciences and Technology, Faculty of Public Health, Lebanese University, Tripoli, Lebanon.
2 Clinical Laboratory, Nini Hospital, Tripoli, Lebanon.
3 Youssef Hospital Center, Akkar, Lebanon.

Contact information:

Monzer Hamze.

Address: Laboratoire Microbiologie Santé et Environnement (LMSE), Doctoral School of Sciences and Technology, Faculty of Public Health, Lebanese University, Tripoli, Lebanon.

✉ mhamze@monzerhamze.com

Abstract

Background: Antimicrobial resistance is a major public health problem worldwide. Numerous epidemiological studies reported that Lebanon is affected with high levels of antibiotic resistance. The aim of this study is to determine the prevalence and antibiotic susceptibility patterns of carbapenem-resistant Gram-negative bacteria in North Lebanon during the period 2015-2017.

Methods: Carbapenem-resistant Gram-negative bacteria were isolated from patients referring to Nini hospital and Youssef hospital center. Identification and antibiotic susceptibility testing were performed through conventional tools according to the manufacturer's recommended procedures and the recommendations of the European Committee on Antimicrobial Susceptibility Testing, respectively.

Results: Overall, a total of 290 carbapenem-resistant Gram-negative bacteria were isolated. *Escherichia coli* was predominant and represented 39.3% of all isolates, followed by *Pseudomonas aeruginosa* (24.8%), *Acinetobacter baumannii* (22.8%), *Klebsiella* spp. (8.6%), *Enterobacter* spp. (6.6%), *Pantoea* spp. (1%), and *Proteus vulgaris* (0.3%). Our findings showed an alarming increase in the prevalence of carbapenem resistant bacteria during the investigation period. On the other hand, colistin, tigecycline, amikacin and fosfomycin remain the most effective agents against carbapenem-resistant Gram-negative bacteria.

Conclusion: This study provided important new data to clinicians in North Lebanon in order to take the appropriate decision in the treatment of patients at risk for infections with carbapenem-resistant Gram-negative germs.

Introduction

Antimicrobial resistance (AMR) is a major ongoing public health problem worldwide. A recent report estimates that, by 2050, 10 million people will die every year due to AMR, and the major mortality cases will be from developing countries [1]. Unfortunately, high levels of AMR were reported in these countries, and were also associated with the emergence of pan-drug resistant (PDR) bacteria [2, 3]. The causes of AMR in middle and low income countries associated with complex issues, including bad behaviors towards antibiotic use among both health care professionals and general population, limited diagnostic facilities, high spread of counterfeit medicines, excessive non-human use of antibiotics in food and agriculture, and absence of a national action plan for antimicrobial resistance [2].

Carbapenems are the most effective ß-lactams antibiotics presenting a broad spectrum of coverage against Gram-negative bacteria. However, Gram-negative bacteria commonly recruit several mechanisms to overcome the effect of these antibiotics. Resistance to carbapenems is mainly due to the production of carbapenemases, the overexpression of efflux pumps, and the decrease in outer membrane permeability [4].

In Lebanon, as the majority of developing countries, antibiotic resistance remains responsible for significant morbidity and mortality. Numerous epidemiological investigations have reported high levels of antibiotic resistance among Gram-negative bacteria in our country in the last decade [5-15]. Recent studies reported the spread of carbapenem-resistant strains in North Lebanon, mainly by OXA-48 production [6, 7, 16-18]. In the same context, other carbapenemases (including NDM, VIM, IMP and OXA-type enzymes)were also reported in this area [5, 13, 16, 19-21].

Both rapid and reliable laboratory clinical investigation and reporting are essential to guide clinicians including infectious diseases physicians to take appropriate treatment decision which is critical to decrease treatment failure and to ensure the best possible outcome. Regrettably, rapid diagnostic tools are very limited in Lebanon, mainly due to financial reasons. The lack of these advanced diagnostic tools in association with poor infection control measures in a large number of healthcare facilities led to the spread of resistant bacteria at national level.

For these reasons, we conducted this investigation in order to determine the prevalence of carbapenem resistant Gram-negative bacteria isolated from patients referring to Nini hospital and Youssef hospital center in North Lebanon during the period 2015-2017 and their antibiotic susceptibility patterns.

