Journal of Infection and Public Health 14 (2021) 12–16

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Prevalence of antibiotic-resistant organisms among hospitalized patients at a tertiary care center in Lebanon, 2010–2018

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ARTICLE INFO

Article history:
Received 7 May 2020
Received in revised form
28 September 2020
Accepted 27 November 2020

Keywords:
Antimicrobial resistance
Surveillance
Infection prevention
Infection control
Multidrug-Resistant organism

ABSTRACT

Background: Infections due to antibiotic resistant organisms (ARO) among hospitalized patients are associated with increased morbidity, mortality, and healthcare costs. Longitudinal data about antimicrobial resistance are scarce in Lebanon and the region. The objective of this study is to describe the temporal trends of resistance of selected pathogens among hospitalized patients at a tertiary care center in Lebanon.
Methods: We conducted a retrospective review of surveillance data from 2010 until 2018. Six target organisms isolated from hospitalized patients were included: carbapenem-resistant *Escherichia coli* (CREC), carbapenem-resistant *Klebsiella* spp. (CRKP), multi-drug resistant *Pseudomonas aeruginosa* (MDRPA), carbapenem-resistant *Acinetobacter baumannii* (CRAB), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* spp. (VRE). Correlation analysis was performed to evaluate for temporal trends.
Results: A total of 15,901 isolates were examined, most of which were obtained from urinary specimens. Among Gram-negative organisms, the highest resistance was found among CRAB (81.7%), followed by CRKP (6.5%) and CREC (3.3%). MDRPA overall prevalence was 0.8%. Among Gram-positive organisms, the prevalence of MRSA and VRE was 26.2% and 2.6%, respectively. CREC, MRSA, and VRE showed statistically significant increasing temporal trends, while CRAB decreased significantly from 2013 to 2018.
Conclusion: These data are helpful in characterizing the epidemiology of antimicrobial resistance in Lebanon and show that controlling emerging resistance is achievable with concerted infection control and antimicrobial stewardship efforts. Caution should be exercised to contain early on the spread of CREC and of resistant Gram-positive pathogens.

Introduction

Antibiotic-resistant organisms (AROs) are encountered both in the community and in healthcare settings and have emerged in numerous countries across the globe to become a public health threat of worldwide proportions [1]. There are fewer drugs available to effectively treat AROs. These organisms are therefore more likely to spread, particularly among vulnerable populations such as the elderly and the immunocompromised. Among hospitalized patients, AROs often cause hospital-acquired infections (HAIs) with significant subsequent morbidity and mortality [2].

Data documenting the effect of antimicrobial resistance on patient mortality are abundant. The Centers for Disease Control and Prevention in the United States estimate that AROs cause at least 2,868,700 infections and 35,900 deaths every year, of which 10,600 deaths are from methicillin-resistant *S. aureus* (MRSA), 5400 deaths from vancomycin-resistant enterococci (VRE), and 2700 deaths from multidrug-resistant *P. aeruginosa* (MDRPA) [3].

Among the countries of the Arab League, the highest resistance rates have been reported from Egypt, followed by the countries of the Levant (Lebanon, Syria, Jordan, Iraq, and the Palestinian territories) [4]. In general, the lowest prevalence of resistance was captured in studies from the Gulf countries. In Lebanon, although longitudinal data on AROs are not widely available, it is well

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https://doi.org/10.1016/j.jiph.2020.11.006
1876-0341/

established that AROs have had a significant impact on society, particularly in hospitalized patients. For example, surveillance studies of device-associated infections in the intensive care unit at our center have revealed carbapenem-resistant *Acinetobacter baumannii* (CRAB) to be the most common isolated pathogen in ventilator-associated pneumonia, with an associated mortality rate exceeding 50% [5,6].

In view of the increasing prevalence of AROs globally and regionally, the present study was conducted with the aim of describing and analyzing the ARO trends at our center over a period of eight years and comparing them to the existing literature.

