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Bacterial resistance to antibiotics and associated factors in two hospital centers in Lebanon from January 2017 to June 2017

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SUMMARY

General presentation: Resistance of bacteria to antibiotics is a universal problem. With the increase in the rate of resistance, knowledge of susceptibility patterns is essential to guide antimicrobial therapy. In Lebanon, many studies investigated this subject.

Objectives: Determine the rate of multidrug and extremely drug-resistant bacteria as well as the patterns of resistance and the factors associated with this resistance.

Materials and methods: A cross-sectional study was performed using the cultures from the labs of two university hospitals in Lebanon. Bacteria were divided into four groups: sensitive, multidrug-, extremely- and pan-drug resistant. Patient information was obtained from the medical records. Using the SPSS software for Windows, version 20 (IBM, Armonk, USA), the frequency of the bacteria, their susceptibilities and the association of resistance with seven potential factors (age, gender, diabetes mellitus, cancer, chronic kidney disease, dialysis, previous hospitalization) were studied.

Results: The frequency of resistance was 53.7% (39.9% multidrug-resistant and 13.8% extremely drug-resistant). *Escherichia coli* strains were mostly susceptible to carbapenems and tigecycline; and nitrofurantoine and fosfomycin in urine. *Pseudomonas* and *Acinetobacter* species were mostly sensitive to colistin. *Klebsiella* species were mostly susceptible to amikacin and carbapenems. MRSA rates were 34.8%. Association was seen between the resistant bacteria and older age, chronic kidney disease, dialysis, and previous hospitalization.

Conclusion: Resistance of bacteria to drugs in Lebanon is increasing. Significant association is seen between these bacteria and older age, chronic kidney disease, dialysis, and previous hospitalization.

Introduction

Like all living creatures, bacteria try to survive. They do so by adapting to adverse environmental conditions and by

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Table I
Most frequently isolated bacteria and their antibiotic susceptibility categories.

Antimicrobial susceptibility								
Organism	Frequency		Sensitive		Multidrug resistant		Extremely drug-resistant	
Gram-negative bacteria								
Escherichia coli	40.8%	(586)	40.4%	(237)	54.3%	(318)	5.3%	(31)
Pseudomonas spp.	11.6%	(167)	66.5%	(111)	8.4%	(14)	25.1%	(42)
Klebsiella spp.	10.0%	(144)	52.1%	(75)	41.7%	(60)	6.2%	(9)
Acinetobacter baumanii	7.7%	(110)	7.3%	(8)	3.6%	(4)	89.1%	(98)
Proteus mirabilis	5.2%	(75)	37.3%	(28)	57.3%	(43)	5.3%	(4)
Gram-positive bacteria								
Coagulase-negative staphylococci	6.2%	(89)	44.9%	(40)	47.2%	(42)	7.9%	(7)
Staphylococcus aureus	4.6%	(66)	68.2%	(45)	28.8%	(19)	3.0%	(2)
Enterococcus faecalis	4.2%	(61)	78.7%	(48)	21.3%	(13)	0.0%	(0)

developing resistance to poisons they are exposed to, mainly antibiotics. Some bacteria are naturally resistant to a drug because of the absent target or entry site for the drug and such resistance is known as intrinsic. In other cases, the process is acquired.

Resistant and multi-drug resistant strains are predictive of increased hospital costs in comparison with non-resistant strains. With the increase of resistant bacteria, susceptibility testing is increasingly important to direct the treatment of infected patients. However, isolation of the etiological agent is not always possible, and even when possible it takes time to obtain results. Therefore, initial antibiotic therapy is typically empiric. Rational empiric prescribing depends on knowledge of patterns of antibiotic resistance obtained through regional and national epidemiological studies of bacterial isolates from patients [1].

In Lebanon, many studies have investigated the patterns of resistance in order to guide antimicrobial therapy. A study published in 2016 of antimicrobial resistance in Lebanese hospitals provided population-specific data that were valuable in guiding antimicrobial use in this country. It concluded that antimicrobial resistance was becoming a major threat in Lebanon [2]. However, since the patterns of resistance are ever-changing, new data should be continuously brought to light to help guiding the treatment.

The primary objective of this study was to determine the incidence rate of multidrug-resistant bacteria among the positive laboratory cultures during the period from January 2017 to June 2017, in Makassed General Hospital and Lebanese Hospital Geitaoui. Secondary objectives were to determine antibiotic susceptibility patterns of bacteria and to determine potential risk factors associated with resistance, including patient age and gender, and the presence of diabetes mellitus, cancer, chronic kidney disease, dialysis and previous hospitalization.

