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ORIGINAL ARTICLE

Co-colonization with carbapenem-resistant Klebsiella pneumoniae and Acinetobacter baumannii in intensive care unit patients

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Abstract

Objectives: This investigation was conducted to study co-colonization by carbapenem-resistant Klebsiella pneumoniae carbapenemase-producing K. pneumoniae (KPC-Kp) and Acinetobacter baumannii (CRAB) in intensive care unit (ICU) patients in Palermo, Sicily, a geographic area where both organisms are endemic in the healthcare setting. Risk factors at admission and during ICU stay and outcomes were also evaluated. *Methods:* All patients colonized by KPC-Kp, or CRAB, or both in 2 ICUs of a large general hospital during the period October 2011–March 2012 were enrolled. Demographics and clinical data were collected. Resistance determinants and clonality of the 2 organisms were characterized by molecular methods. *Results:* Seventy-five of 391 patients (19.2%) proved to be colonized by KPC-Kp, CRAB, or both: 30 (40%) were co-colonized and 44 (58.7%) were mono-colonized by CRAB and 1 by KPC-Kp. Younger age, major trauma, and length of stay were positively associated with co-colonization. However, no significant differences were detected between co-colonized and non co-colonized patients in infection and ICU mortality rates and length of stay after the first isolation. Both organisms proved to be circulating in a clonal way. *Conclusions:* In our setting, co-colonization by KPC-Kp and CRAB disproportionately affected young trauma patients with those with a prolonged ICU stay.

Keywords: *Carbapenem resistance, co-colonization, intensive care unit, risk factors*

Introduction

Klebsiella pneumoniae carbapenemase-producing K. pneumoniae (KPC-Kp) and carbapenem-resistant Acinetobacter baumannii (CRAB) are the most challenging multidrug-resistant organisms in the healthcare setting [1,2]. Due to the unavailability of effective antimicrobial drugs, they are generally associated with serious outcomes and high case-fatality rates in critically ill patients [3]. Intensive care unit (ICU) patients are especially prone to colonization and infection by multidrug-resistant (MDR) bacterial strains because of their severe underlying conditions requiring the application of invasive devices and procedures, coupled with selective pressure due to the extensive use of broad-spectrum antibiotics [3,4].

Little is known about the prevalence, epidemiological characteristics, and clinical outcomes of ICU patients co-colonized by KPC-Kp and CRAB. Co-colonization with carbapenem-resistant Enterobacteriaceae (CRE) and a non-fermenter, such as A. baumannii or Pseudomonas aeruginosa, was described as an independent predictor of mortality at the Detroit Medical Center [5]. Carbapenem-resistant K. pneumoniae was the predominant species of CRE [5]. In a subsequent study, 40% of 86 patients proved to be co-colonized with carbapenem-resistant A. baumannii or P. aeruginosa [6]. Co-colonized

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patients were severely ill, older, and more likely than the non co-colonized patients to have had a stay in an ICU, long-term care facility, and/or long-term acute care facility and to have undergone surgery [6].

The aim of the present study was to describe the epidemiology of patients colonized with CRAB and/or KPC-Kp in 2 ICUs of an acute general hospital of Palermo, Italy, during the 6-month period October 2011–March 2012. Both organisms have been endemic for some years in the geographic area of interest and in the 2 ICUs under study [7,8]. Patients co-colonized by CRAB and KPC-Kp were compared with those who were non co-colonized for their risk factors at admission and during ICU stay and their clinical outcomes.

Materials and methods

Setting

The ARNAS general hospital "Civico, Di Cristina e Benfratelli" in Palermo, Italy, is the largest acute general hospital in Sicily. During the study period it had a capacity of 901 beds in total, including 24 beds in 2 general ICUs, identified as ICUs I and II. Each unit has dedicated nursing and medical staff. At the time of the outbreak, the infection control policy in the ICUs did not include routine surveillance cultures or screening of high-risk patients on admission. Contact isolation precautions were applied for proven cases of infection with KPC-Kp or CRAB. Isolation and cohorting could not be performed because of structural or logistic issues. A hand-hygiene compliance monitoring system was not in place. Training courses involving the staff of both ICUs, highlighting the role and procedures of hand hygiene and contact precautions, were periodically held by the medical directorate of the hospital.

