Epidemiology and mortality outcome of carbapenem- and colistin-resistant *Klebsiella pneumoniae, Escherichia coli, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* bloodstream infections

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ABSTRACT

Background: Bloodstream infections caused by carbapenem-resistant Gram-negative bacteria represent a major therapeutic challenge to clinicians worldwide. This study examined the epidemiology of carbapenem and colistin resistance in *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* blood isolates in an academic institution in Oman.

Methods: Adult patients with bloodstream infections caused by *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, between January 1, 2017, and December 31, 2020, were identified. Rates of carbapenem resistance, carbapenem-colistin dual resistance, and 30-day all-cause mortality were examined.

Results: 585 non-repeat bloodstream infections due to *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* were identified during the study period. OXA-48 was the most prevalent carbapenemase gene in carbapenem-resistant *K. pneumoniae* blood isolates. Carbapenem resistance was observed in 160 (27.7%) of blood isolates, with 131 (81.9%) of these being healthcare-onset cases. Carbapenem resistance was highest in *Acinetobacter baumannii* (80.4%), followed by *Klebsiella pneumoniae* (46.4%), and *Pseudomonas aeruginosa* (29.9%). Sixteen (13.4%) of the carbapenem-resistant blood isolates were found to be colistin resistant. Thirty-day all-cause mortality was 68.1% in patients with bloodstream infections caused by carbapenem-resistant isolates, versus 21.3% in patients with bloodstream infections caused by carbapenem-susceptible isolates.

Conclusion: The prevalence of carbapenem resistance and carbapenem-colistin dual resistance in Gram-negative blood culture isolates from patients with bloodstream infections is unacceptably high. Patients with bloodstream infections due to carbapenem-resistant isolates had substantially higher mortality.

Introduction

Infections caused by carbapenem-resistant Gram-negative bacteria present a substantial therapeutic challenge, severely limiting and complicating treatment options for serious infections caused by these isolates [1]. Occurrences of these difficult-to-treat infections have increased dramatically over the past decade, and have become a major public health threat globally [2]. Carbapenem resistance poses a potential public-health emergency, especially in developing countries, accounting for high morbidity, mortality, and healthcare costs [3]. Published data on the epidemiology of carbapenem resistance in blood culture isolates from the Oman region are scarce [4,5]. Likewise, information on the prevalence of colistin resistance in carbapenem-resistant Gram-negative bacteria from the region is severely limited [6].

Carbapenem resistance in blood-culture Gram-negative isolates has been shown to correlate with poor clinical outcomes, including higher mortality [5,7]. Pooled outcomes in one study showed that the number of deaths was significantly higher in patients with carbapenem-resistant infections, and that the number of deaths attributable to carbapenem resistance was considerable [8].

With the emergence of carbapenem resistance among *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacterales*, and the scarcity of new and affordable antibiotics, the use of polymyxins has become essential in the management of bloodstream infections caused by these extensively drug-resistant pathogens [9]. Predictably, growing use of colistin has resulted in the development of colistin-resistant strains, further depriving clinicians from viable therapeutic options [10]. Furthermore, several studies have demonstrated that colistin resistance in

Table 1

Rates of carbapenem resistance in 578 evaluable blood culture isolates.

	Total blood culture isolates	Carbapenem resistant (%)	Carbapenem susceptible (%)	Carbapenem not tested
Escherichia coli	244 (41.7%)	7/244 (2.9%)	237/244 (97.1%)	0
Klebsiella pneumoniae	183 (31.3%)	84/181 (46.4%)	97/181 (53.6%)	2
Pseudomonas aeruginosa	110 (18.8%)	32/107 (29.9%)	75/107 (70.1%)	3
Acinetobacter baumannii	48 (8.2%)	37/46 (80.4%)	9/46 (19.6%)	2
	585	160/578 (27.7%)	418/578 (72.3%)	

Table 2

Distribution of carbapenem resistance genes, according to Xpert Carba-R testing, in carbapenem-resistant *Klebsiella pneumoniae* and *Escherichia coli* blood isolates.

	Carbapenem-resistant (isolates from 2017–2020)	Xpert Carba-R tested (isolates from 2019 and 2020)	OXA-48	NDM	OXA-48 and NDM
Carbapenem-resistant *Klebsiella pneumoniae*	84	52 (62%)	35	8	9
Carbapenem-resistant *Escherichia coli*	7	5 (71%)	0	5	0
	91	57 (63%)	35	13	9

carbapenem-resistant *A. baumannii, P. aeruginosa*, and *K. pneumoniae* bloodstream infections increases mortality [11].