Methods

A cross-sectional analytical laboratory-based study was conducted in the Bacteriology laboratories of two hospitals (Makassed General Hospital, Lebanese Hospital Geitaoui) from January 2017 to June 2017. These hospitals serve mainly the population of Beirut as well as other parts of Lebanon where cases are referred to these university hospitals. All cultures with positive growth for bacteria were collected. The laboratories use the disc diffusion technique to determine antimicrobial susceptibility.

The following cultures were excluded from the study:

- Cultures with incomplete antibiogram (that is, an antibiogram that cannot be used to define multidrug resistance) or no antibiogram.
- Duplicates from the same patient.

For each culture included in the study, the following patient information were collected from their medical records: age, sex, presence of co-morbidities (diabetes mellitus, chronic kidney disease, dialysis, cancer) and history of hospitalization in the last three months.

Bacteria were divided in four groups: antibiotic-sensitive bacteria, multidrug resistant bacteria (MDR) (defined as non-susceptible to at least one agent in three or more classes of antimicrobial drugs among those that are available at the time of use of the definition and that are regarded as potentially effective against the respective pathogen), extensive drug resistant bacteria (XDR) (resistant to all but one or two classes of antimicrobial agents) and pan-drug resistant bacteria (resistant to all the antimicrobial classes) [3].

Using SPSS software for Windows, version 20 (IBM, Armonk, USA), we determined the distribution of different isolates frequencies as well as the frequency of their susceptibility. The existence of a relationship between different factors and the incidence of drug-resistant bacteria was determined using the Chi-square test. A P value of < 0.05 was considered significant.

Results

A total of 1437 cultures were collected from the hospitals. The most frequently cultured organism was *Escherichia coli*, accounting for 40.8% of the cultures, followed by *Pseudomonas* spp. (11.6%), *Klebsiella* spp. (10%), *Acinetobacter* spp. (7.7%), coagulase-negative staphylococci (SCN) (6.2%), *Proteus mirabilis* (5.2%) and *Staphylococcus aureus* (4.6%) (Table I).

46.3% of bacteria were antibiotic-sensitive. The frequencies of MDR and XDR bacteria were 39.9% and 13.8%, respectively. The antibiograms of the most common organisms are shown in

Table II. Most strains of *E. coli* were antibiotic-resistant (59.6%). Resistance rates were highest to ampicillin (76.5%) followed by amoxicillin + clavulanate (49%), ciprofloxacin (48%) and trimethoprim-sulfamethoxazole (TMP-SMX) (47.8%). Minimal resistance was observed to carbapenems and tigecycline as well as fosfomycin and nitrofurantoine for the urine specimen. For *Pseudomonas* spp., most isolates (66.5%) were deemed antibiotic-sensitive, with MDR and XDR strains accounting for 8.4% and 25.1%, respectively. Resistance was minimal to colistin (0.6%), but over one third of isolates were resistant to gentamicin (34.7%) and ciprofloxacin (34.1%).

Among *Klebsiella* spp. 52.1% were antibiotic sensitive, 41.7% were MDR and 6.3% XDR. Highest resistance rates were seen with nitrofurantoine (52.1) and TMP-SMX (45.8%). Lowest resistance rates were seen with amikacin and carbapenems. The majority (89.1%) of *A. baumanii* isolates were XDR. There was a high rate of resistance to almost all the antibiotics except for colistin for which no resistance was found.

For *S. aureus*, the resistance rate was 31.8% (MDR 28.8% and XDR 3%). The percentage of meticillin-resistant *S. aureus* (MRSA) was 34.8%. No resistance was seen against teicoplanin and minimal resistance was observed for linezolid (1.5%) and vancomycin (3%) (Table III).

Factors investigated for an association with antibiotic resistance are shown in Table IV. There was a significant association between older age (≥65 years) and bacterial resistance to antibiotics ($P = 0.001$). Patients with chronic kidney disease, whether receiving dialysis or not, tended to have more drug resistant bacterial infections than people with normal kidney function. The prevalence of chronic kidney disease is higher in older patients, making it possible that age is the main factor determining the likelihood of resistance. When the population was divided in two groups according to their age, the number of antibiotic-resistant cases almost doubles when CKD is present in both age groups showing that age is not the main factor determining the likelihood of resistance (Table V). Previous hospitalization within the preceding three months was the strongest risk factor for having antibiotic-resistant bacteria. In addition, Table VI shows that dialysis was a risk factor for antibiotic resistance, even in the absence of previous hospitalization.

