MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 219-224
DOI: 10.12659/MSM.892516

Received: 2014.09.17
Accepted: 2014.09.29
Published: 2015.01.17

Risk Factors of Carbapenem-Resistant *Klebsiella pneumoniae* Infection: A Serious Threat in ICUs

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Source of support: Departmental sources

Background: Nosocomial infections caused by Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) are increasing. Our aim in this study was to investigate the risk factors of CRKP infections.

Material/Methods: A retrospective cohort study was performed between 1 January and 31 December 2012 in ICU patients. Data was taken from the hospital infection control database for CRKP. The clinical samples collected from the patients were tested by an automatized system and disk diffusion. SPSS software v11.5 was used for statistical analysis.

Results: Totally, 105 *Klebsiella pneumoniae* isolates were found in 2012 and the carbapenem resistance rate was 48%. The first episode of infection was taken into risk factor analysis. Of the 98 patients, 61 (62.2%) were male and the mean and median ages were 30.4±29.8 and 25 (0–93). The length of stay was longer in the resistant group (p=0.026). Mortality was 48% in the whole group and similar between groups (p=0.533). There was a relationship between meropenem and third-generation cephalosporin use and resistance (OR 3.244 (1.193–8.819) and OR: 3.590 (1.056–12.209). The other risk factors in univariate analysis were: Immunosuppression OR: 2.186 (1.754–2.724), nasogastric catheter OR: 3.562 (1.317–9.634), peripheral arterial catheter OR: 2.545 (1.027–6.307), and being admitted to the neurosurgical unit OR: 4.324 (1.110–16.842).
The multivariate analysis showed use of third-generation cephalosporin OR: 4.699 (1.292–17.089), nasogastric catheter use OR: 3.983 (1.356–11.698), and being admitted to neurosurgical ICU OR: 4.603 (1.084–19.555) as independent risk factors.

Conclusions: Restriction of third-generation cephalosporin and carbapenem use and invasive procedures, along with infection control precautions and disinfection policies, may be effective in reducing the carbapenem resistance in ICUs.

MeSH Keywords: Carbapenems • Drug Resistance, Microbial • *Klebsiella pneumoniae*

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/892516

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Backgroud

Nosocomial infections such as pneumonia and bloodstream infections caused by *Klebsiella pneumoniae* and other gram-negative organisms are increasing [1]. Besides increasing incidence, resistance became an important problem. Approximately 10% of hospitalizations are complicated by a healthcare-associated infection, and up to 75% of these are due to organisms resistant to first-line antimicrobial therapy [2]. In recent years, Gram-negative microorganisms, particularly carbapenem-resistant *K. pneumoniae* (CRKP), has become a major threat for hospitals worldwide, with high mortality and morbidity rates [3–5].

Several studies have investigated the risk factors of CRKP acquisition [6–11]. Recent reports point to risk factors such as antibiotic use, ventilator use, and admission to the ICU. We performed a retrospective cohort study to evaluate the risk factors of infections caused by CRKP in hospitalized patients in our hospital to better understand how to decrease the resistance rates.

Material and Methods

An observational retrospective cohort study was performed in the ICUs of a 1200-bed university teaching hospital in Adana, Turkey. Data were extracted from the infection control committee surveillance database.

All of the patients diagnosed with nosocomial infection with *Klebsiella pneumoniae* in the culture were taken into the study, between 1 January 2012 and 31 December 2012. If there were multiple episodes of *K. pneumoniae* infection in a patient, only the first one was included in the risk factors analysis.

Identification and susceptibility testing was performed by an automated broth microdilution method (bioMerieux, Vitek II). CRKP was defined by MIC levels ≥ 4 mg/L. Confirmation for carbapenem resistance was made by disk diffusion method. All isolates with intermediate susceptibility or resistance to carbapenem were considered as resistant. The Clinical and Laboratory Standards Institute (CLSI) document M100-S22 (January 2012) was used for interpretation of antimicrobial susceptibility testing.

Active surveillance was performed on a daily bases by infection control nurses and doctors using Centers for Disease Control and Prevention (CDC) definitions in the ICUs [12].

Data were collected from medical records, including age, sex, length of hospital stay, hospital admission, site of infection, causative microorganism, the date of infection and isolation. Microbiological data included *in vitro* susceptibilities to several antibiotics, including carbapenems, tigecycline, and colistin. Risk factors analyzed included age, sex, co-morbidities, prior hospitalization, surgery, invasive procedures, central vascular catheterization, mechanical ventilation, tracheotomy, urinary catheterization, immunosuppression, administered treatments, previous exposure to antibiotics, and length of stay.

