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SHORT COMMUNICATION

Early KPC-Producing *Klebsiella pneumoniae* Bacteremia among Intensive Care Unit Patients Non-Colonized upon Admission

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Abstract

Among 140 patients colonized by KPC-producing *Klebsiella pneumoniae* (KPC-Kp) between fourth and seventh day of Intensive Care Unit stay, 24 developed bacteraemia immediately after colonization. Colistin-resistance of the colonizing isolate was the factor significantly associated with early KPC-Kp bacteraemia ($P < 0.001$; OR 6.6, 95% CI 2.4–18.4), a worrisome finding since infections by colistin-resistant isolates is associated with increased mortality due to limited remaining therapeutic options.

Key words: bacteremia, carbapenemase, colistin-resistance, critically ill patients

Carbapenemase-producing *Klebsiella pneumoniae*, and especially KPC-producing (KPC-Kp) constitutes an important worldwide issue since it is endemic in many countries and provokes serious infections associated with increased mortality especially among patients hospitalized in Intensive Care Units (ICUs) (Falcone *et al*., 2016). Many patients develop primary bacteremia probably due to bacterial translocation, suggesting that enteric colonization is an important first step for the induction of infection (Schechner *et al*., 2013; Giannella *et al*., 2014; Giacobbe *et al*., 2015). It is reported that 16.5% (7.6–44.4%) of colonized patients develop a bloodstream infection (BSI), which renders the surveillance with rectal swabs imperative for every infection control program (Borer *et al*., 2012; Tischendorf *et al*., 2016).

The aim of the present study was to determine the risk factors for early KPC-Kp BSI (during the first nine days of ICU stay) among non-colonized patients upon admission in two Greek ICUs.

This retrospective study was performed in the ICUs of the University General Hospital of Patras, Greece (13 beds) during a 28-month period (November 2009-February 2012) and of the General Hospital of Patras "Agios Andreas" (6 beds) during a 16-month period (November 2009-February 2011). Epidemiologic data were collected from patients' chart reviews. The study was carried out under the Hospital Surveillance Programme for multi-drug resistant infections of hospitalized patients, and was approved by the University Hospital Ethics Committee (HEC No: 571).

According to CDC definition, BSI was defined as presence of at least one positive blood culture for *K. pneumoniae* and clinical symptoms consistent with bacteremia. Rectal samples were obtained upon ICU admission and afterwards at days 4, 7 and once weekly until discharge. Only patients that had an ICU stay of at least seven days were included. Swabs were inoculated on a selective chromogenic agar (CHROMagar™ KPC, Paris, France) and incubated at 37°C for 24 hours. Representative colonies were identified as *K. pneumoniae* by standard methods and Vitek 2 Advanced Expert System (bioMerieux, Marci l'Etoile, France).

Susceptibility to carbapenems (imipenem, meropenem, ertapenem), colistin and tigecycline was determined by Etest (bioMerieux) whereas, susceptibility to

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Table I
Univariate and multivariate analyses of risk factors for KPC-producing *K. pneumoniae* (KPC-Kp) bloodstream infection (BSI) immediately after early enteric colonization during Intensive Care Unit (ICU) hospitalization.

Characteristics	Univariate analysis			Multivariate analysis	
	KPC-Kp colonization (n = 116)	KPC-Kp infection (n = 24)	*P*	*P*	OR (95% CI)
Demographics					
Age (years)	57.6 ± 18.4	54.8 ± 17.8	0.500		
Male gender	83 (71.6%)	16 (66.7%)	0.629		
Chronic diseases (number)	0.9 ± 1.0	0.8 ± 1.0	0.929		
Diabetes Mellitus	15 (12.9%)	1 (4.2%)	0.307		
Chronic Obstructive Pulmonary Disease	16 (13.8%)	1 (4.2%)	0.306		
Chronic Heart Failure	13 (11.2%)	1 (4.2%)	0.464		
Chronic Renal Failure	4 (3.4%)	2 (8.3%)	0.273		
Malignancy	11 (9.5%)	3 (12.5%)	0.708		
Cortisone use	8 (6.9%)	1 (4.2%)	1.000		
Obesity	30 (25.9%)	8 (33.3%)	0.458		
Admission data					
APACHE II Score upon admission	17.1 ± 7.0	16.0 ± 8.1	0.499		
SAPS II Score upon admission	39.2 ± 13.4	34.8 ± 9.5	0.156		
SOFA Score upon admission	8.1 ± 3.4	8.9 ± 3.4	0.296		
Respiratory insufficiency	25 (21.6%)	6 (25.0%)	1.000		
Prior emergency surgery	46 (39.7%)	10 (41.7%)	1.000		
Prior abdominal surgery	32 (27.6%)	6 (25.0%)	1.000		
Antibiotics administered					
Carbapenems	101 (87.1%)	23 (95.8%)	0.307		
Quinolones	19 (16.4%)	4 (16.7%)	1.000		
3rd- and 4th-generation cephalosporins	16 (13.8%)	2 (8.3%)	0.738		
Piperacillin/tazobactam	30 (25.9%)	10 (41.7%)	0.139		
Colistin	29 (25.0%)	10 (41.7%)	0.132		
Aminoglycosides	30 (25.9%)	10 (41.7%)	0.139		
Glycopeptides	95 (81.9%)	21 (87.5%)	0.766		
Metronidazole	17 (14.7%)	4 (16.7%)	0.759		
Tigecycline	3 (2.6%)	0 (0.0%)	1.000		
Linezolid	19 (16.4%)	3 (12.5%)	0.766		
Mean antibiotic use per day	2.6 ± 1.0	2.6 ± 0.6	0.324		
Hospitalization data					
Mechanical ventilation	115 (99.1%)	24 (100%)	1.000		
Tracheostomy	49 (42.2%)	16 (66.7%)	0.042		
Number of catheters[a]	1.1 ± 1.3	1.4 ± 1.4	0.208		
Abdominal catheter and/or colostomy	27 (23.3%)	6 (25.0%)	0.798		
Dialysis	12 (10.3%)	5 (20.8%)	0.172		
Cortisone administration	58 (50.0%)	16 (66.7%)	0.179		
Parenteral nutrition	49 (42.2%)	14 (54.2%)	0.367		
Enteral nutrition	74 (63.8%)	16 (66.7%)	1.000		
Resistance of colonizing isolate					
Imipenem resistance	56 (48.3%)	18 (75.0%)	0.024		
Gentamicin resistance	36 (31.0%)	14 (58.3%)	0.018		
Colistin resistance	22 (19.0%)	14 (58.3%)	< 0.001	< 0.001	6.6 (2.4–18.4)
Tigecycline resistance	18 (15.5%)	9 (37.5%)	0.021		