Table III
Resistance to individual antibiotics in *Staphylococcus aureus*

Antibiotic	Resistance
Oxacillin	34.8% (23)
TMP-SMX	13.6% (9)
Erythromycin	31.8% (21)
Clindamycin	18.2% (12)
Vancomycin	3% (2)
Teicoplanin	0% (0)
Linezolid	1.5% (1)
Rifampicin	4.5% (3)
Quinolones	25.8% (17)

The class quinolones was used instead of the specific drug because different labs used different drugs from this class.

Discussion

Up to 59.6% of the *E. coli* strains were resistant to at least three antimicrobial classes. This number is significantly different from that of European countries, where one study showed that these strains represent only 12.3% of the cases [4]. TMP-SMX should be avoided as empirical treatment for urinary

Table II
Resistance to individual antibiotics in major isolated Gram-negative bacteria

Antibiotic	*Escherichia coli*		*Pseudomonas* spp.		*Klebsiella* spp.		*Acinetobacter baumanii*	
Ampicillin	76.5%	(448)	-		-		-	
Amoxicillin + clavulanate	49.0%	(287)	-		39.6%	(57)	-	
Piperacillin + tazobactam	18.4%	(108)	31.1%	(52)	18.8%	(27)	91.8%	(101)
Cefoxitine	31.9%	(187)	-		29.2%	(42)	-	
Cefuroxime	47.1%	(276)	-		35.4%	(51)	-	
Ceftriaxone	45.6%	(267)	-		34.0%	(49)	-	
Ceftazidime	42.8%	(251)	25.1%	(42)	34.7%	(50)	90.9%	(100)
Cefepime	37.7%	(221)	28.7%	(48)	28.5%	(41)	89.1%	(98)
Imipenem	1.4%	(8)	31.7%	(53)	1.4%	(2)	90.9%	(100)
Ertapenem	2.7%	(16)	-		2.8%	(4)	-	
Gentamicin	20.3%	(119)	34.7%	(58)	20.1%	(29)	88.2%	(97)
Amikacin	5.1%	(30)	26.9%	(45)	0.0%	(0)	90.9%	(100)
Tobramycin	-		22.8%	(38)	-		-	
Ciprofloxacin	48%	(281)	34.1%	(57)	31.2%	(45)	92.7%	(102)
Tigecycline	0.7%	(4)	-		6.2%	(9)	43.6%	(48)
Aztreonam	41.5%	(243)	21.6%	(36)	34%	(49)	-	
TMP-SMX	47.8%	(280)	-		45.8%	(66)	93.6%	(103)
Fosfomycin (urine)	3.4%	(16)	-		6.4%	(6)	-	
Nitrofurantoine (urine)	8.6%	(41)	-		52.1%	(49)	-	
Colistin	-		0.6%	(1)			0.0%	(0)

The percentages represent the frequency of resistance. The numbers in brackets represent the count.

Table IV
Relationship between various factors and isolation of antibiotic-sensitive and antibiotic-resistant bacteria

		Susceptibility		χ^2	p
		Sensitive	Resistant		
Age	< 65 years	262	266	10.591	0.001*
	≥ 65 years	269	400		
Gender	Male	237	322	1.431	0.232^{ns}
	Female	292	345		
Diabetes	Yes	115	185	3.414	0.065^{ns}
	No	354	441		
Cancer	Yes	89	138	1.536	0.215^{ns}
	No	380	488		
CKD	Yes	39	78	4.826	0.028*
	No	430	548		
Dialysis	Yes	8	34	10.089	0.001*
	No	461	592		
Hospitalization	Yes	118	235	24.2	10^{-6}**
	No	404	421		

^{ns}: non-significant; *: $P < 0.05$; **: $P < 0.001$.

tract infections (UTI) since the resistance is around 47.8% (>20% as upper limit of acceptable resistance by Infectious Disease Society of America) [5]. This number does not differ significantly from that of 1994, when Araj *et al*. described 42% resistance to TMP-SMX [6]. Resistance to ciprofloxacin in our study was the same rate as reported by Chamoun et al., and a major increase when compared to 1994 when resistance to norfloxacin and pefloxacin were only 2% and 8% respectively [2,6]. This could be due to the extensive and uncontrolled use of these agents in treatment, and/or non-compliance of patients in completing full courses of treatment.

In Europe in 2018 only 11.6% of pseudomonas isolates were reported to be antibiotic-resistant [4], a far lower rate than in our study. The most common resistances in our study were to gentamicin (34.7%) and ciprofloxacin (34.1%), these rates also being higher than in a previous Lebanese study between 2011 and 2013 (27.5% for gentamicin and 19.7% for ciprofloxacin) [2]. Amikacin resistance has also increased in Lebanon, rising from 5% in 1994, through 9.5% in 2013, to 26.9% in 2017 [2,6].

