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Prevalence and 30-day all-cause mortality of carbapenem-and colistin-resistant bacteraemia caused by *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*: Description of a decade-long trend

A. Balkhair[a,*], Z. Al-Muharrmi[b], B. Al'Adawi[b], I. Al Busaidi[a], H.B. Taher[a], T. Al-Siyabi[b], M. Al Amin[a], K.S. Hassan[a]

[a] Department of Medicine, Infectious Diseases Unit, Sultan Qaboos University Hospital, Muscat, Oman
[b] Department of Microbiology and Immunology, Sultan Qaboos University Hospital, Muscat, Oman

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ABSTRACT

Background: Bacteraemia due to carbapenem-resistant gram-negative bacteria is challenging. This study examined the burden of carbapenem and colistin resistance in *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* bacteraemia in Oman.
Methods: Adult patients admitted to Sultan Qaboos University Hospital between January 1, 2007 and December 31, 2016 with positive blood cultures for *P. aeruginosa*, *A. baumannii*, or *K. pneumoniae* were identified. Rates of carbapenem resistance, trends in prevalence, and 30-day all-cause mortality were examined.
Results: Two hundred and twenty-seven (29.8%) of 761 bacteraemia cases due to these three isolates were carbapenem-resistant, with 87.2% being healthcare-associated. *A. baumannii* caused 52% of all carbapenem-resistant bacteraemia, *K. pneumoniae* caused 30%, and *P. aeruginosa* caused 18%. Rates of carbapenem resistance in *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* bacteraemia increased from 20%, 67%, and 0%, respectively, in 2007 to 25%, 86%, and 35%, respectively, in 2016. Seventeen (7.9%) carbapenem-resistant bacteraemia cases were also colistin-resistant. Thirty-day all-cause mortality was 62% in patients with carbapenem-resistant bacteraemia and 22% in patients with carbapenem-sensitive bacteraemia.
Conclusions: The prevalence of carbapenem-resistant *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* bacteraemia is increasing alarmingly in Oman, with a large proportion of *K. pneumoniae* and *P. aeruginosa* demonstrating additional resistance to colistin. Patients with carbapenem-resistant bacteraemia had higher 30-day all-cause mortality.

Introduction

Carbapenem resistance is a major global public health threat (Codjoe and Donkor, 2017). Infections due to carbapenem-resistant gram-negative bacteria, especially bacteraemia, are increasingly challenging and have become a major concern for clinicians worldwide (Codjoe and Donkor, 2017). Carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*, specifically *Klebsiella pneumoniae*, were recognized as critical-priority pathogens posing the utmost threat to human health by the World Health Organization (WHO) in February 2017 (Tacconelli et al., 2018). This critical ranking was largely based on the associated overall mortality, unavailability of effective therapy, increasing healthcare burden, and antibiotic resistance characteristics of these pathogens (Balkhair, 2017).

A study from the USA found that the rate of carbapenem resistance among blood culture isolates was 40.1% for *A. baumannii*, 10.3% for *P. aeruginosa*, and 3.6% for *K. pneumoniae* (Cai et al., 2017). In China, a study of blood culture isolates reported overall prevalence rates of carbapenem-resistant *K. pneumoniae*, extensively drug-resistant *A. baumannii*, and extensively drug-resistant *P. aeruginosa* of 5.5%, 13.7%, and 4.2%, respectively (Xu et al., 2016).

* Corresponding author.
E-mail address: balkhair2020@gmail.com (A. Balkhair).

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Increasing rates of carbapenem resistance in invasive infections caused by *K. pneumoniae* isolates have been reported progressively from more countries in Europe, with increasing trends of carbapenem resistance among invasive *K. pneumoniae* isolates in several countries (Magiorakos et al., 2013). The prevalence of carbapenem-resistant invasive *K. pneumoniae* has been reported to be 49.8% in Greece and 12.5% in Italy (Magiorakos et al., 2013).