For continuous normally distributed variables, the 2-sample t-test was used for comparing the mean values. The Mann-Whitney U test was performed for non-normally distributed continuous variables to compare medians. The chi-square test or Fisher's exact test was used for categorical variables when appropriate. Mean values are reported in ±1 standard deviation. Median values are reported as median (minimum-maximum). Two-tailed significance was used in all tests. The association of independent variables is shown as OR with 95% confidence intervals (CI). A backward, conditional, stepwise, multivariable, logistic regression model was used for variables associated with CRKP infections with $P<0.05$.

Results

A total of 105 *Klebsiella pneumoniae* isolates were detected as pathogens and carbapenem resistance was 48% in 2012. The first of multiple infection episodes was included to the study (n=98). Of the patients, 61 (62.2%) were male and the mean and median ages were 30.4±29.8 and 25 (0-93). Age and length of stay according to carbapenem resistance is shown in Table 1. Length of stay was longer in the resistant group (p=0.026). Mortality was 48% in the whole group and 44.7% and 51% in the carbapenem resistant and susceptible groups, respectively (p=0.533).

Diagnoses of the patients according to carbapenem resistance is shown in Table 2 (p=0.051). The most frequent diagnoses were catheter-associated bloodstream infection (BSI) and urinary infections. Catheter-related urinary and soft-tissue infections tended to be more frequent in the resistant group.

The main risk factors are summarized in Table 3. Antibiotic use was 73.2% in the carbapenem-resistant group and 52.9% in the susceptible group (p=0.061). There was a relationship between meropenem use and resistance (OR: 3.244 95% CI 1.193–8.819, p=0.030). Meropenem use was 34% in the resistant group and 13.7% in the latter. Third-generation cephalosporin use was also different; 23.4% *vs.* 7.8% (OR 3.590, 95% CI 1.056–12.209, p=0.048). The other risk factors found in univariate analysis were: immunosuppression was 8.5% *vs.* 0% in the resistant and susceptible groups (OR 2.186, 95% CI 1.754–2.724, p=0.049); nasogastric catheter use was 36.2% *vs.* 13.7%, in the resistant and susceptible groups (OR 3.562, 95% CI 1.317–9.634, p=0.018); peripheral arterial catheter use rates were 38.3% *vs.* 19.6% in the resistant and susceptible groups (OR 2.545, 95% CI 1.027–6.307, p=0.047).

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Table 1. Age and duration of stay according to carbapenem resistance.

	Carbapenem resistance	Mean	N	Std. Deviation	Median	Min	Max	P*
Age	Resistant	36.66	47	29.807	38.00	0	83	0.053
	Susceptible	24.67	51	27.552	8.00	0	86	
	Total	30.42	98	29.136	25.00	0	86	
Duration of stay	Resistant	37.30	47	50.838	19.00	1	280	**0.026**
	Susceptible	29.94	51	94.558	11.00	3	682	
	Total	33.47	98	76.474	14.00	1	682	

* Mann-Whitney U test.

Table 2. Hospital infection diagnoses in the patients with or without carbapenem resistance.

Diagnosis	Carbapenem resistance, n (%)				Total	
	R		S			
Laboratory diagnosed BSI	0	(0.0)	4	(100.0)	4	(100.0)
Catheter associated BSI	8	(44.4)	10	(55.6)	18	(100.0)
Catheter associated urinary system infection	11	(61.1)	7	(38.9)	18	(100.0)
Urinary system infection (NCR)	0	(0.0)	2	(100.0)	2	(100.0)
Ventilator associated pneumonia	22	(48.9)	23	(51.1)	45	(100.0)
Soft tissue infection	4	(100.0)	0	(0.0)	4	(100.0)
Pneumonia	2	(50.0)	2	(50.0)	4	(100.0)
Burn infection	0	(0.0)	3	(100.0)	3	(100.0)
Total	47	(49.0)	51	(52.0)	98	(100.0)

BSI – blood stream infection; R – resistant; S – susceptible; NCR – not catheter related), p=0.051, Pearson Chi-Square test.

The place of admittance was found as a risk factor (p=0.026). In the neurosurgical unit, carbapenem resistance was 76.9% and it was 43.5% at the rest of the hospital (OR 4.324, 95% CI 1.110–16.842, p=0.036). In the burn unit, carbapenem resistance was 11.1% and in the rest of the hospital it was 51.7%. (OR 0.117, 95% CI 0.014–0.973, p=0.032).

The multivariate analysis showed use of third-generation cephalosporin (OR 4.699, 95% CI 1.292–17.089, p=0. 019), nasogastric catheter use (OR 3.983,%95 CI, 1.356–11.698, p=0.012) and being admitted to the neurosurgical ICU (OR 4.603, 95% CI 1.084–19.555, p=0.039) as independent risk factors.