This study was conducted to examine the prevalence of carbapenem resistance and carbapenem-colistin dual resistance in *A. baumannii, P. aeruginosa, K. pneumoniae*, and *E. coli* blood isolates from patients with bloodstream infections, and to describe the mortality outcome in these patients.

Methods

This was a retrospective study examining carbapenem and colistin resistance in *P. aeruginosa, A. baumannii, K. pneumoniae*, and *E. coli* bloodstream infections in adult patients, between January 1, 2017, and December 31, 2020. Data were obtained using the hospital's real-time bloodstream infection surveillance system. This semi-automated surveillance system captures microbiological and demographic patient data relating to bloodstream infections and antimicrobial resistance. Bacterial identification and antibiotic susceptibility testing followed the standard operating procedures of the clinical microbiology laboratory. Antimicrobial susceptibility testing (including carbapenems and colistin) was performed using a commercial automated system (BD Phoenix). Furthermore, a commercialized broth microdilution method (Thermo Scientific™ Sensititre™ Gram Negative GNX3F AST) was performed to determine the minimum inhibitory concentration for colistin, and to confirm colistin susceptibility.

From 2019 onwards, carbapenem-resistant *Enterobacterales* blood isolates were further tested using the Xpert Carba-R (Cepheid, Sunnyvale, CA) assay for the detection of five carbapenemase genes (bla_{OXA-48}, bla_{NDM}, bla_{KPC}, bla_{VIM}, bla_{IMP}). Blood cultures with monomicrobial growth of *P. aeruginosa, A. baumannii, E. coli*, and *K. pneumoniae*, and only first non-repeat bacteremia episodes, were included in the study. The classification of bloodstream infections into either healthcare onset or community onset was based on internationally accepted definitions whereby community-onset bloodstream infection is defined as occurring within < 48 hours of admission to hospital, whereas healthcare-onset bloodstream infection is defined as being first identified ≥ 48 hours following hospital admission or within < 48 hours of hospital discharge. The main outcomes were the rates of carbapenem and carbapenem-colistin dual resistance in *P. aeruginosa, A. baumannii, E. coli*, and *K. pneumoniae* blood culture isolates, and their associated 30-day all-cause mortality.

Study population

Hospitalized patients (> 18 years old) with bloodstream infections caused by *P. aeruginosa, A. baumannii, E. coli*, or *K. pneumoniae*, between January 1, 2017 and December 31, 2020, were included.

Statistical analyses

Data were expressed as mean ± standard deviation (SD). Comparisons between groups were performed using non-parametric test analysis. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the SPSS version 19.0 software package.

Results

In total, 585 non-repeat bloodstream infections resulting from *P. aeruginosa, A. baumannii, E. coli*, or *K. pneumoniae*, between January 1, 2017, and December 31, 2020, were identified. The distribution of these blood isolates is shown in Table 1.

Rate of carbapenem resistance

Records on carbapenem susceptibility were available for 578 (98.8%) of the blood culture isolates. As shown in Table 1, 160 cases of bloodstream infection were caused by a carbapenem-resistant isolate, with an overall rate of carbapenem resistance of 27.7%. *A. baumannii* had the highest carbapenem resistance rate at 37/46 (80.4%), whereas *E. coli* had the lowest rate (2.9%). Rates of carbapenem resistance in *K. pneumoniae* and *P. aeruginosa* blood isolates were 46.4% and 29.9%, respectively. *K. pneumoniae* and *P. aeruginosa* caused 52.5% and 20.0% of all carbapenem-resistant bloodstream infections, respectively. In total, 52 carbapenem-resistant *Klebsiella pneumoniae* and five carbapenem-resistant *Escherichia coli* blood isolates from 2019 and 2020 were tested for the presence of carbapenemase genes, using Xpert Carba-R. All 57 isolates were found to harbor at least one carbapenemase gene, with OXA-48, NDM, and OXA-48 plus NDM present in 35, 13, and nine of the isolates, respectively (Table 2).