Material and Methods

This study was conducted in the clinical microbiology laboratories of Nini hospital (Tripoli, North governorate) and Youssef hospital center (Halba, Akkar governorate) during the period from January 2015 through to December 2017. Every hospital contains 120 beds available to deliver high-quality patient care all in one center. Gram-negative bacteria were isolated on MacConkey Agar with crystal violet (Bio-Rad®, France) from many types of specimen including respiratory, urine, blood, catheter, gastric juice, pus, wound, cornea, gallbladder, semen, and cerebrospinal fluid samples. The bacterial identification was performed according to the manufacturer's recommended procedures and through the use of API-20E and API-20NE (bioMérieux® - France). The antibiotic susceptibility testing was performed by the disk diffusion method on Mueller Hinton agar for *Enterobacteriaceae* and non-*Enterobacteriaceae* Gram-negative rods (Bio-Rad®, France) according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). In addition, statistical analyses were performed with GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA) using the Fisher's exact test to confirm the increase in the prevalence of carbapenem resistant Gram-negative bacteria including carbapenem-resistant *Enterobacteriaceae* (CRE). The significance level considered for all statistical tests was a P-value < 0.05.

Results

A total of 6103 consecutive non-duplicate strains of Gram-negative bacteria were included in our study. Only *Enterobacteriaceae* resistant to ertapenem and *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resistant to imipenem and/or meropenem were included in this study. Hence, out of these isolates, 290 (4.75%) were carbapenem-resistant. **Table 1** shows the major strains distribution based on type of specimen and hospital. Carbapenem-resistant bacteria were mainly isolated from the following samples; urine (114/290; 39.3%), respiratory (82/290; 28.3%), and pus/wound (50/290; 17.2%). *E. coli* presented the highest infection rate (35.9%), followed by *P. aeruginosa* (24.8%), *A. baumannii* (22.8%), *Klebsiella* spp. (8.6%), *Enterobacter* spp. (6.6%), *Pantoea* spp. (1%), and *Proteus vulgaris*

Table 1. Distribution of carbapenem-resistant Gram-negative bacteria strains according to specimen origin.

Origin of specimen	Nini Hospital (Tripoli)				Youssef Hospital Center (Halba)				Total	
	Enterobacteriaceae		*P. aeruginosa / A.baumannii*		*Enterobacteriaceae*		*P. aeruginosa / A.baumannii*			
	N	%	N	%	N	%	N	%	N	%
Respiratory	33	39.8	10	17.9	6	8.7	33	40.2	82	28.3
Urine	29	34.9	10	17.9	46	66.7	29	35.4	114	39.3
Pus / Wound	12	14.4	13	23.2	12	17.4	13	15.9	50	17.3
Blood	3	3.6	3	5.3	2	2.9	4	4.9	12	4.2
Gallbladder	3	3.6	0	0	0	0	0	3	1.0	70.05
Catheter	2	2.4	12	21.4	0	0	2	2.4	16	5.5
Semen	1	1.2	0	0	0	0	0	0	1	0.3
Cornea	0	0	7	12.5	0	0	0	0	7	2.4
Cerebrospinal fluid	0	0	1	1.8	0	0	0	0	1	0.3
Gastric juice	0	0	0	0	3	4.3	1	1.2	4	1.4
Total	83	100	56	100	69	100	82	100	290	100

(0.3%). The prevalence of carbapenem-resistant bacteria was alarmingly increased every year from 3.09% in 2015 to 4.52% in 2016 (OR: 1.48, CI: 1.07–2.07, P: 0.02) in comparison with data of 2015 and 6.57% in 2017 (OR: 2.2, CI: 1.6–3.05, P< 0.0001) in comparison with data of 2015 and (OR: 1.48, CI: 1.14–1.93, P: 0.003) in comparison with data of 2016 . Besides, a significant increase in the prevalence of carbapenem-resistant *Enterobacteriaceae* was also found (OR: 3.15, CI: 2.04–4.88, P< 0.0001) **(Table 2** & **Figure 1)**. Moreover, according to antimicrobial susceptibility tests and EUCAST guidelines, the mean percentage of sensitivity of all isolates was showed in **Table 3** and **4**. Briefly, out

Table 2. Prevalence of carbapenem-resistant Gram-negative bacteria according to the year of isolation.