Several studies have consistently shown that bacteraemia caused by carbapenem-resistant isolates is associated with unacceptably high mortality when compared to bacteraemia caused by carbapenem-sensitive isolates (Kohler et al., 2017; Falagas et al., 2014; Daikos et al., 2014). In a study of mortality risk factors in 182 patients with carbapenem-resistant *A. baumannii* bacteraemia in Taiwan, the attributable mortality rate was 58% (Liu et al., 2016). In a retrospective observational study of a cohort of 118 patients with *A. baumannii* bacteraemia in Korea, the 30-day mortality rate was 34.1% and resistance to carbapenems was identified as one of the significant risk factors for mortality (Park et al., 2013). In a recent retrospective case–control study, patients with carbapenem-resistant *P. aeruginosa* bacteraemia had a 30-day mortality rate of 72.0% as compared to 26.0% for patients with bacteraemia due to *P. aeruginosa* susceptible to all classes of antipseudomonal antibiotics (Lee et al., 2017). Another retrospective study from Barcelona, Spain reported an overall 30-day mortality of 41% (Suárez et al., 2009).

Polymyxins including colistin are the essential last-resort treatment for infections caused by carbapenem-resistant *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*, among others. However, with the increased use of colistin in recent years, reports of resistance have also been increasing. This is of great concern, given the limited number of antimicrobial agents available to treat such infections (Srinivas and Rivard, 2017). In a study from the USA, 13% of 246 patients with carbapenem-resistant *K. pneumoniae* isolates were found to have colistin resistance, which was shown in that study to be associated with increased mortality (Rojas et al., 2017).

In an Italian case–control study on carbapenem-resistant *K. pneumoniae* bloodstream infections, the 30-day mortality of colistin-resistant carbapenemase-producing *K. pneumoniae* blood isolates was as high as 51% (Giacobbe et al., 2015).

There are limited published data on antimicrobial resistance in Oman. A study by Balkhair et al. found that multidrug resistance among clinical isolates of *A. baumannii*, *P. aeruginosa*, and *Enterobacteriaceae* was prevalent in hospitalized patients (Balkhair et al., 2014).

The current study was performed to examine the burden of carbapenem resistance in *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* blood isolates, describe trends in carbapenem resistance in blood isolates over a 10-year period, and investigate 30-day all-cause mortality in patients with bacteraemia caused by carbapenem-resistant isolates in Oman.

Methods

This was a retrospective study of carbapenem-resistant *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* bacteraemia in adult patients between 2007 and 2016. This study was conducted at Sultan Qaboos University Hospital, a 600-bed teaching and referral hospital in Oman, using the bacteraemia surveillance registry (BSR) of the infection prevention and control department. The BSR is a component of a hospital-based semi-automated electronic surveillance system for healthcare-associated infections that captures electronically available patient data including microbiology reports and generates real-team surveillance data.

Isolate identification was based on standard operating procedures in the clinical microbiology laboratory. The presence of carbapenem resistance was detected by commercial automated system (BD Phoenix). The modified Hodge test was used for confirmation, as recommended by the Clinical and Laboratory Standards Institute (CLSI). The interpretation of carbapenem susceptibility was based on the CLSI definitions and reported as resistant (R), susceptible (S), or not tested (NT). *K. pneumoniae* isolates were defined as carbapenem-resistant if they were resistant to at least one of the carbapenems tested and as carbapenem-susceptible if the isolate was susceptible to all carbapenems tested. *P. aeruginosa* and *A. baumannii* isolates were considered resistant to carbapenems if they were resistant to either imipenem or meropenem but not ertapenem. For patients with multiple bacteraemia events resulting from the same isolate or caused by more than one of the study pathogens during the study period, only data from the first bacteraemia episode were used. Blood cultures that were simultaneously positive for two or more of the study isolates were excluded from the study. The classification of bacteraemia into either healthcare-associated or community-acquired was based on the hospital infection prevention and control categorization using WHO definitions.

The primary outcomes were the rates of carbapenem resistance in *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* bacteraemia and 30-day all-cause mortality for carbapenem-resistant bacteraemia isolates. Secondary outcome variables included the rates of carbapenem resistance in healthcare-associated versus community-acquired bacteraemia, 30-day all-cause mortality in a subset of patients with carbapenem-resistant and colistin-resistant *K. pneumoniae* bacteraemia and *P. aeruginosa* bacteraemia, and trends in carbapenem resistance in blood culture isolates over the study period.

