Letter to the Editor

Risk factors for carbapenem resistant *Klebsiella pneumoniae* rectal colonization in pediatric units

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Klebsiella pneumoniae is a Gram-negative, non-motile, facultative anaerobe belonging to the *Enterobacteriaceae* family. Carbapenem resistant *K. pneumoniae* (CRKP) has become increasingly problematic in recent years. CRKP has also emerged as a significant nosocomial pathogen in the pediatric population [1]. Due to the growing prevalence and therapeutic challenges of this bacterium, we aimed at identifying the risk factors for patient rectal colonization with CRKP in pediatric units of Erciyes University Hospital, located in Kayseri, Turkey.

The study

This study was conducted in the 1300-bed tertiary care hospital of Erciyes University, between June 2012 and December 2012. The Pediatric hospital is located into a separate building with a 205–bed capacity. Patients under 16 years of age hospitalized in the pediatric units were enrolled. A case-control study was conducted to identify risk factors for rectal colonization with CRKP. Patients were defined as cases if they had a rectal CRKP colonization. Colonization on admission was defined as CRKP carriage if documented within 48 hours of admission. Controls were defined as culture-negative patients during their hospitalization. If control patients became positive during their hospital stay, they were also included to case group. Risk factors for colonization were determined by reviewing patient files. Collected data included: demographic characteristics, birth weight, prematurity, primary diagnosis, diaper use, previous admission to another health-care institution, duration of hospitalization, co-morbidities, use of H2 receptor antagonists, and invasive procedures prior to colonization with CRKP (including tracheotomy, intubation, mechanical ventilation, endoscopic procedures, endovascular catheterization, surgery). Data were collected from case patients until positive cultures were obtained and for control patients until they were discharged or died.

CRKP colonization was detected by rectal swabs culture. Samples were cultured onto freshly prepared eosine-methylene blue agar plates including 2 mg/L ertapenem (Merck Sharp Dohme, Turkey) as described elsewhere [2]. For all bacteria isolated on ertapenem-EMB agar and identified as *K. pneumoniae* by using routine microbiological techniques, the E-test method (BioMerieux, Marcy l'Etoile, France) was used to confirm resistance to ertapenem [2]. Minimum inhibitory concentration (MIC) values were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) breakpoints [3].

Statistical analysis was performed using SPSS software version 15.0 (IBM, USA). The chi-square test was used for categorical variables. The Mann-Whitney U test was used to compare the differences between two groups. Univariate and multiple binary logistic regression analyses (model: backward Wald) were performed to analyze the effects of variables. The level of significance was set at $p < 0.05$ for all tests.

A total of 285 patients were prospectively scanned for CRKP colonization between June and December 2012. Of 285 patients, 4 (1.4%) were colonized on admission and thus excluded from the study. Of the remaining 281, 245 patients had been directly admitted to the hospital, and 36 had been transferred-from other health care institutions. Eighty-three patients 83 (29.5 %) became colonized with CRKP (case patients). Eighteen out of case patients were transfer patients. Median time for acquisition of colonization was 12 days (3-52) for the patients with a history of being transferred from another institution, whereas this period of time was 18.5 days (3-210) for the other case patients ($p = 0.02$).

The characteristics and the risk factors of children with and without CRKP colonization are shown in Table 1. By univariate analysis CRKP colonization was associated with a previous use of aminoglycosides and carbapenems, being transferred from another health care institution and total duration of the antibiotic use. Multiple binary logistic regression analysis revealed that previous use of carbapenem and being transferred from another health care institution were also significant risk factors for CRKP colonization. Of all colonized patients, 3 (3.4%) developed CRKP infection including bacteremia, urinary tract infection and soft tissue infection.

The rapid dissemination of CRKP was associated with a considerably increasing rate over the past few years in Turkey, alongside the growing global prevalence [4,5]. In Turkey, the first outbreak of CRKP isolates producing OXA-48 was reported in 2008 in Istanbul [6]. Then, in all strains described subsequently from our country, carbapenem resistance was mediated by OXA-48 [7-9]. Recently we reported the first NDM-1 producing CRKP isolates, expressed from 4.3% of isolates obtained from pediatric units. However, OXA-48 type carbapenemases are still the predominant mechanism of resistance (91.5%) in our institution [10]. This recent study has also shown that there were three main clones causing several outbreaks clustered in our pediatric units [10]. The open-plan layout of the pediatric units, with limited single rooms, excessive number of patients, high workload, inadequate staffing levels are the major limitations to colonization control among patients. Due to these reasons, we aimed to identify risk factors for colonization with CRKP in pediatric units.

Several risk factors for colonization have previously been identified, including prolonged length of stay in ICUs, malignancy, surgery and previous use of fluoroquinolones [1,11,12]. As previous use of carbapenems is the a well-known culprit of colonization and infection with CRKP, our results based on multivariate analysis were consistent with earlier studies, which found carbapenems as a risk factor [11,13]. Total duration of antibiotic treatment is also significantly correlated with the CRKP colonization. Application of strict rational antibiotic utilizations policies as well as conducting infection surveillance and control activities in pediatric units are valuable measures to prevent transmission of this organism.

Interfacility transfers, particularly from long-term care facilities have been held accountable for the spread of this pathogen [5]. Similarly, patients with a history of transfer from another institution were found to be a related risk factor for colonization in this study. Therefore, adoption of policies to take immediate essential precautions and to prevent the cross-transmission of the microorganism is crucial. Likewise, automatic alerts for colonized patients in every admission recorded by a tagging system would be beneficial. In case of a transfer between hospitals the infection status of patients with any potential antibiotic resistant microorganism should be reported or a disclosure document accompanying the patient should be sent, including the identity, date and the site of the organism detected.