Patients

The study cohort included all ICU patients who had at least 1 culture positive for KPC-Kp and/or CRAB from any anatomic site between 1 October 2011 and 31 March 2012.

Data recovered from the patient charts comprised: demographic information, admission source, comorbidities at admission, reason for admission, severity of illness index, antimicrobial therapy ≤ 30 days before isolation of a carbapenem-resistant organism, clinical syndrome, and outcome (general mortality and length of ICU stay after the first isolation).

Co-colonization was defined as the isolation of KPC-Kp and CRAB from the same patient during their entire ICU stay.

The diagnosis of infection was made in accordance with the criteria of the US Centers for Disease Control and Prevention [9].

Microbiology and molecular epidemiology

Bacterial identification and antibiotic susceptibility testing were performed at the Laboratory of Microbiology of ARNAS General Hospital "Civico, di Cristina e Benfratelli" using the VITEK-2 automated system (bioMérieux, Marcy l'Etoile, France). The Etest (bioMérieux) was used to determine susceptibility to colistin. Susceptibility and resistance categories were assigned in accordance with the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [10]. Phenotypic confirmation of the presence of carbapenemases or overexpression of AmpC in combination with porin loss was performed using a commercial synergy test (Rosco Diagnostica, Taastrup, Denmark). This test was carried out on putative carbapenemase-producing K. pneumoniae isolates based upon their screening cut-off values for meropenem, following the recommended methods for the detection of carbapenemases in Enterobacteriaceae [10].

Carbapenem-resistant K. pneumoniae isolates were examined for the presence of KPC enzymes by polymerase chain reaction (PCR) and sequencing [8]. CRAB isolates were submitted to multiplex PCR with primers that anneal to bla_{OXA-51}, bla_{OXA-23}, bla_{OXA-24}, and bla_{OXA-58} carbapenemases and the metallo-β-lactamases bla_{IMP} and bla_{VIM}, as previously described [11]. Clonality of KPC-Kp and CRAB isolates was assessed by rep-PCR using an automated system (DiversiLab, bioMérieux). DNA fragment separation and detection were done using the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA) and results were analyzed and interpreted using the Kullback–Leibler method, as previously described [2].

Statistical analysis

The statistical analysis was performed using Epi Info (version 6.4; CDC, Atlanta, GA, USA) and Statplus software (AnalystSoft Inc., http://www.analystsoft.com).

The descriptive analysis was performed by calculating the means (standard deviation) and frequencies, and the significance of differences was assessed with the Chi-square test or Fisher's exact test, or by 1-way analysis of variance (ANOVA) test or Kruskal–Wallis, when appropriate, respectively. The associations between the variables under examination were evaluated using contingency tables. *p*-Values of

≤ 0.05 were considered significant. All *p*-values were 2-sided.

Results

A total of 75 patients were included in the study. They accounted for 19.2% of the 391 patients admitted to the 2 ICUs during the period under study. Thirty (40%) patients were co-colonized by KPC-Kp and CRAB, 44 (58.7%) were colonized by CRAB only, and 1 patient was colonized by KPC-Kp only. Patients were followed up for a median of 23 days (interquartile range (IQR) 13–42 days).

Fifty (66.7%) of the 75 patients had been hospitalized before their ICU admission. Twenty-nine (38.7%) patients had at least 1 comorbid condition. The most frequent reason for admission was respiratory failure (30 cases, 40%), followed by major trauma (18 cases, 24%).

Comparison of co-colonized and non co-colonized patients

Results of the bivariate analysis comparing the 30 co-colonized and the 45 non co-colonized patients based upon their risk factors for the acquisition of KPC-Kp and CRAB are showed in Table I. Younger age was positively associated with co-colonization, whereas cardiovascular comorbidity at admission was negatively associated (Table I). Of interest, major trauma was significantly, positively associated with the co-colonized status, whereas respiratory failure was negatively associated (Table I). We found no association between source of admission or exposure

Table I. Risk factors for the acquisition of carbapenem-resistant Klebsiella pneumoniae and Acinetobacter baumannii.