Study population

All adult patients (age $\geq$18 years) admitted to Sultan Qaboos University Hospital between January 1, 2007 and December 31, 2016 with blood cultures positive for *P. aeruginosa*, *A. baumannii*, or *K. pneumoniae* and meeting the pre-specified study inclusion criteria were included.

Statistical analyses

Categorical variables were recorded as the number and percentage of patients and were compared between the carbapenem-resistant and carbapenem-sensitive cases in each isolate-specific bacteraemia group using the Chi-square test. Crude 30-day all-cause mortality was compared between carbapenem-resistant and carbapenem-sensitive bacteraemia. A *p*-value of $<$0.05 indicated a statistically significant difference between cohorts. The statistical analysis was performed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA).

Results

This study included a total of 775 non-repeat bacteraemia events resulting from *P. aeruginosa*, *A. baumannii*, or *K. pneumoniae* between January 1, 2007 and December 31, 2016. Of these bacteraemia cases, *K. pneumoniae* accounted for 375, *P. aeruginosa* for 231, and *A. baumannii* for 169 (Table 1).

Rate of carbapenem resistance

Data on carbapenem susceptibility were available for 761 blood culture isolates. As shown in Table 2, 227 bacteraemia cases were caused by a carbapenem-resistant isolate, with an overall prevalence of carbapenem resistance of 29.8%. *A. baumannii* had the highest carbapenem resistance rate (70.5%) and caused 51.5% of

Table 1
Distribution of bacteraemia according to acquisition (community vs. healthcare acquired).

	Number of isolates	Community-acquired	Healthcare-associated
Klebsiella pneumoniae bacteremia	375 (48%)	148 (39%)	227 (61%)
Pseudomonas aeruginosa bacteremia	231 (30%)	72 (31%)	159 (69%)
Acinetobacter baumannii bacteremia	169 (22%)	23 (14%)	146 (86%)
Total	775	243 (31%)	532 (69%)

all carbapenem-resistant bacteraemia. Rates of carbapenem resistance in *K. pneumoniae* and *P. aeruginosa* blood isolates were 18.4% and 18.6%, respectively. *K. pneumoniae* and *P. aeruginosa* caused 30.4% and 18.1% of all carbapenem-resistant bacteraemia, respectively.

Out of the 227 carbapenem-resistant bacteraemia, 198 (87%) were categorized as healthcare-associated. *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* caused 53%, 29%, and 18%, respectively, of healthcare-associated carbapenem-resistant bacteraemia, with 90% of carbapenem-resistant *A. baumannii*, 88% of carbapenem-resistant *P. aeruginosa*, and 83% of carbapenem-resistant *K. pneumoniae* bacteraemia being of healthcare origin. This is shown in Table 3.

Demographic characteristics

Table 4 shows the demographic characteristics of the study patients. Of the 775 patients with bacteraemia caused by any of these three isolates, 441 were male (57%) and 334 (43%) were female ($p = 0.72$). Patients with *A. baumannii* bacteraemia were significantly younger than patients with *P. aeruginosa* or *K. pneumoniae* bacteraemia (41.2 years vs. 51.3 and 52.1 years, respectively) ($p = 0.049$). Among patients with carbapenem-resistant bacteraemia, those with carbapenem-resistant *P. aeruginosa* bacteraemia were the youngest (mean age 46.9 years), whereas those with carbapenem-resistant *K. pneumoniae* bacteraemia were the oldest (mean age 52.5 years). Seventy-two percent of patients with carbapenem-resistant *K. pneumoniae* bacteraemia and 67% of patients with carbapenem-resistant *A. baumannii* bacteraemia were male.

Trends in carbapenem resistance among blood culture isolates: 2007–2016

Rates of carbapenem resistance in *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* blood culture isolates over the 10-year period are shown in Figure 1. None of the *K. pneumoniae* blood culture isolates prior to 2010 (82 isolates) had carbapenem resistance. Starting in 2010, the prevalence of carbapenem resistance in *K. pneumoniae* bacteraemia increased significantly, reaching a peak in 2014 (40%). Rates of carbapenem resistance in *P. aeruginosa* blood isolates demonstrated a different pattern, with 20% of blood isolates in 2007 and 2008 demonstrating carbapenem resistance; this increased sharply to 43% in 2015. Finally, rates of carbapenem resistance in *A. baumannii* blood culture isolates remained relatively stable but high over the 10 years, and varied between 50% and 80%, with a peak at 86% in 2016. Table 5 shows the trends in carbapenem resistance among these three blood isolates categorized into two 5-year intervals.