	Carbapenem-resistant Gram-negative bacteria			
	Gram-negative bacteria	*Enterobacteriaceae*	*P. aeruginosa*	*A. baumannii*
	%	%	%	%
2015	3.09	1.7	9.04	75
2016	4.52	1.71	14.93	82.35
2017	6.57	5.19	13.98	37.5
Total	3.9	2.8	12.8	66.7

Figure 1: Prevalence of carbapenem-resistant Gram-negative bacteria isolated from Nini hospital and Youssef hospital center in 2015, 2016 and 2017.
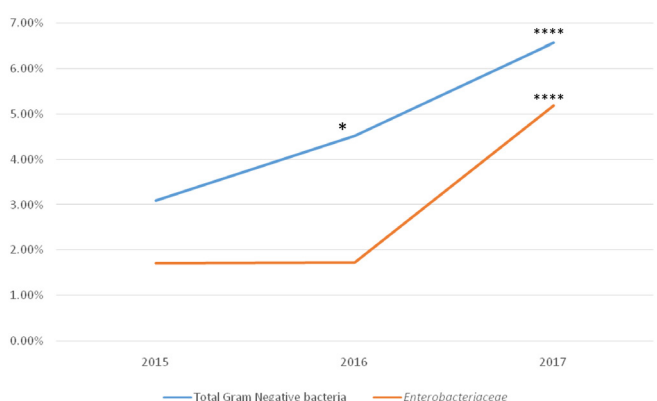
*: P-value < 0.05.

Table 3. Susceptibility profiles of carbapenem-resistant *Enterobacteriaceae* strains isolated from two tertiary care hospitals in North Lebanon.

	Escherichia coli N=104 %	*Klebsiella spp.* N=25 %	*Enterobacter spp.* N=19 %	*Pantoea spp.* N=3 %	*Proteus vulgaris* N=1 %	Total N=152 %
AMP	0	0	0	0	0	0
TIC	0	0	5.3	0	0	0.7
PIP	0	0	5.3	0	0	0.7
AMC	1	4	0	0	0	1.3
TCC	3.8	4	10.5	0	0	4.6
PPT	3.8	4	15.8	0	0	5.2
CFX	6.7	4	0	0	0	5.2
CXM	16.3	12	0	0	0	13.1
FOX	31.7	28	5.3	0	0	27
CFM	17.3	20	5.3	0	0	15.8
CTX	19.2	20	10.5	0	0	17.7
CAZ	24	20	10.5	0	0	21
FEP	30.8	20	31.6	0	0	28.3
ATM	22.1	20	10.5	0	0	19.7
ERT	0	0	0	0	0	0
IMP	43.3	36	52.6	33.3	0	42.8
MEM	67.3	32	57.9	0	0	58.5
GMN	62.5	48	57.9	66.7	100	59.9
TMN	52.9	56	57.9	33.3	100	54
NET	74	64	73.7	66.7	100	72.3
AKN	92.3	72	78.9	66.7	100	86.8
NA	21.2	28	47.4	0	0	25
NXM	25	32	52.6	0	100	29.6
OFX	25	32	52.6	0	100	29.6
CIP	25	40	63.2	0	100	32.2
LVX	43.3	44	68.4	0	100	46.1
TET	10	25	33.3	0	NA	15.2
MNO	35.4	76	75	0	NA	46.4
TGC	94.2	80	84.2	100	NA	90.7
CS	100	100	100	100	NA	100
FSF	92.3	52	84.2	66.7	0	83.5
SXT	32.7	40	68.4	0	100	38.2
FUR	67.8	36	100	100	NA	67.2

*AMP, ampicillin (10 µg); TIC, ticarcillin (75 µg); PIP, piperacillin (30 µg); AMC, amoxicillin/clavulanic acid (20/10 µg); TCC, ticarcillin/clavulanic acid (75/10 µg); PPT, piperacillin/tazobactam (30/4 µg); ATM, aztreonam (30 µg); IMP, imipenem (10 µg); MEM, meropenem (10 µg); ERT, ertapenem (10 µg); CFX, cefalexin (30 µg); CXM, cefuroxime (30 µg); FOX, cefoxitin (30 µg); CFM, cefixim (5 µg); CTX, cefotaxime (5 µg); FEP, cefepime (30 µg); CAZ, ceftazidime (30 µg); GMN, gentamicin (10 µg); TMN, tobramycin (10 µg); AKN, amikacin (30 µg); NET, netilmicin (10 µg); NA, nalidixic acid (30 µg); NXM, norfloxacin (10 µg); OFX, ofloxacin (5 µg); CIP, ciprofloxacin (5 µg); LVX, levofloxacin (5 µg); TET, tetracycline; MNO, minocycline; TGC, tigecycline (15 µg); CS, colistin (50 µg); FSF, fosfomycin (200 µg); SXT, trimethoprim/sulfamethoxazole (1,25/23,75 µg); FUR, nitrofurantoin (100 µg).