Carbapenem resistance in community- vs healthcare-onset bloodstream infections

Of the 160 carbapenem-resistant blood culture isolates, 81.9% were classified as healthcare onset. *A. baumannii, K. pneumoniae, P. aeruginosa*, and *E. coli* caused 24.4%, 51.9%, 19.8%, and 3.8% of healthcare-onset carbapenem-resistant bloodstream infections, respectively, with 86.5% of carbapenem-resistant *A. baumannii*, 81% of carbapenem-resistant *P. aeruginosa*, 81% of carbapenem-resistant *K. pneumoniae*, and 71.4% of carbapenem-resistant *E. coli* bloodstream infections being of healthcare origin (Table 3).

Demographic features

Table 4 shows the demographic characteristics of the study patients. Of the 578 evaluable patients with bloodstream infections caused by

Table 3

Distribution of carbapenem-resistant bloodstream infections according to source of onset.

	Number of carbapenem-resistant isolates	Community onset	Healthcare onset
Klebsiella pneumoniae	84 (52.5%)	16 (19%)	68 (81%)
Pseudomonas aeruginosa	32 (20.0%)	6 (19%)	26 (81%)
Acinetobacter baumannii	37 (23.1%)	5 (13.5%)	32 (86.5%)
Escherichia coli	7 (4.4%)	2 (28.6%)	5 (71.4%)
Total	160	29 (18.1%)	131 (81.9%)

Table 4

Sex and age characteristics of patients with carbapenem-resistant and carbapenem-susceptible blood culture isolates.

	Bacteremia episodes (known carbapenem susceptibility)	Carbapenem resistant	Carbapenem susceptible
Escherichia coli			
Total	244 (244)	7 (2.9%)	237 (97.1%)
Male		0 (0%)	104 (43.9%)
Female		7 (100%)	133 (56.1%)
Age (mean in years)		49.43	61.28
Klebsiella pneumoniae			
Total	183 (181)	84 (46.4%)	97 (53.6%)
Male		66 (78.6%)	57 (58.8%)
Female		18 (21.4%)	40 (41.2%)
Age (mean in years)		56.29	51.22
Pseudomonas aeruginosa			
Total	110 (107)	32 (29.9%)	75 (70.1%)
Male		17 (53.1%)	42 (55.3%)
Female		15 (46.9%)	33 (44.7%)
Age (mean in years)		55.8	58.2
Acinetobacter baumannii			
Total	48 (46)	37 (80.4%)	9 (19.6%)
Male		32 (86.5%)	3 (36.4%)
Female		5 (13.5%)	6 (63.6%)
Age (mean in years)		54.1	53.6

Table 5

Prevalence of colistin resistance in carbapenem-resistant blood culture isolates.

	Tested for colistin susceptibility (%)	Colistin resistant	Colistin susceptible	Colistin not tested
Carbapenem-resistant *Acinetobacter baumannii*	29/37 (78.4%)	0/29 (0%)	29/29 (100%)	8
Carbapenem-resistant *Klebsiella pneumoniae*	62/84 (73.8%)	15/62 (24.2%)	47/62 (75.8%)	22
Carbapenem-resistant *Pseudomonas aeruginosa*	21/32 (65.6%)	1/21 (4.8%)	20/21 (95.2%)	11
Carbapenem-resistant *Escherichia coli*	7/7 (100%)	0/7 (0%)	7/7 (100%)	0
	119/160 (74.4%)	16/119 (13.4%)	103/119 (86.6%)	41/160 (25.6%)

any of these four isolates, 55.5% were male. Of the 160 patients with carbapenem-resistant blood isolates, 71.9% were male.

Prevalence of colistin-carbapenem dual resistance in K. pneumoniae, E. coli, P. aeruginosa, and A. baumannii bloodstream infections

Of the 160 bloodstream infections caused by any of these four carbapenem-resistant isolates, colistin susceptibility data were obtainable for 119 isolates (Table 4). Sixteen isolates (15 *K. pneumoniae* and one *P. aeruginosa*) were found to be dually resistant to both carbapenem and colistin, with an overall rate of 13.4%. Prevalences of colistin re-

sistance among carbapenem-resistant *K. pneumoniae* and *P. aeruginosa* blood isolates were 24.2% and 4.8%, respectively.

Mortality

Table 6 shows the 30-day all-cause mortality for *P. aeruginosa, A. baumannii, E. coli*, and *K. pneumoniae* bloodstream infections categorized by susceptibility to carbapenem. Out of the 578 patients with bloodstream infections caused by any of the four examined blood culture isolates with known susceptibility to carbapenems, 34.3% died within 30 days of the onset of bloodstream infection. Patients with bloodstream infections

Table 6

Thirty-day all-cause mortality for bloodstream infections according to carbapenem susceptibility.