Rate of colistin resistance in carbapenem-resistant blood culture isolates

Of the 227 carbapenem-resistant bacteraemia cases, colistin susceptibility data were available for 216 isolates (Table 6). Seventeen isolates (14 *K. pneumoniae* and 3 *P. aeruginosa*) were found to be dually resistant to both carbapenems and colistin, with an overall rate of 7.9%. Rates of colistin resistance among carbapenem-resistant *K. pneumoniae* and *P. aeruginosa* blood isolates were 21.2% and 9.1%, respectively. None of the carbapenem-resistant *A. baumannii* blood culture isolates was colistin-resistant.

Antibiotic therapy

Of the 199 evaluable patients with carbapenem-resistant, colistin-susceptible blood isolates, 141 (71%) were alive at the time of confirmation of carbapenem resistance and were treated with a combination of intravenous colistin and meropenem. Tigecycline was an additional antibiotic in 25 patients (excluding patients with carbapenem-resistant *P. aeruginosa*).

Mortality

Table 7 below depicts the 30-day all-cause mortality rates for *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* bacteraemia according to carbapenem and colistin susceptibility status and origin of acquisition (community vs. healthcare). Out of the 775 patients with any of the three defined types of bacteraemia, 252 patients (32.5%) died in hospital within 30 days of onset of bacteraemia. *A. baumannii* bacteraemia had the highest 30-day all-cause mortality (40.2%), followed by *K. pneumoniae* bacteraemia (31.5%) and *P. aeruginosa* bacteraemia (28.6%). Patients with healthcare-associated bacteraemia had consistently worse outcomes with higher 30-day all-cause mortality when compared to patients with community-origin bacteraemia ($p = 0.0002$), irrespective of the isolate and irrespective of the carbapenem susceptibility, as shown in Table 7. Similarly, patients with bacteraemia caused by carbapenem-resistant isolates had numerically higher mortality rates ($p = 0.000$) when compared to patients with carbapenem-sensitive isolates, with 30-day all-cause mortality of 62.1% and 21.9%, respectively. Carbapenem-resistant *P. aeruginosa* bacteraemia had the highest 30-day all-cause mortality (80.5%), followed by *K. pneumoniae* bacteraemia (63.8%) and *A. baumannii* bacteraemia (54.7%). Out of the 17 patients with carbapenem-resistant and colistin-resistant bacteraemia (14 *K. pneumoniae* and 3 *P. aeruginosa*), 12 patients with carbapenem-resistant and colistin-resistant *K. pneumoniae* and all three patients with carbapenem-resistant and colistin-resistant *P. aeruginosa* died, with 30-day all-cause mortality of 85.7% and 100%, respectively.

Table 2
Prevalence rates for carbapenem resistance in 761 evaluable bacteraemia isolates.

	Total (evaluable)	Carbapenem-resistant (%)	Carbapenem-sensitive (%)	Carbapenem-intermediate	Carbapenem not tested
Klebsiella pneumoniae bacteremia	375 (374)	69 (18.4%)	305 (81.6%)	1	0
Pseudomonas aeruginosa bacteremia	231 (221)	41 (18.6%)	180 (81.4%)	7	3
Acinetobacter baumannii bacteremia	169 (166)	117 (70.5%)	49 (29.5%)	1	2
	775 (761)	227 (29.8%)	534 (70.2%)		

Table 3
Relative frequencies and distribution of carbapenem-resistant bacteraemia isolates.

	Bacteremia episodes	Healthcare-associated (%)	Community-acquired (%)
Carbapenem-resistant *Pseudomonas aeruginosa* bacteremia	41	36 (88%)	5 (12%)
Carbapenem-resistant *Acinetobacter baumannii* bacteremia	117	105 (90%)	12 (10%)
Carbapenem-resistant *Klebsiella pneumoniae* bacteremia	69	57 (83%)	12 (17%)
Total (%)	227	198 (87%)	29 (13%)

Table 4
Sex and age characteristics of patients with carbapenem-resistant and carbapenem-sensitive blood culture isolates.