Data are number (%) of patients or mean ±standard deviation
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation I; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; [a] All patients after ICU admission were intubated, mechanically ventilated and were continuously monitored with a central venous catheter, an arterial catheter and a urinary catheter. Number of catheters does not include the aforementioned catheters.

other antimicrobials (amoxicillin/clavulanic acid, piperacillin, cefoxitin, ceftriaxone, aztreonam, ciprofloxacin, co-trimoxazole, amikacin, gentamicin) was determined by the disk diffusion method. Results were interpreted according to EUCAST guidelines (EUCAST, 2016). Presence of bla_{KPC} gene in all *K. pneumoniae* strains was confirmed by PCR (Queenan and Bush, 2007)

Statistical analysis was performed with SPSS version 22.0 (SPSS, Chicago, IL) software. Categorical variables were analyzed by using the Fisher exact test or chi^2 and continuous variables with Mann-Whitney U test, as appropriate. Backward stepwise multiple logistic regression analysis used all those variables from the univariate analysis with a $P<0.1$. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association. All statistic tests were 2-tailed and $P<0.05$ was considered statistically significant.

From 349 patients that had an ICU stay of at least seven days in both ICUs, 304 were not colonized by KPC-Kp upon admission. Among them, 140 patients (46.1%) were colonized in day seven and they were included in the analysis. No patient was colonized in fourth day. In total 58 patients (16.6%) developed KPC-Kp BSI within an average of 19.3 days, from which 24 (41.4%) within nine days of ICU stay (two days after colonization). Table I shows the univariate and multivariate analyses of factors that differed among patients that developed a KPC-Kp BSI until day nine of ICU stay and those that did not. Multivariate analysis revealed that colistin-resistance of the colonizing isolate was significantly associated with early KPC-Kp BSI.

A high percentage of patients admitted in the ICU (46.1%) were colonized during their first seven days of their stay, while 17.1% among them developed a BSI within two days from enteric colonization. In contrast, in previous studies (Schechner *et al*., 2013; Giannella *et al*., 2014), colonization preceded infection by 11 (range 3–27) and 19 days (range 6–28), far later than in our study (8 days; range 1–25).

The only independent factor associated with the occurrence of bacteremia was the resistance of colonizing isolate to colistin, since among 36 colistin-resistant KPC-Kp colonizing isolates, 14 (38.9%) resulted in immediate bacteremia, while no difference in colistin administration was observed among infected and colonized patients (25.9% vs 41.7%; *P* 0.132). This finding suggests that not all KPC-Kp isolates share the same virulence capacity, consistent with results of previous studies (Diago-Navarro *et al*., 2014; Chiang *et al*., 2016). The capacity of colistin-resistant isolates to induce infection is a worrisome finding since BSI from such isolates is associated with increased mortality due to limited remaining therapeutic options (Giacobbe *et al*., 2015, Falcone *et al*., 2016). As previously shown, colonization by colistin-resistant isolate was a prerequisite to an infection by such isolate (Giacobbe *et al*., 2015).

Chronic diseases, invasive procedures, severity of disease and antibiotic administration were commonly identified as risk factors for infections by carbapenemase-producing *K. pneumoniae* (Borer *et al*., 2012; Schechner *et al*., 2013; Giannella *et al*., 2014; Giacobbe *et al*., 2015, Falcone *et al*., 2016). In contrast to previous studies, none of aforementioned factors differed between colonized and infected patients in the present study, suggesting that induction of BSI by translocation may be mostly influenced by bacteria's than patients' characteristics.

The present study has limitations; it was conducted in two Greek ICUs with high colonization rates and results might not be generalized for other institutions. Another limitation is its retrospective nature and the small number of patients included.

To conclude, a high percentage of ICU patients developed bacteremia by KPC-Kp within two days from colonization, a finding more common for colistin-resistant isolates.

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