Parameter	Co-colonized ($n=30$)	Not co-colonized ($n=45$)	OR	95% CI	*p*-Value
Demographics					
Age, y, mean (SD)	53.6 (23.6)	66.2 (14.7)	–	–	0.005
Female sex, *n* (%)	7 (23.3)	15 (33.3)	1.64	0.57–4.69	0.18
Admission from, *n* (%)					
Emergency room	8 (26.7)	17 (37.8)	0.60	0.19–1.83	0.32
Medical unit	2 (6.7)	1 (2.22)	3.14	0.21–92.19	0.56
Surgical unit	17 (56.7)	20 (44.4)	0.92	0.36–2.38	0.86
Intensive care unit	3 (10)	7 (15.5)	0.60	0.11–2.95	0.49
Comorbidities at admission, *n* (%)					
Cardiovascular	9 (30.0)	27 (60.0)	0.29	0.11–0.76	0.006
Respiratory	8 (26.7)	14 (31.1)	0.80	0.29–2.25	0.35
Neurologic	6 (20.0)	8 (17.8)	1.15	0.36–3.75	0.40
Renal	5 (16.7)	7 (15.6)	1.09	0.31–3.80	0.45
Endocrine	4 (13.3)	11(24.4)	0.47	1.14–1.66	0.19
>2 comorbid conditions	4 (13.3)	10 (22.2)	0.54	0.15–1.91	0.18
Reason for admission, *n* (%)					
Major trauma	12 (40.0)	6 (12.0)	4.33	1.24–15.60	0.008
Respiratory failure	4 (13.3)	26 (57.8)	0.11	0.03–0.42	0.0001
Acute myocardial infarction	6 (20.0)	8 (17.8)	1.16	0.31–4.31	0.81
Surgical procedure	0	1 (2.2)	–	–	
Sepsis	1 (3.33)	3 (6.7)	0.48	0.02–5.67	0.53
SAPS II index score,[a] median (IQR)	38.5 (26.5–47.0)	37.0 (27.0–47.0)	–	–	0.65
Antibiotic therapy ≤ 30 days before CRAB isolation	27 (90.0)	40 (88.9)	1.12	0.25–5.10	0.45
Cephalosporins[b]	20 (69.0)	16 (38.1)	1.36	0.52–3.50	0.27
Quinolones[b]	8 (27.6)	8 (19.0)	1.62	0.53–4.97	0.21
Carbapenems[b]	8 (27.6)	7 (16.7)	1.35	0.43–4.26	0.31
Other beta-lactams[c]	6 (20.7)	4 (9.5)	0.96	0.25–3.76	0.48
Anti-Gram-positive therapy[d]	6 (20.7)	14 (31.1)	0.55	0.18–1.65	0.15
LOS from admission to first isolation of CRAB, days, median (IQR)	13.0 (8.0-23.0)	7.0 (4.5-11.5)	–	–	0.006
LOS from admission to first isolation of KPC-Kp, days, median (IQR)	16.5 (13.0-28.0)	–	–	–	–

OR, odds ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CRAB, carbapenem-resistant A. baumannii; LOS, length of stay; KPC-Kp, Klebsiella pneumoniae carbapenemase-producing K. pneumoniae.

[a]Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270:2957–63.

[b]Co-colonized $n=29$; non co-colonized $n=42$.

[c]beta-Lactam–lactamase inhibitor combinations.

[d]Glycopeptides, linezolid, daptomycin.

to antibiotics ≤30 days before CRAB isolation and co-colonization (Table I). The median length of stay (LOS) from admission to first isolation of CRAB was significantly shorter for the non co-colonized patients (co-colonized vs. non co-colonized, 13.0 days vs. 7.0 days, $p = 0.02$). Among the co-colonized patients, the median LOS from admission to first isolation of KPC-Kp was longer than the corresponding interval of time for CRAB (16.5 vs. 13.0 days).

In 15 out of the 30 co-colonized patients, KPC-Kp and CRAB were simultaneously detected in the same or different clinical samples, whereas in 12 cases CRAB was isolated 3–25 days before KPC-Kp. In 3 cases KPC-Kp isolation preceded CRAB by 13–71 days. There was an association between the simultaneous detection of both organisms, older age (simultaneous vs. sequential acquisition, 58.3 vs. 48.8 y, $p = 0.25$) and the presence of at least 2 comorbid conditions (simultaneous vs. sequential acquisition, 75.0% vs. 53.8%, $p = 0.18$). In contrast, a sequential colonization by CRAB followed by KPC-Kp was more frequent in major trauma patients (trauma vs. no trauma, 66.7% vs. 38.9%, $p = 0.08$).