		All	Carbapenem-resistant	Carbapenem-sensitive
Pseudomonas aeruginosa				
	Total	231[a]	41	180
	Male	131 (57%)	19 (46%)	105 (58%)
	Female	100 (43%)	22 (54%)	75 (42%)
	Age (mean in years)	51.3	46.9	52.1
Acinetobacter baumannii				
	Total	169[b]	117	49
	Male	92 (54%)	78 (67%)	13 (27%)
	Female	77 (46%)	39 (33%)	36 (73%)
	Age (mean in years)	41.2	49.6	44.2
Klebsiella pneumoniae				
	Total	375[c]	69	305
	Male	218 (58%)	50 (72%)	167 (55%)
	Female	157 (42%)	19 (28%)	138 (45%)
	Age (mean in years)	52.1	52.5	52.2

[a] Seven isolates are intermediate, three isolates not tested (221 carbapenem evaluable).
[b] One isolate is intermediate, two isolates not tested (166 evaluable).
[c] One isolate is intermediate (374 carbapenem evaluable).

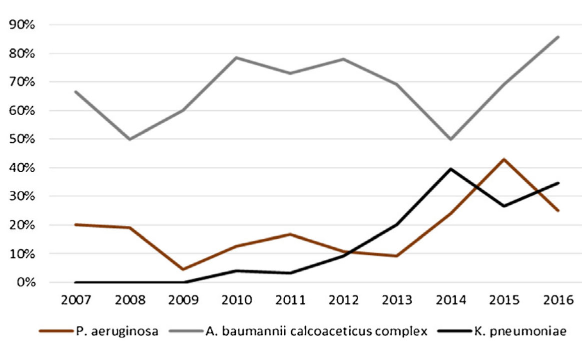

Figure 1. Carbapenem resistance rates over time for *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* blood culture isolates: period 2007–2016.

Table 5
Trends in carbapenem resistance prevalence rates among blood isolates categorized into two 5-year intervals.

	Overall	Period	
		2007–2011	2012–2016
Klebsiella pneumoniae	18.4%	1.4%	28%
Pseudomonas aeruginosa	18.6%	14%	22%
Acinetobacter baumannii	70.5%	68%	73%

Discussion

Carbapenem-resistant *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* have unfortunately been reported with increasing frequency worldwide in recent years (Codjoe and Donkor, 2017). This study found an alarmingly high rate of carbapenem resistance among these three blood isolates, with an overall prevalence of 29.8%. It is believed that this finding presents an unprecedented challenge to clinicians in this setting regarding the choice of both empirical and targeted antibiotic treatment for serious infections caused by these pathogens.

In this study, *A. baumannii* was not only the most frequent carbapenem-resistant blood isolate, but it was also the isolate with the highest rate of carbapenem resistance. Similarly, high rates of carbapenem resistance were found in *P. aeruginosa* and *K. pneumoniae* blood culture isolates (18.6% and 18.4%, respectively).

It was possible to examine the trend in carbapenem resistance for these three selected blood isolates, demonstrating an alarming increasing prevalence over the decade of cumulative data from the study institution. These observed trends are troublesome. This examination of the trends resulted in a few interesting observations. First, carbapenem-resistant *K. pneumoniae* blood isolates were first recognized in the hospital in 2010. It is believed that the emergence of carbapenem-resistant *K. pneumoniae* in this setting may have been a result of the introduction of NDM-1 isolates via increasing medical tourism of Omani patients to the Indian subcontinent. Although molecular typing on these isolates was not performed to substantiate this, unpublished epidemiological data show that carbapenem-resistant *K. pneumoniae* was first and repeatedly (over the subsequent 2 years) isolated from returning patients who had undergone surgical and chemotherapy treatments in India. Similar observations have been reported elsewhere (Yong et al., 2009; Johnson and Woodford, 2013).

Second, carbapenem resistance among *P. aeruginosa* blood culture isolates was stable but high for most of the years. However, 2015 witnessed a dramatic increase with 43% of *P. aeruginosa* blood isolates in that year being carbapenem-resistant. It is believed that this was largely due to two outbreaks of carbapenem-resistant *P. aeruginosa* bacteraemia in haematology wards (unpublished data).