Methods

This is a single center retrospective study at the American University of Beirut Medical Center (AUBMC). AUBMC is a 366-bed academic tertiary care center in Lebanon and is considered as a referral center at the national and regional levels. The hospital offers outpatient and inpatient services including medical and surgical care in regular as well as intensive care units. The bed occupancy rate in the hospital was rather stable during the period of the study and ranged from 79% to 85%. On a regular weekday, the Clinical Microbiology Laboratory handles around 300 samples. Data on AROs from January 1, 2010 to December 31, 2018 were extracted from the Infection Control and Prevention Program (ICPP) database at AUBMC. This database includes microbiology results of all patients admitted to AUBMC during the study period that are routinely collected by ICPP as part of its daily surveillance activities.

All reported positive cultures from hospitalized patients were recorded, whether they corresponded to a clinical infection or to asymptomatic colonization. The data were obtained from the Clinical Microbiology Laboratory and were filtered against the patients' medical record numbers to exclude repetitive specimens. Six target organisms were included in the analysis: *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus aureus*, and *Enterococcus* spp. These organisms were chosen based on local endemicity, clinical importance, as well as infection control implications and they have been the targets for antimicrobial resistance surveillance at AUBMC for several years. The classification of an organism as ARO was based on the following microbiological phenotypes via antimicrobial susceptibility testing: carbapenem-resistant *E. coli* (CREC), carbapenem-resistant *Klebsiella* spp. (CRKP), CRAB, MDRPA that has tested either intermediate or resistant to at least three categories of antimicrobial agents, MRSA, and VRE. Susceptibility testing was performed in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [7].

ARO prevalence for each organism was calculated as the number of resistant isolates divided by the total number of isolates for that organism. A yearly ARO rate for each organism was also calculated as the number of resistant isolates divided by the total number of patient-days for that year. This measure has been used in the literature previously and allows us to account for variations in bed occupancy, individual lengths of hospital stay, etc. [8]. Correlation analysis was performed to evaluate for statistical significance of the temporal trend over the study period for each target organism.

Exemption for this study was sought from the Institutional Review Board at AUBMC since the project involved secondary analysis of information collected routinely as part of the daily surveillance activities of ICPP.

Results

A total of 15,901 isolates from cultures of various clinical specimens were included in the analysis (Table 1). The most frequently identified organism was *E. coli* (43.7%, n = 6953), followed by *Klebsiella* spp. (15.7%, n = 2494), and *P. aeruginosa* (13.7%, n = 2176). Most clinical specimens consisted of urine (39%), wounds (29%), and respiratory secretions (sputum, tracheal aspirate, and bronchoalveolar lavage) (26%). Blood accounted for only 5% of the total specimens (Fig. 1). Isolates originated from specimens representing community-acquired as well as hospital-acquired infections, except for CRAB where the majority of isolates were from hospital-acquired infections.

The highest overall percentage of resistance was found among *A. baumannii* isolates (81.7%) (Table 2). All the other target organisms had significantly lower overall resistance rates, ranging from 26.2% for *S. aureus* down to 0.8% for *P. aeruginosa* isolates.

Upon examining temporal trends of resistance (Fig. 2), only CREC showed a statistically significant increase over the study period among all Gram-negative organisms, from 0 per 10,000 patient-days in 2010 to 4.44 per 10,000 patient-days in 2018 (Pearson correlation coefficient = 0.91; $p < 0.001$). Resistance trends for *Klebsiella* spp., while showing an increase comparable to those encountered with *E. coli*, did not reach statistical significance ($p = 0.14$). On the other hand, CRAB prevalence increased between 2010 and 2013 then started to decrease again. While the overall trend for resistance from 2010 to 2018 was not significant ($p = 0.65$), the decrease in resistance from a peak in 2013 (14.32 per 10,000 patient-days) until 2018 (5.65 per 10,000 patient-days) was highly statistically significant (Pearson correlation coefficient = −0.95; $p = 0.003$). Finally, MDR *P. aeruginosa* remained low over the years ($p = 0.26$). Among Gram-positive organisms, both MRSA and VRE

Table 1
Distribution of organisms identified during the study period.