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Table 4. Susceptibility profiles of carbapenem-resistant *P. aeruginosa* and *A. baumannii* strains isolated from two tertiary care hospitals in North Lebanon.

	P. aeruginosa	*A. baumannii*
	N=72	N=66
	%	%
TIC	27.8	0
PIP	29.2	0
TCC	29.2	0
PPT	37.5	0
CTX	NA	0
CAZ	41.7	0
FEP	40.3	0
ATM	56.9	NA
IMP	8.3	0
MEM	0	0
GMN	58.3	1.5
TMN	65.2	3
NET	61.1	1.5
AKN	65.2	3
CIP	34.7	0
LVX	34.7	0
TET	NA	26.3
MNO	NA	89.2
TGC	NA	97.4
CS	100	100
FSF	84.7	NA
SXT	NA	26.3

* TIC, ticarcillin (75 µg); PIP, piperacillin (30 µg) [100/10 µg for *Acinetobacter baumannii*]; TCC, ticarcillin/clavulanic acid (75/10 µg); PPT, piperacillin/tazobactam (30/6 µg) [100/10 µg for *Acinetobacter baumannii*]; ATM, aztreonam (30 µg); IMP, imipenem (10 µg); MEM, meropenem (10 µg); FEP, cefepime (30 µg); CAZ, ceftazidime (10 µg); GMN, gentamicin (10 µg); TMN, tobramycin (10 µg); AKN, amikacin (30 µg); NET, netilmicin (10 µg); CIP, ciprofloxacin (5 µg);LVX, levofloxacin (5 µg); TET, tetracycline; MNO, minocycline; TGC, tigecycline (15 µg); CS, colistin (50 µg); FSF, fosfomycin (200 µg); SXT, trimethoprim/sulfamethoxazole (1,25/23,75 µg).

of *Enterobacteriaceae* isolates, 41.5%, 57.2% and 100% were resistant to meropenem, imipenem and ertapenem, respectively. The higher active antibiotics against carbapenem-resistant *Enterobacteriaceae* were colistin (100%), tigecycline (90.7%), fosfomycin (83.5%), amikacin (83.5%), and nitrofurantoin (67.2%). Moreover, high rates of resistance were detected to tetracycline (84.8%), minocycline (53.6%), nalidixic acid (75%), ciprofloxacin (67.8%), and co-trimoxazole (61.8%). Regarding *A. bauman-* *nii* isolates, high rates of resistance were detected to aminoglycosides (97-98.5%), fluoroquinolones (100%), tetracycline (73.7%), and cotrimoxazole (73.7%). Furthermore, out of *P. aeruginosa* isolates, aztreonam was the most effective beta-lactam antibiotic (56.9%). However, the lower rates of activity were detected to fluoroquinolones (34.7%).

Discussion

The clinical microbiology laboratory has a crucial role in rapid detecting and reporting drug resistant bacteria to infectious disease specialists in order to choose appropriate antibiotic therapy. Multidrug resistant (MDR) bacteria such as carbapenem-resistant pathogens are difficult to treat even when appropriate initial antibiotic therapy is used because they require different treatment regimens to those usually recommended in guidelines [22]. Hence, reliable treatment of MDR pathogens should be based on drug susceptibility testing since only few antibiotics remain as last-resort agents.

Furthermore, empirical treatment for patients who have risk factors to be infected by carbapenem-resistant pathogens should be based on the local available resistance data. Nevertheless, to our knowledge, few data are available in the literature regarding the antibiotic resistance patterns of carbapenem-resistant Gram-negative bacteria in the region of North Lebanon. Therefore, this investigation aimed to provide important new laboratory data that could support specialists in infectious diseases in North Lebanon to take the appropriate decision in the treatment of patients infected with MDR germs. Overall, a total of 290 carbapenem resistant Gram-negative bacterial strains were isolated from patients referred to two tertiary care hospitals in North Lebanon. A significant increase in the prevalence of carbapenem-resistant bacteria was found **(Figure 1** & **Table 2)**. The rise in prevalence of carbapenem-resistant isolates is mainly due to the overuse of carbapenem forced by the increase in percentage of ESBL-producing strains