Discussion

The main independent risk factors found in our study were prior third-generation cephalosporin use, nasogastric catheter use, and being admitted to the neurosurgical ICU. Except one study that found fluoroquinolones were preventive, most studies have revealed different kinds of antibiotics as risk factors. It was the first time that nasogastric catheter use, and being admitted to the neurosurgical ICU were found as risk factors in a study. Admission to a neurosurgical unit as a risk factor can be explained by that unit's lack of infection control practices and preference of meropenem in this clinic because of the antibiotic's ability to penetrate the blood-brain barrier.

According to a case-control study by Kwak et al., risk factors for the acquisition of CRKP were previous use of carbapenem (adjusted odds ratio [AOR], 28.68; 95% confidence interval [CI] 9.08–90.55) and cephalosporin (AOR, 4.10; 95% CI 1.35–12.43), whereas previous use of fluoroquinolone was negatively associated with isolation of CRKP (AOR 0.26; 95% CI 0.07-0.97) [6]. In contrast, according to Ahn et al., along with carbapenem use (OR 4.56; 95% CI 1.44–14.46; P=.01), fluoroquinolone use (OR 2.81; 95% CI 1.14-6.99; P=.03) was also an independent risk factor [13]. In the study of Hussein et al., designed to identify

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Table 3. Summary of risk factors associated with carbapenem-resistant *K. pneumoniae* infection.

Risk factor	CR (N=47)		CS (N=51)		OR (95% CI)		p
Male sex	31	(66.0)	30	(58.8)	1.356	(0.596–3.084)	0.534
Adult	31	(66)	25	(49)	2.015	(0.891–4.556)	0.105
Median age	38	(0–83)	8	(0–86)			0.053
Median length of stay	19	(1–280)	11	(3–682)			**0.026***
Antibiotic use	34	(72.3)	27	(52.9)	2.325	(1.001–5.402)	0.061
Meropenem	16	(34)	7	(13.7)	3.244	(1.193–8.819)	**0.030***
3rd generation SF	11	(23.4)	4	(7.8)	3.590	(1.056–12.209)	**0.048***
Piperacillin tazobactam	13	(27.7)	6	(11.8)	2.868	(0.989–8.318)	0.072
Renal failure	3	(6.4)	1	(1.9)	3.409	(0.342–33.974)	0.347
Diabetes mellitus	0	(0)	1	(1.9)			1.000
Haematological malignancy	1	(1.9)	2	(3.9)	0.533	(0.047–6.074)	1.000
Enteral feeding	12		7	(13.7)	2.155	(0.767–6.051)	0.201
Endotracheal intubation	30	(25.5)	27	(52.9)	1.569	(0.698–3.527)	0.310
Immunosuppression	4	(8.5)	0	(0)	2.186	(1.754–2.724)	**0.049***
Mechanical ventilation	31	(66)	28	(54.9)	1.592	(0.703–3.604)	0.305
Nasogastric catheter	17	(36.2)	7	(13.7)	3.562	(1.317–9.634)	**0.018***
Peripheral arterial catheter	18	(38.3)	10	(19.6)	2.545	(1.027–6.307)	**0.047***
Central venous catheter	28	(59.6)	35	(68.6)	0.674	(0.294–1.545)	0.402
Urinary catheter	34	(72.3)	32	(62.8)	1.553	(0.661–3.651)	0.213
Admitting neurosurgical ICU	10	(21.3)	3	(5.9)	4.324	(1.110–16.842)	**0.036***

risk factors for carbapenem resistance among patients with healthcare-related (HCR), *K. pneumoniae* bacteriemia, prior use of macrolides, and antibiotic exposure for ≥14 days remained the only independent factors associated with CRKP bacteriemia [14]. Although we found carbapenem use associated with resistance in univariate analysis, it was not an independent risk factor in multivariate analysis. Kritsotakis et al. investigated the effects of treatment and duration of treatment with antibiotics to carbapenem resistance by adjusting for major non-antibiotic risk factors and controlling for confounding effects. This study highlights the major role of treatment and duration of treatment with β-lactam/β-lactamase inhibitor combinations and combinations of carbapenems with fluoroquinolones [15]. But because of matching the non-antibiotic risk factors, we cannot know if there were risk factors other than antibiotics. Liu et al. found that prior exposure to fourth-generation cephalosporins (OR 28.05; 95% CI 2.92–269.85; p=0.004), COPD (OR 21.38; 95% CI 2.95–154.92; p=0.002) and higher Pittsburgh bacteremia score (OR 1.35; 95% CI 1.10–1.66; p=0.004) were independent factors for ertapenem non-susceptible KP bacteremia [16]. We showed third-generation cephalosporins as a risk factor and disease severity indexes were not used in our study. In the study of Orsi et al., logistic regression analysis showed that carbapenems (OR 12.9; 95% CI 3.09–53.7; P<0.001), second-generation cephalosporins (11.8; 1.87–74.4; P < 0.01), endoscopy (5.59; 1.32–23.6; P<0.02), acute renal failure (5.32; 1.13–25.1; P=0.034), and third-generation cephalosporins (4.15; 1.09–15.8; P<0.01) were independent risk factors for acquisition of ertapenem-resistant KP [17].