Organism	N	%
E. coli	6953	43.7
Klebsiella spp.	2494	15.7
P. aeruginosa	2176	13.7
Enterococcus spp.	1849	11.6
S. aureus	1385	8.7
A. baumannii	1044	6.6
Total isolates	15,901	100

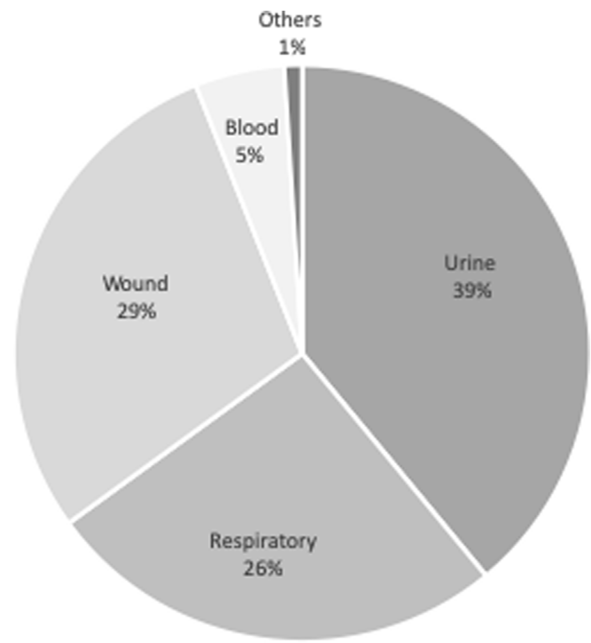

Fig. 1. Clinical sources of organisms isolated during the study period.

Table 2
Yearly distribution of resistant organisms.

Organism	2010	2011	2012	2013	2014	2015	2016	2017	2018	Overall
CREC	0/767 (0)	0/720 (0)	7/657 (1.1)	33/749 (4.4)	22/787 (2.8)	40/795 (5.0)	38/764 (5.0)	46/871 (5.3)	44/843 (5.2)	230/6953 (3.3)
CRKP	0/226 (0)	0/266 (0)	16/266 (6.0)	37/231 (16.0)	19/233 (8.1)	28/326 (8.6)	21/287 (7.3)	18/347 (5.2)	24/312 (7.7)	163/2494 (6.5)
MDRPA	4/270 (1.5)	0/290 (0)	0/242 (0)	0/212 (0)	0/220 (0)	0/260 (0)	4/224 (1.8)	2/215 (0.9)	7/243 (2.9)	17/2176 (0.8)
CRAB	49/94 (52.1)	93/116 (80.2)	115/125 (92.0)	127/145 (87.6)	120/135 (88.9)	125/153 (81.7)	92/113 (81.4)	76/94 (80.8)	56/69 (81.2)	853/1044 (81.7)
MRSA	18/145 (12.4)	30/152 (19.7)	25/116 (21.5)	40/161 (24.8)	35/136 (25.7)	58/190 (30.5)	49/160 (30.6)	57/175 (32.6)	51/150 (34.0)	363/1385 (26.2)
VRE	1/166 (0.6)	0/225 (0)	4/183 (2.2)	4/217 (1.8)	1/175 (0.6)	6/180 (3.3)	7/183 (3.8)	11/264 (4.2)	15/256 (5.9)	49/1849 (2.6)

CREC = carbapenem-resistant *E. coli*, CRKP = carbapenem-resistant *Klebsiella* spp., CRAB = carbapenem-resistant *A. baumannii*, MDRPA = multidrug-resistant *P. aeruginosa*, MRSA = methicillin-resistant *S. aureus*, VRE = vancomycin-resistant *Enterococcus* spp.
Numbers represent n/N (%).