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in the last decade in Lebanon [8]. Moreover, this alarming increase in carbapenem-resistance rate is a challenge that is associated with high morbidity and mortality [23]. According to our laboratory records, *A. baumannii* was the most resistant bacteria to carbapenem (66.7%), followed by *P. aeruginosa* (12.8%) and *Enterobacteriaceae* (2.8%). These data are in the range of previous reports conducted in the same geographical region [8, 14]. Moreover, our findings highlight the importance of tackling AMR across medical and non-medical sectors in order to prevent the emergence and spread of PDR bacterial clones in Lebanon. A recent nationwide cross-sectional study showed a striking low level of antibiotic knowledge among Lebanese population and confirmed the crucial role of awareness to reinforce the key messages about the appropriate use of antibiotics [24]. However, despite the importance of such initiative, this movement should be supported with further awareness campaigns and pressure movements to implement policy-based changes.

On the other hand, the antibiotic susceptibility testing showed that colistin was the most active antibiotic against carbapenem-resistant bacteria. Despite the high renal and neurological side effects of colistin, this antibiotic is used as first option in combination therapy due to its clinical importance [25]. However, most of Lebanese routine laboratories uses the standard disc antimicrobial susceptibility method for testing this compound.

The disk diffusion method does not work properly due to the poor diffusion of the large colistin molecule and the failure to detect the majority of resistant strains [26].

In addition, tigecycline has also been recommended as part of the combination regimen in the treatment of cases with carbapenem resistant *Enterobacteriaceae* and *A. baumannii*. This study demonstrates that tigecycline was the second most active compound against *Enterobacteriaceae* and to less extent against *A. baumannii*. However, this antibiotic is used to treat infections in different body sites, other than urinary tract and bloodstream infections. The second generation of tetracycline family (minocycline) was also active, but with less percentage of activity against the recorded bacteria isolates. Tetracycline was only active against 15.2% and 26.3% of carbapenem-resistant *Enterobacteriaceae* and *A. baumannii*, respectively. This study indicates a very low rate of tigecycline resistance against carbapenem-resistant isolates in Lebanon as it has been observed in previous reports [8, 12, 14, 27].

Furthermore, aminoglycosides and fosfomycin families showed a good activity against the isolates. Interestingly, amikacin had the higher activity compared to netilmicin, gentamicin and tobramycin against carbapenem-resistant Gram-negative bacteria. Out of 290 isolates, amikacin was the third most active compound against both *Enterobacteriaceae* and *P. aeruginosa*. In contrast, very high levels of aminoglycoside resistance (97%-98.5%) were detected among carbapenem-resistant *A. baumannii*. Recently, a clinical study showed that fosfomycin is active in combination with colistin or tigecycline in the treatment of invasive infections caused by extensively drug-resistant (XDR) and PDR *Enterobacteriaceae* and *P. aeruginosa* strains [28]. The prevalence of fosfomycin-resistant *Enterobacteriaceae* was close to that found in previous studies conducted in the same geographic region, where 15% and 11% of strains isolated from ear infections [11] and urinary tract infections [14], respectively, were resistant to fosfomycin.

The present study shows that quinolones, levofloxacin was the most active among the tested compounds. Levofloxacin and ciprofloxacin resistance rates among *Enterobacteriaceae* and *P. aeruginosa* isolates were higher than other tested antibiotic families, but they were within the range of previous Lebanese studies [8, 11, 12, 14]. Surprisingly, no *A. baumannii* strain was susceptible to fluoroquinolones. This alarming high rates of fluoroquinolone resistance could be explained by the extensive misuse

and overuse of this class of antibiotics in our country. In addition to unauthorized sale of fluoroquinolones in pharmacies and inadequate use by general population, this family of antibiotics is extensively prescribed by Lebanese physicians.

In conclusion, this study indicates an alarming increase in the prevalence of carbapenem- resistant Gram-negative bacteria in North Lebanon. Our findings are crucial to guide clinicians for selection of optimal antibiotic treatment. To date, colistin, tigecycline, amikacin and fosfomycin remain the most effective agents against carbapenem-resistant Gram-negative bacteria. Therefore, we have a major challenge to combat AMR by forcing the implementation of efficient infection control measures and antibiotic stewardship programs in clinical settings and increasing the public awareness on this issue.

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Competing Interests

The authors declare that they have no competing interests.

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