Table II summarizes the clinical features and outcomes of the ICU patients under study. Only 11 of 75 patients (14.7%) had no signs or symptoms of infection, with no significant difference between co-colonized and non co-colonized patients. However, isolation of CRAB from blood or central venous catheter (CVC) was positively associated with the co-colonized status (OR 4.0, 95% CI 1.06–15.82, $p = 0.02$). Median LOS from first CRAB isolation to discharge was shorter, although not significantly, among the non co-colonized patients (co-colonized vs. non co-colonized, 25.0 days vs. 19.5 days, $p = 0.10$). The median LOS from the first isolation of KPC-Kp to discharge was shorter than that for CRAB (19.0 vs. 25.0 days).

The crude mortality was higher, although not significantly, within the group of non co-colonized vs. co-colonized patients (Table II).

Microbiology and molecular epidemiology findings

During the period under study, a total of 92 isolates of KPC-Kp and 254 of CRAB were identified from 75 patients. All isolates of KPC-Kp were resistant to imipenem and meropenem with minimum inhibitory concentrations (MICs) ranging from 4 to ≥16 mg/l. Forty-four KPC-Kp isolates from 13 different patients were also resistant to colistin with MICs ranging from 3 to 128 mg/l. Three isolates had MICs for gentamicin ≥8 mg/l. All isolates of A. baumannii were resistant to carbapenems with MICs ≥8 mg/l. MICs for colistin of CRAB isolates ranged between ≤0.5 μg/ml and 1 μg/ml.

Table II. Clinical syndrome and outcomes in co-colonized and non co-colonized patients by KPC-Kp and CRAB.

Parameter	Co-colonized ($n = 30$)	Not co-colonized ($n = 45$)	OR	95% CI	p-Value
Clinical syndrome, *n* (%)					
Colonization only	3 (10)	8 (17.8)	0.51	0.12–2.12	0.19
Central line-associated bloodstream infection	9 (30)	12 (26.7)	1.18	0.42–3.28	0.38
Pneumonia	22 (73.3)	30 (66.7)	1.37	0.49–3.81	0.28
Urinary tract infection	7 (23.3)	10 (22.2)	1.06	0.35–3.20	0.45
Microbiology					
Anatomic site of CRAB culture, *n* (%)					
Respiratory	25 (83.3)	39 (86.7)	0.77	0.18–3.32	0.69
Urine	7 (23.3)	8 (17.8)	1.41	0.39–5.05	0.56
Blood/central venous catheter	10 (33.3)	5 (11.1)	4.00	1.06–15.82	0.02
Other	5 (16.7)	8 (17.8)	0.93	0.23–3.63	0.90
Anatomic site of KPC-Kp culture, *n* (%)					
Respiratory	19 (63.3)				
Urine	5 (16.7)				
Blood/central venous catheter	12 (40.0)				
Other	5 (16.7)	–	–	–	–
LOS from first CRAB isolation to discharge after excluding the dead, days, median (IQR)	25.0 (14.0–50.0)	19.5 (10.0–28.0)			0.10
LOS from first KPC-Kp isolation to discharge after excluding the dead, days, median (IQR)	18.5 (7–32)	–	–	–	–
Crude mortality, *n* (%)[a]	13 (48.1)	28 (65.1)	2.01	0.75–5.36	0.09

KPC-Kp, Klebsiella pneumoniae carbapenemase-producing K. pneumoniae; CRAB, carbapenem-resistant A. baumannii; OR, odds ratio; CI, confidence interval; LOS, length of stay; IQR, interquartile range.
IQR, interquartile range; LOS = length of stay (days)
[a]Co-colonized $n = 27$; non co-colonized $n = 43$.

The first isolates of KPC-Kp and CRAB from each patient were submitted to genotyping by rep-PCR. Genotyping of KPC-Kp isolates showed that they were ≥95% similar. Phenotypic screening for the presence of carbapenemases or AmpC/porin loss suggested KPC production. PCR analysis and nucleotide sequencing revealed that all isolates carried the $bla_{\text{KPC-3}}$ sequence.