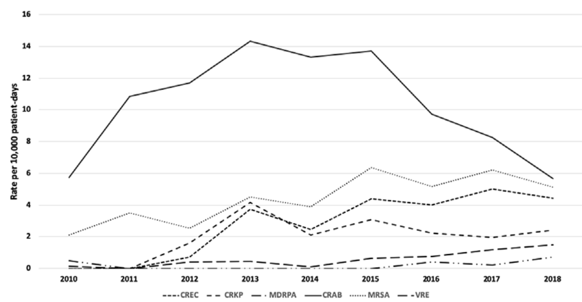

Fig. 2. Temporal trends of resistant organisms.
CREC = carbapenem-resistant *E. coli* (r = 0.91, p-value < 0.0001), CRKP = carbapenem-resistant *Klebsiella* spp. (r = 0.54, p-value = 0.14), MDRPA = multidrug-resistant *P. aeruginosa* (r = 0.42, p-value = 0.26), CRAB = carbapenem-resistant *A. baumannii* (r = −0.17, p-value = 0.65), MRSA = methicillin-resistant *S. aureus* (r = 0.83, p-value = 0.005), VRE = vancomycin-resistant *Enterococcus* spp (r = 0.89, p-value = 0.001).

prevalence increased significantly over time (Pearson correlation coefficient = 0.83 and 0.89; p = 0.005 and 0.001, respectively).

Discussion

This is to our knowledge the largest longitudinal study on antimicrobial resistance in Lebanon encompassing a period of nine years. We found a statistically significant increase over time of CREC, MRSA, and VRE and a decreasing prevalence of CRAB from 2013 onwards. Data about antimicrobial resistance in the region is not well systematized. Reports are available about various organisms in different healthcare settings, mostly representing cross-sectional studies and including a small number of isolates. A recent review has gathered the available data about the most prominent resistant pathogens in the countries of the Arab League, providing a preliminary mapping of antimicrobial resistance in these countries while awaiting the results of larger national and multi-centered surveillance studies [4].

A. baumannii had the highest prevalence of resistance (81.7% of 1044 isolates) during the study period. This finding is in accordance with increasing CRAB proportions seen worldwide [9]. In the Arab world, the prevalence of CRAB was highest in Qatar, followed by Egypt [10] and Iraq (100% of 48, 93% of 320, and 89% of 126 isolates respectively). In previous studies from Lebanon, it was reported in 82% of 3552 isolates [11–13]. Figures from the United States have indicated that more than 60% of *Acinetobacter* spp. among hospital acquired infections were MDR [14]. Another report showed an increase in resistance from 24% in 2004 to 52% in 2008 [15]. Similarly, a study done in Vietnam on bacterial isolates from tracheal aspirates in ICU patients showed an increase in CRAB from 15.8% in 2002 to 88.6% in 2010 [16]. In our study, after an initial increase between 2010 and 2013, CRAB prevalence started dropping steadily reaching an overall minimum of 5.65 per 10,000 patient-days in 2018. This came as the result of extensive work by the ICPP over several years to curb the in-hospital transmission of CRAB, the majority of which were isolated from hospital-acquired infections. Interventions included reinforcement of hand hygiene, active screening for AROs, universal contact precautions in ICU, and changes to environmental cleaning and disinfection processes [6]. Of note is that the percent of resistant isolates among *A. baumannii* decreased only marginally with time, indicating that a control of the transmission of resistant isolates was achieved rather than re-emergence of susceptible clones. Most of the reports in the literature describe the control of short-term outbreaks with the implementation of various infection control measures [17,18]. However, controlling what became with time an endemic infection and reversing a heavy transmission burden required a continuous and consorted effort that involved the entire institution.

As for Enterobacteriaceae, carbapenem resistance is still relatively low at our center (3.3% for CREC and 6.5% for CRKP), and this is similar to a previous study from Lebanon in 2013 [19]. Despite such low prevalence, temporal trends indicate a significant increase in CREC over time, and a substantial albeit non-statistically significant increase in CRKP. In the Arab world, the majority of studies have reported a low prevalence of CRE not exceeding 5% of isolates [20,21], with a few reports quoting higher numbers in the Palestinian territories (22%) [22], Jordan (22.5%) [23], and Egypt (28%) [24]. Continued surveillance in our country and the region will determine whether high endemic levels of CRE will be reached, such as those observed in southern Europe, particularly in Greece, Italy, and Cyprus [25].