		Klebsiella pneumoniae	Pseudomonas aeruginosa	Acinetobacter baumannii	Escherichia coli
Number of deaths/total	198/578 (34.3%)	87/181 (48%)	35/107 (32.7%)	27/46 (58.6%)	49/244 (20.1%)
Deaths in carbapenem-susceptible group	89/418 (21.3%)	30/97 (30.9)	13/75 (17.3%)	2/9 (22.2%)	44/237 (18.6%)
Deaths in carbapenem-resistant group	109/160 (68.1%)	57/84 (67.8%)	22/32 (68.8%)	25/37 (67.6%)	5/7 (71.4%)

caused by carbapenem-resistant isolates showed significantly higher mortality in comparison with patients with carbapenem-susceptible isolates, with 30-day all-cause mortality rates of 68.1% and 21.3%, respectively. Thirty-day all-cause mortality was similar for all four carbapenem-resistant blood isolates, with rates of 68.8%, 67.8%, 67.6%, and 71.4% for *P. aeruginosa, K. pneumoniae, A. baumannii*, and *E. coli*, respectively.

Discussion

Bloodstream infections caused by carbapenem-resistant *K. pneumoniae, E. coli, A. baumannii,* and *P. aeruginosa* are a growing global health concern [12]. Our study found that 27.7% of the examined Gram-negative blood culture isolates were resistant to carbapenems. Carbapenem resistance among *K. pneumoniae, A. baumannii,* and *P. aeruginosa* isolates has shown a staggering 54% increase when compared with a previously reported combined rate of 29.8%, from a study in the same center between 2007 and 2016 [5]. *K. pneumoniae* was the most prevalent carbapenem-resistant blood isolate, causing 54.9% of all carbapenem-resistant bloodstream infections, while *A. baumannii* had the highest rate of carbapenem resistance (80.4%). It is interesting to note that carbapenem resistance in *K. pneumoniae* has been steadily increasing [5].

Since the introduction of Xpert Carba-R testing in 2019 in this center, all Enterobacterales blood isolates have been tested for the presence of carbapenemase genes. OXA-48 has been shown to be the most prevalent carbapenemase gene in carbapenem-resistant *K. pneumoniae* blood isolates, accounting for 85% of carbapenemase genes. In contrast, all tested *Escherichia coli* blood isolates were NDM producers.

Although no single definition has been accepted as a reference standard, categorization of bloodstream infections as either community-onset or healthcare-onset infections provides a discrete and objective means of classification [13]. In our study, rates of carbapenem resistance in healthcare-onset and community-onset bloodstream infections were examined. Predictably, most cases of carbapenem-resistant blood culture isolates (81.9%) were classed as healthcare onset. This finding was in agreement with previous reports [5,14]. Our study found that nearly one in every six carbapenem-resistant blood isolates (18.1%) was classed as community onset — a finding of great public health concern. This compares with a rate of 13% reported in a previous study from the same institution [5]. Increasing reports of community-onset bloodstream infections caused by carbapenem-resistant isolates are disturbing [15].

The prevalence of colistin resistance among the carbapenem-resistant blood culture isolates was also explored. Sixteen of 119 blood culture isolates (13.4%) were found to simultaneously have dual resistance to carbapenem and colistin. This shows a startling (70%) increase in dual resistance when compared with a prevalence of 7.9% reported by a previous study from the same setting [5]. One confounder to consider when comparing the findings of the two studies on dual carbapenem-colistin resistance is that, after the previous study, the microbiology lab in this center introduced a confirmatory broth microdilution method (Thermo Scientific™ Sensititre™ Gram Negative GNX3F AST) for colistin susceptibility testing. The Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) both recommend broth microdilution as the reference method for determining susceptibility to colistin [16,17].

Notably, carbapenem-resistant *K. pneumoniae* accounted for 93.7% of all colistin-resistant blood isolates in our study. Moreover, the prevalence of colistin resistance among carbapenem-resistant *K. pneumoniae* blood isolates was the highest, at 24.2%. A recent systematic review and meta-analysis from Iran also showed a high prevalence of colistin resistance in *K. pneumoniae* isolates [18]. These findings reveal a worrisome trend in the prevalence of carbapenem-colistin dual resistance, especially among *K. pneumoniae* blood isolates. Such resistance severely limits antimicrobial options for the management of these serious infections [9]. Interestingly, none of the examined carbapenem-resistant *E. coli* or *A. baumannii* blood isolates showed resistance to colistin.