Table 6
Prevalence of colistin resistance in carbapenem-resistant blood culture isolates.

	Total (tested)	Colistin-resistant	Colistin-sensitive	Colistin not tested
Carbapenem-resistant *Acinetobacter baumannii* bacteremia	117 (117)	0	117 (100%)	0
Carbapenem-resistant *Klebsiella pneumoniae* bacteremia	69 (66)	14 (21.2%)	52 (78.8%)	3
Carbapenem-resistant *Pseudomonas aeruginosa* bacteremia	41 (33)	3 (9.1%)	30 (90.9%)	8

Table 7
Thirty-day all-cause mortality rates for *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* bacteraemia according to carbapenem and colistin susceptibility status and origin of acquisition (community vs. healthcare).

		Pseudomonas aeruginosa	*Acinetobacter baumannii*	*Klebsiella pneumoniae*
Number of deaths/totals	252/775 (32.5%)	66/231 (28.6%)	68/169 (40.2%)	118/375 (31.5%)
Deaths in community-acquired group	57/243 (23.5%)	15/72 (20.8%)	6/23 (26.1%)	36/148 (24.3%)
Deaths in healthcare-associated group	195/532 (36.7%)	51/159 (32.1%)	62/146 (42.5%)	82/227 (36.1%)
Deaths in carbapenem-sensitive group	117/534 (21.9%)	39/180 (21.7%)	4/49 (8.2%)	74/305 (24.3%)
Deaths in carbapenem-resistant group	141/227 (62.1%)	33/41 (80.5%)	64/117 (54.7%)	44/69 (63.8%)
Deaths in community-acquired carbapenem-sensitive	44/212 (20.8%)	13/65 (20%)	0/11 (0%)	31/136 (22.8%)
Deaths in community-acquired carbapenem-resistant	12/29 (41.4%)	1/5 (20%)	6/12 (50%)	5/12 (41.7%)
Deaths in healthcare-associated carbapenem-sensitive	73/322 (22.7%)	26/115 (22.6%)	4/38 (10.5%)	43/169 (25.4%)
Deaths in healthcare-associated carbapenem-resistant	119/198 (60.1%)	22/36 (61.1%)	58/105 (55.2%)	39/57 (68.4%)
Deaths in carbapenem-resistant AND colistin-resistant bacteremia	15/17 (88.2%)	3/3 (100%)	No colistin resistance	12/14 (85.7%)

The categorization of bacteraemia caused by carbapenem-resistant isolates into community-origin versus healthcare-associated was examined. As expected, most cases of carbapenem-resistant bacteraemia (87%) in this study were healthcare-acquired. This is consistent with the results of several studies from different parts of the world, which have attributed most of the carbapenem-resistant blood isolates to healthcare (Chen et al., 2018; Hattemer et al., 2013; Veeraraghavan et al., 2017).

An unexpected finding was that 13% of carbapenem-resistant bacteraemia in this study was of community origin. This finding is justifiably of great concern. Increasing reports of community-acquired infections by carbapenem-resistant and multidrug-resistant bacteria are alarming (van Duin and Paterson, 2016).

Although studying the prevalence of carbapenem resistance amongst selected bacteraemia isolates was the primary goal of this study, it was also possible to examine the prevalence of colistin resistance among the carbapenem-resistant blood culture isolates. Seventeen of the 216 evaluable blood isolates (7.9%) were found to be dually resistant to both carbapenems and colistin. In contrast to carbapenem-resistant *A. baumannii* bacteraemia, where none of the 117 isolates was resistant to colistin, it was found that colistin susceptibility in carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *P. aeruginosa* bacteraemia was very much different, with 21.2% of carbapenem-resistant *K. pneumoniae* and 9.1% of carbapenem-resistant *P. aeruginosa* blood isolates being colistin-resistant. It is suspected that the increasing 'justifiable' use of colistin as rescue therapy for severe infections in critically ill patients in the study setting may have been contributory to these disturbing rates, underlining the need for its rational use.

A recent study from the USA on colistin resistance in carbapenem-resistant *K. pneumoniae* bacteraemia reported a rate of 13% (Rojas et al., 2017). A similar study from Italy found a high rate of colistin resistance (36.1%) (Capone et al., 2013).