By adopting a similarity coefficient of ≥95% as the threshold, all CRAB isolates clustered into a large group. Moreover all CRAB isolates had the $bla_{\text{OXA-23}}$ gene. No MBL (IMP and VIM) gene sequence was detected.

Discussion

Co-colonization with CRE and carbapenem-resistant Gram-negative non-fermenters has recently been reported as a threatening development with regard to MDR organisms in healthcare settings [5,6]. Our findings show some remarkable differences when compared to those reports. In our study, co-colonization by KPC-Kp and CRAB was a frequent event, involving 40% of patients colonized by a carbapenem-resistant organism. Co-colonized patients have been described to be older and to have more severe underlying chronic diseases than non co-colonized ones [5,6]. In contrast, in our setting co-colonized patients were most frequently younger patients. Major trauma patients in particular, were especially affected. Moreover, in contrast to the results of Marchaim et al. [6], who reported recent antimicrobial exposure to antibiotics, in particular those with Gram-positive activity, as an independent predictor of co-colonization by CRE and carbapenem-resistant non-fermenter Gram-negatives, the previous receipt of antibiotics was not significantly associated with this condition in our study. Previous exposure to antibiotics has been reported to be a risk factor for the acquisition of carbapenem-resistant K. pneumoniae and A. baumannii [12,13]. The lack of statistically significant differences could be the consequence of the high prevalence of antibiotic therapy in both groups of patients and the small number of patients in each of the strata obtained, except for cephalosporins, when comparing by class of antibacterial drugs.

In our study co-colonization with KPC-Kp and CRAB was not found to be significantly associated with invasive infections. This somewhat unexpected finding could be attributable to the low number of patients under investigation. Concurrently, the large proportion of younger, major trauma patients, with less prevalent comorbid conditions and more protracted ICU stays, could have diluted the association of co-colonization with worse clinical outcomes, including invasive infection and crude mortality. It is significant in this respect that non co-colonized patients acquired CRAB at an earlier stage of hospitalization than did co-colonized subjects, and had significantly shorter ICU stays.

In our setting, CRAB was by far the most prevalent carbapenem-resistant organism and was generally acquired simultaneously with or earlier than KPC-Kp. Recently, Arvaniti et al. [13] demonstrated the prominent role of colonization pressure in the acquisition of multi-resistant A. baumannii in the ICU. In our hyperendemic epidemiological context, it is very likely that a high level of colonization pressure, along with lapses in infection control measures and structural–logistic obstacles, have driven the dissemination of CRAB.

The results of our study confirm previously reported characteristics of co-colonization that require careful consideration when implementing strategies aimed at limiting the spread of MDR organisms. Current guidelines for the control of transmission of MDR organisms recommend active surveillance cultures or point-prevalence surveys in some high-risk settings and, in the event of CRE, aggressive infection control interventions [14]. Indeed, it has been demonstrated that comprehensive infection control programs are effective in reducing the number of patients carrying KPC-Kp [14]. In contrast, the persistence of CRAB after these interventions suggests that additional factors could be involved in the control of transmission, such as airborne spread. So, screening of respiratory colonization and possibly respiratory isolation may be needed to control CRAB [15]. It has also been hypothesized that patients who are colonized by multiple MDR species could be 'superspreaders', being more effective sources of MDR organisms compared to mono-colonized patients, and thus require more stringent infection control interventions [16].

This study presents some inherent limitations. The peculiar case mix of patients included in our analysis makes it difficult to generalize our results. Moreover, the relatively low numbers did not allow any solid inferences to be drawn concerning the impact of co-colonization on the clinical outcomes of severity and crude mortality. Cross-transmission in a high prevalence setting could have contributed to diminish the differences between the 2 groups of patients. Finally, no information was available on post-discharge outcomes, such as admission to a non-hospital setting or hospital readmissions and the consequences on functional status. Further studies with larger cohorts will be required to determine the risk factors and the effect of co-colonization by KPC-Kp and CRAB in endemic settings.

However, our findings once again confirm that the spread of carbapenem-resistant organisms in ICUs in our geographic area has reached dramatic proportions. Because of commonality of risk factors, KPC-Kp and CRAB co-colonization disproportionately affected young trauma patients, who had more prolonged ICU stays. Later acquisition of colonization compared to the non co-colonized patients indicates a wide window of opportunity to minimize cross-transmission.

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