Several previous studies, including one from the same institution, have reported higher mortality rates for patients with bloodstream infections caused by carbapenem-resistant isolates when compared with patients with carbapenem-susceptible blood isolates [5,19]. Similarly, a recent systematic review and meta-analysis of 2462 patients infected with carbapenem-resistant *K. pneumoniae* showed that these patients had higher mortality than those infected with carbapenem-susceptible *K. pneumoniae*, especially among critically ill patients with bacteremia [20]. Our study observed that patients with carbapenem-resistant bloodstream infections had three times higher mortality rates when compared with patients with carbapenem-susceptible bloodstream infections, with 30-day mortality rates of 68.1% and 21.3%, respectively. Intriguingly, 30-day all-cause mortality rates were similar, albeit ominously high, for all four carbapenem-resistant blood isolates. These findings are in contrast with those of a similar study from India and a larger study from the same center, both of which suggested higher mortality rates for carbapenem-resistant *P. aeruginosa* bacteremia when compared with carbapenem-resistant *A. baumannii* bacteremia [21,5]. Although, the exact reasons for the unrivaled mortality found for the cohort of patients with carbapenem-resistant Gram negative blood isolates in this study are unclear, several recent studies have reported similar mortality rates. A recent systematic review of the impact of carbapenem resistance on mortality among patients with Enterobacterales suggested that, for any type of mortality outcome, carbapenem resistance was associated with a greater probability of death among patients infected with carbapenem-resistant isolates [8]. Several other studies examining mortality outcomes in *A. baumannii* and *P. aeruginosa* bacteremia have demonstrated similar outcomes [22,23].

Our study had several limitations, in addition to its retrospective nature. First, the prevalence of carbapenem resistance was only examined in four isolates and only from blood cultures, hence the extents of carbapenem resistance in other Gram-negative isolates and in the same four isolates from other clinical sites remain unknown. Second, the dichotomy of carbapenem-resistant bloodstream infections into healthcare-onset and community-onset was based solely on a retrospective review of clinical records, making it impossible to accurately ascertain what percentage of community-onset bloodstream infections was indeed community-acquired. This limitation may have resulted in overestimating community acquisition of carbapenem resistance. Third, notwithstanding having a well-defined 30-day all-cause mortality endpoint, factors known to impact mortality outcomes, such as timing and appropriateness of empirical antibiotics, sources of bacteremia and their control, and the severity of infection, were not studied. It is worth mentioning that intravenous colistin in combination with high-dose meropenem was the main antimicrobial therapeutic option available to most patients with carbapenem-resistant, colistin-susceptible bloodstream infections in this institution during the study period, while intravenous fosfomycin was used in instances of colistin resistance.

Despite these limitations, this study illustrated the temporal trend of carbapenem resistance in blood culture isolates in the same institution, included a relatively large number of patients, had a clearly defined study population, studied colistin and carbapenem dual resistance, and examined mortality in these double-resistance cases. Unlike the previous study from the same institution, in which only non-molecular, phenotypic laboratory methods were used to detect carbapenem resistance, the present study used Xpert Carba-R as an additional diagnostic tool. The Xpert Carba-R assay is a reliable and accurate reference standard for detecting carbapenem resistance caused by the production of carbapenemases [24].

In summary, this research revealed a startling rise in the prevalence of carbapenem resistance and dual carbapenem-colistin resistance in the examined blood culture isolates from a single academic institution. These findings present an unparalleled therapeutic challenge associated

with an unacceptably greater mortality. Furthermore, this research highlights the urgent need for implementing effective national antibiotic stewardship practices, and for implementing stringent infection prevention and control actions.

Conclusion

Our data demonstrate an alarming increase in the prevalence of carbapenem resistance in *K. pneumoniae, E. coli, A. baumannii*, and *P. aeruginosa* blood culture isolates, with a large proportion of *K. pneumoniae* demonstrating additional resistance to colistin. This poses a significant and unprecedented therapeutic challenge, combined with unacceptably higher mortality. These findings call for urgent public health action to combat this threat.

Funding

Ethical approval

This study was approved by the institutional research ethics committee (MREC #1468).

Conflicts of interest

The authors declare that they have no conflicts of interest.

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