Colistin resistance in carbapenem-resistant *P. aeruginosa* blood isolates is particularly challenging since most isolates in the present study were uniformly resistant to all known antipseudomonal agents (data not shown). This is in contrast to the results of a recent review of 37 patients from the USA treated for bacteraemia due to carbapenem-resistant *P. aeruginosa*, where therapeutic options were available (Buehrle et al., 2017).

Several previous studies have reported higher mortality for patients with carbapenem-resistant bacteraemia compared to patients with carbapenem-susceptible blood isolates (Cai et al., 2017; Kohler et al., 2017; Falagas et al., 2014). Similarly, the present study found that patients with carbapenem-resistant bacteraemia had higher mortality rates (nearly three times higher) when compared to patients with carbapenem-sensitive bacteraemia, with 30-day mortality rates of 62.1% and 21.9%, respectively. A recent study from India on the mortality outcome of carbapenem-resistant *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii* bloodstream infections reported 30-day all-cause mortality rates of 50%, 40%, and 60%, respectively (Exner, 2017). The corresponding 30-day all-cause mortality rates in the present study were 80.5%, 63.8%, and 54.7%, respectively. The reasons for the higher rates in this cohort of patients with carbapenem-resistant *P. aeruginosa* and *K. pneumoniae* are unclear. It is believed that this may be due to differences in patient population and underlying comorbidities, which were not examined in the present study. Other studies, however, have reported similar rates (Lee et al., 2017; Daikos et al., 2014; Liu et al., 2016). Of even greater concern is the finding in a subset of patients with carbapenem-resistant and colistin-resistant bacteraemia: in this cohort, albeit small, the 30-day all-cause mortality was exceptionally high at 88.2%. In other studies, this excess in mortality was attributed to the limited number of effective antimicrobial options available to treat such serious infections (Rojas et al., 2017; Giacobbe et al., 2015).

Another interesting finding was that patients with healthcare-associated bacteraemia had higher 30-day all-cause mortality when compared to patients with community-acquired bacteraemia, irrespective of carbapenem susceptibility or the type of isolate. Additionally, patients with healthcare-associated carbapenem-resistant bacteraemia had the worst outcomes and this holds true for all three isolates. The exact explanation for this difference is unclear. This mortality trend is consistent with those reported in other studies albeit not addressing carbapenem resistance (Hattemer et al., 2013).

This study had some limitations, in addition to those inherent in its retrospective nature. First, the prevalence of carbapenem resistance was studied in selected isolates from blood cultures only. Despite this limitation, it is believed that understanding the burden of carbapenem resistance in patients with gram-negative bacteraemia has a more significant impact. Second, the non-molecular laboratory methods used to detect and confirm carbapenem resistance in this cohort may have overestimated their prevalence. However, similar trends were observed after the introduction of the Xpert Carba-R in the laboratory after 2017. Notably NDM-1 and OXA are the most prevalent carbapenemases among these three isolates (unpublished data, 2018). Studying the prevalence of carbapenem resistance using molecular methods in this setting is being proposed. Third, the categorization of carbapenem-resistant bacteraemia into healthcare-associated versus community-origin was solely based on the available clinical records, where prior hospitalizations may have been overlooked, potentially resulting in erroneous classification of a subset of patients. Fourth, despite having a well-defined 30-day all-cause mortality end-point, factors known to affect outcomes such as timing and appropriateness of empirical antibiotics, source of bacteraemia and its control, and the severity of infection were not studied. Despite these limitations, this study included a large number of patients, had a clearly defined study population, examined colistin resistance in carbapenem-resistant isolates, and assessed mortality in these unwelcome dual resistance cases.

In conclusion, the study data demonstrate an alarming increase in the prevalence of carbapenem resistance in *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* blood culture isolates, with a large proportion of *K. pneumoniae* demonstrating additional resistance to colistin and posing a significant and unprecedented therapeutic challenge with an unacceptably higher mortality. It is believed that the findings of this study will stimulate further research and will highlight the urgent need for implementing antibiotic stewardship, developing carbapenem and colistin prescribing restriction policies, and realizing the critical need for targeted infection prevention and control measures and formulating relevant national policies.

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Ethical approval

This study was approved by the institutional research ethics committee.

Conflict of interest

The authors declare that they have no conflict of interest.

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