Although patient transfer from another institution was defined as a risk factor in our study, only four patients (4.6%) were detected to be colonized at admission. However, median time for acquisition of colonization among the patients transferred from another facility was shorter than the other case patients. Therefore, this situation was thought to be related to the characteristics of these patients who were more likely to be colonized with resistant organisms such as: a more severe underlying disease, longer hospital stay, and longer duration of antibiotic utilization. Also, it is crucial to take into consideration that only one negative culture for CRKP is not enough for defining these patients as non-colonized. Consecutive negative cultures are required to remove the patient from the contact isolation precaution list.

Although previous studies comprised a mixed group of study populations, the current study was limited to patients in the pediatric age group. The risk of developing CRKP infection found to be 3.4% in this study, which has not been reported in this age group before. Besides, there were noteworthy limitations in this study, including lack of carbapenemase resistance encoding gene detection and also application of any additional infection control measures.

Table 1. Risk factors for rectal colonization with CRKP in pediatric units, comparison of case and control patients

Risk factors	Case patients (%) n: 83 (29.5%)	Control patients (%) n: 198 (70.5%)	P	Multiple analysis R (95% CI) / P
Male gender	49 (59)	112 (56.6)	0.792	
Median age in months (min-max)	1 (1-192)	1 (1-192)	0.597	
Age groups				
0-1 month	45 (54.2)	100 (50.5)		
1 month-3 year	25 (30.1)	67 (33.8)	0.820	
3 year-16 year	13 (15.7)	31 (15.7)		
ICU admission	45 (54.2)	94 (47.5)	0.360	
Transfer from another institution	18 (21.7)	19 (9.6)	0.008	2.460 (1.188-5.092) / 0.015
Low birth weight (0-1 months)	36 (66.7)	96 (76.2)	0.201	
Diaper use	79 (95.2)	177 (89.4)	0.167	
Specialized units - total				
Neonatal ICU	20 (24.1)	57 (28.8)		
Pediatric ICU	11 (13.3)	15 (7.6)		
Premature baby units	21 (25.3)	46 (23.2)		
Mature baby units	14 (16.9)	21 (10.6)	0.262	
Hematology/Oncology	6 (7.2)	13 (6.6)		
Infectious Disease	7 (8.4)	24 (12.1)		
Nursing unit	4 (4.8)	22 (11.1)		
Co morbidities - total				
Malignancy	4 (4.8)	10 (5.1)	1.000	
Immune-suppression	2 (2.4)	3 (1.5)	0.634	
Prematurity†	31 (37.3)	76 (38.4)	0.894	
Respiratory failure	35 (42.2)	69 (34.8)	0.279	
Neutropenia	2 (2.4)	8 (4.0)	0.728	
Use of corticosteroids	1 (1.2)	9 (4.5)	0.290	
Impairment of consciousness	4 (4.8)	4 (2.0)	0.241	
Use of H_2 receptor antagonists	7 (8.4)	30 (15.2)	0.175	
Invasive procedures				
Enteral nutrition	48 (57.8)	105 (53)	0.512	
Total parenteral nutrition	38 (45.8)	73 (36.9)	0.182	
CVC*	8 (9.6)	16 (8.1)	0.815	
PVC*	69 (83.1)	167 (84.3)	0.859	
Transfusion	16 (19.3)	35 (17.7)	0.865	
Operation	6 (7.2)	17 (8.6)	0.815	
Colostomy	0 (0.0)	3 (1.5)	0.558	
Urinary catheter	6 (7.2)	10 (5.1)	0.573	
Umbilical catheter	1 (1.2)	11 (5.6)	0.118	
Intubation	32 (38.6)	64 (32.3)	0.336	
Mechanical ventilation	31 (37.3)	65 (32.8)	0.492	
Tracheostomy	2 (2.4)	7 (3.5)	0.731	
NTD*	8 (9.6)	18 (9.1)	1.000	
OTD*	37 (44.6)	92 (46.5)	0.794	
Other invasive procedures	1 (1.2)	5 (2.5)	0.674	
Previous antibiotic use	68 (81.9)	156 (78.8)	0.627	
Aminoglycosides	44 (53)	77 (38.9)	0.035	
Beta lactams	34 (41)	74 (37.4)	0.593	
Glycopeptides	33 (39.8)	67 (33.8)	0.413	
Carbapenems	39 (47)	51 (25.8)	0.001	2.329 (1.346-4.029) / 0.003
Ciprofloxacin	6 (7.2)	23 (11.6)	0.294	
Cephalosporins	15 (18.1)	38 (19.2)	0.869	
Other antibiotics	5 (6.0)	13 (6.6)	1.000	
Total duration of antibiotics use (in days) (n = 224)**	16 (range 5-56)	11.5 (range 1-69)	0.013	

*CVC: Central venous catheter, PVC: peripheral venous catheter, NTD: Nasogastric tube drainage, OTD: Orogastric tube drainage, ¥ Low birth weight: birth weight less than 2500 g, † Infants born before 37 weeks of gestation,

** Analysis performed for 68 patients in case group and 156 patients in controls. The patients who did not use any antibiotics are excluded from univariate analysis, so the variable of "total duration of antibiotic use" is not included to multiple binary logistic regression analyses.

Conclusions

As carbapenem is a drug of the last resort for the bacterial infections difficult to treat, resistance to this group of antibiotics constitutes a challenge of complexity in the treatment of serious infections, particularly in the pediatric population, due to more limited antibiotic alternatives approved for children. Screening high-risk patients for CRKP colonization and restriction of the widespread use of carbapenems are mandatory components of infection control measures.

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