47.9% of *Klebsiella* spp. were antibiotic-resistant, compared with 22.3% in Europe [4]. Most species are resistant to TMP-SMX and nitrofurantoin. Since 1994 resistance to TMP-SMX has risen from 30% to 45.8% [6]. However, resistance to amikacin (0%), imipenem (1.4%) and ertapenem (2.8%) remain at low levels; Chamoun *et al*. also found low rates of resistance to amikacin (4.9%) and imipenem (2.7%) [2].

Table V
Relationship between presence of chronic kidney disease and age on bacterial susceptibility to antibiotics

		Susceptibility		χ^2	p
		Sensitive	Resistant		
Age <64	CKD	8	19	3.644	0.056^{ns}
	No CKD	214	227		
Age ≥65	CKD	31	59	1.078	0.299^{ns}
	No CKD	216	321		

^{ns}: non-significant; *: $P < 0.05$; **: $P < 0.001$.

Table VI
Relationship between dialysis and previous hospitalization on and bacterial susceptibility to antibiotics

		Susceptibility		χ^2	Fischer's exact test
		Sensitive	Resistant		
Hospitalized	Dialysis	4	19	2.727	0.099^{ns}
	No dialysis	112	216		
Not hospitalized	Dialysis	4	15	5.447	0.020*
	No dialysis	349	376		

^{ns}: non-significant; *: $P < 0.05$; **: $P < 0.001$.

A. baumanii was the most resistant bacterium with 92.7% of strains being antibiotic-resistant, and 89.1% being XDR. This is markedly different to the situation in Europe, where 45.7% of strains were antibiotic-resistant [4]. It is notable that in 1994 Araj *et al*. found sensitivity rates of 90% to imipenem and 74% to quinolones [6].

The proportion of *S. aureus* isolates that were MRSA (34.8%) represents an increase from previous reports of 27.1% in 2013 and 18% in 1994 [2,6]. In Europe 2018, MRSA represented only 16.4% of isolates [4].

We know of no local studies that have previously investigated the association of age with antibiotic resistance. Data from other countries are conflicting. Wolfe *et al*. reported that age was significantly associated with resistance to antibiotics [7]. However other studies have reported that age is not a factor in determining antibiotic resistance in patients with febrile UTI specifically, or in patients generally [8,9]. An Iranian study also found no significant association between age and the likelihood of having extended-spectrum beta-lactamase (ESBL)-producing bacteria [10].

Several studies have investigated the relationship between gender and antibiotic resistance. An Iranian study found no association between gender and ESBL production [10], and an American study showed no difference in the susceptibility patterns of *E. coli* causing UTI in men and women [11]. However, a German study found that uropathogenic *E. coli* were more antibiotic-resistant in women [12]. This is probably explained by the higher frequency of UTI in women and the repetitive use of antibiotics to treat such infections which leads to the acquisition of resistance to these drugs.

As in our study, an Iranian study found no association between the presence of diabetes and antibiotic resistance [10]. Likewise, others have also found that presence of malignancy is not a risk factor for the antibiotic resistance [7].

Multiple studies have addressed the association of CKD and dialysis with resistance. Guobin-Su *et al*. found that poorer kidney function at the time of hospital admission is associated with higher probabilities of having multidrug resistant organisms [13]. Majeed *et al*. found that all bacterial isolates in patients with CKD were more virulent than isolates from those without kidney disease [14].

We found that patients with previous hospitalizations during the past three months have more resistant bacterial strains than those without such hospitalization. The possibility of the age of the patient being a confounding factor was eliminated by rechecking the association between previous hospitalization and resistance in each age group. with the same association seen in both groups Many studies have addressed this issue. For

example, Toubes *et al*. found that previous hospitalization within 30 days was associated with resistance (*P* value of 0.04) [15]. Tenny *et al*. also reported that previous hospitalization was one of the most probable risk factors for MDR pathogens, which supports our results [16].

In conclusion, we found that MDR bacteria represented 39.9% of cultures, and XDR bacteria 13.8%. Older age, chronic kidney disease, dialysis and previous hospitalization within the past three months prior to the culture dates were factors associated with resistance. Cancer, diabetes mellitus and gender were not found to be associated with resistance. We recommend yearly surveillance of patterns of resistance to guide the empiric prescribing of antibiotics.

Declaration of interests

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