We found a low prevalence of MDRPA throughout the study period (overall 0.8%; range 0–2.9%). While the proportion of carbapenem-resistant *P. aeruginosa* in Lebanon has been reported to be 28%, most of the isolates at our center remain sensitive to aminoglycosides and anti-pseudomonal beta-lactams (data from the Clinical Microbiology Laboratory). In the region, carbapenem resistance among *P. aeruginosa* ranges widely from 3% in Kuwait to 93% in Jordan [4]. Globally, MDRPA prevalence is considerably higher compared to our data. For example, in the SMART 2015-17 database, 27.4% of *P. aeruginosa* isolates were characterized as multidrug-resistant (750 out of 2732 isolates) [26].

The overall prevalence of MRSA (26.2% of 1385 samples) at AUBMC is similar to that reported by the Lebanese Society of Infectious Diseases Study Group (27.6%) [13]. The proportion of MRSA among all *S. aureus* isolates has hovered around 18–25% for several years, corresponding to rates of 2.11–4.51 per 10,000 patient-days. However, starting in 2015, those numbers have increased consistently in our hospitalized population (p = 0.005). While the proportion of MRSA among community isolates remains relatively stable (data from the Clinical Microbiology Laboratory), the significant increase in MRSA among inpatients has widespread repercussions on infection control practices as well as on empiric antibiotic use. This recent emergence of MRSA is bringing us closer to the epidemiology of *S. aureus* in the region, where most countries report an MRSA prevalence ranging between 30% and 60% [4]. However, it is rather delayed compared to the worldwide epidemiology which has witnessed for the past several years alarmingly high proportions of MRSA [27]. Only this trend has started to reverse globally, with studies showing that MRSA transmission, hence prevalence, have been curbed as a result of the implementation of infection control practices [28]. For example, in the United States, the Veterans Affairs medical centers have reported a 55% decrease in MRSA [29]. At our center, heightened suspicion for MRSA should now prevail in the appropriate setting, thereby introducing anti-MRSA therapy and instituting contact precautions promptly.

Vancomycin resistance among enterococci has been rarely reported from Lebanon and the region. In the Arab world, a single study at a tertiary care center in Saudi Arabia reported a prevalence of 17.3% [30]. At our medical center, infections due to VRE have traditionally amounted to a handful of cases every year. Recently, however, a larger number of VRE isolates have been recovered, with a prevalence reaching 5.9% (1.51 per 10,000 patient-days) in 2018. We could expect this trend to either continue its upward stroke or to at least stabilize since at the moment, the colonization pressure in the hospital is higher compared to earlier years. However, and as is the case with MRSA, expeditious initiation of appropriate infection control measures is key to controlling or reversing this emergence. Data from international centers mirror this increase, albeit to much higher levels. For example, according to the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2016 report, 7 out of 25 countries in the European Union reported significant increases in the percentage of VRE isolates between 2013 and 2016 [31].

Our study has several limitations. First, it reflects data from a single tertiary care center in an urban area. Generalizability to national levels may therefore be challenging. However, our institution serves a wide variety of the Lebanese population and it represents a referral center for the entire region. The catchment population is therefore quite large. Another limitation is that we included hospitalized patients without differentiating whether the infections were community- or hospital-acquired. In addition, we were not able to capture whether our patients were re-admitted to other hospitals after their index hospitalization.

Conclusions

This study offers the advantage of establishing antimicrobial resistance trends among hospitalized patients at a tertiary care center over almost a decade. After an initial increase, CRAB rates decreased. In contrast, rates of CREC, MRSA, and VRE have increased significantly. These results should inform antimicrobial stewardship and infection control initiatives. Future studies should attempt at obtaining national-level surveillance data and stratifying infection episodes based on place of acquisition in order to delineate the resistance epidemiology in the community versus the hospital settings.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

CRediT authorship contribution statement

Moustafa Moussally: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Nada Zahreddine:** Conceptualization, Data curation, Formal analysis, Writing - original draft. **Jamil Kazma:** Conceptualization, Writing - review & editing. **Rihab Ahmadieh:** Data curation, Resources. **Souha S. Kan:** Conceptualization, Writing - review & editing. **Zeina A. Kanafan:** Conceptualization, Formal analysis, Writing - review & editing, Supervision.

Acknowledgement

The authors would like to acknowledge the contribution of Mr. Guillermo Adame who participated in data collection and analysis.

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