Different mechanisms of resistances may have different risk factors. This may be why different risk factors were found in various studies. Most of the isolates from Turkey produce oxacillinase (OXA-48), and there have been recent, reports of New Delhi metallo-beta-lactamase (NDM-1). KPC production was only recently reported once in a letter to the editor [18–20]. Gasink et al. investigated the risk factors related to carbapenemase (KPC)-producing *K. pneumoniae*. In multivariable analysis, independent risk factors were severe illness (AOR 4.31; 95% CI 2.25–8.25), prior fluoroquinolone use (AOR 3.39;

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95% CI 1.50, 7.66), and prior extended-spectrum cephalosporin use (AOR 2.55; 95% CI 1.18, 5.52) [21]. In a study identifying risk factors for bloodstream infections (BSIs) caused by VIM-1-producing *K. pneumoniae* (VPKP), in multivariate analysis, cases were more likely to have been in an ICU (OR 6.78; 95% CI 2.69–17.06; P<0.001), have had prior exposure to >3 different classes of antibiotics (OR 12.6; 95% CI 2.17–73.27; P=0.01), and have had prior carbapenem use (OR 2.83; 95% CI 1.07–7.49; P=0.03) [22]. In another study investigating risk factors for nosocomial CRKP infections, ICU admission (OR 4.68, 95% CI 1.15–19.09, P=0.031), carbapenems (OR 12.69, 95% CI 2.09–77.10, P=0.006), and glycopeptides (OR 3.57, 95% CI 1.11–11.42, P=0.032) exposures were found as independent risk factors in multivariate analysis [23].

On the contrary, another study investigating independent risk factors for CRKP infection/ colonization found ICU admission (p=0.004), prior surgical procedure (p=0.036), and renal disease (p=0.037) as risk factors, and found no association between CRKP and prior antimicrobial exposure [24]. Again, in a matched case-control study, the length of central venous catheter use was the only independent risk factor in the multivariable analysis [11]. ICU admission and maybe the other invasive devices not being risk factors in our study, was linked to the design of the study being conducted in ICUs and most of the patients being exposed to these devices. In a prospective study, risk factors for development of carbapenem-resistant Gram-negative bacilli (CR-GNB) were investigated using 2 groups of case patients: the first group consisted of patients who acquired carbapenem-susceptible (CS) GNB and the second group included patients with CR-GNB, compared to a shared control group defined as patients without bacteremia and hospitalized in the ICU during the same period. Presence of ventilator-associated pneumonia (VAP) (OR 7.59, 95% CI 4.54–12.69, p<0.001) and additional intravascular devices (OR 3.69, 95% CI 2.20–6.20, p<0.001) were independently associated with CR-GNB. The duration of carbapenem use (OR 1.079, 95% CI 1.022-1.139, p=0.006) and colistin (OR 1.113, 95% CI 1.046–1.184, p=0.001) were independent risk factors for acquisition of CR-GNB. When the source of bacteremia was other than VAP, previous administration of carbapenems was the only factor related with the development of CR-GNB (OR 1.086, 95% CI 1.003–1.177, p=0.042) [25]. In another study investigating risk factors for the development of CRKP infection in patients who were colonized with CRKP, antibiotic therapy (OR 5.76, P≤.0001), amino-penicillin therapy (OR 7.753, P=0.004), being bedridden (OR 3.09, P=0.021), and nursing home residency (OR 3.09, P=0.013) were predictors of CRKP rectal colonization. Risk factors for CRKP infection in initially colonized positive patients were invasive procedure (OR 5.737, P=.021), diabetes mellitus (OR 4.362, P=.017), solid tumor (OR 3.422, P=0.025), tracheostomy (OR 4.978, P=.042), urinary catheter insertion (OR 4.696, P=0.037), and antipseudomonal penicillin (OR 23.09, P≤0.0001). They suggested that in patients colonized with CRKP, limiting anti-pseudomonal penicillin and carbapenem use and preventing infections by closely following compliance with infection control rules would be a preventive strategy for infection [26].

High levels of resistance in the hospital setting raise the question "Is there any carbapenem resistance in the community?" In a case-control study investigating risk factors associated with carbapenem-resistant Enterobacteriaceae (CRE) colonization among patients admitted to a hospital or long-term care facility, 905 cultures were performed on 679 patients. Independent predictors for CRE colonization included Charlson score greater than 3 (OR 4.85, 95% CI 1.64–14.41), immunosuppression (OR 3.92, 95% CI 1.08–1.28), presence of indwelling devices (OR 5.21, 95% CI 1.09–2.96), and prior antimicrobial exposures (OR 3.89, 95% CI 0.71–21.47). These results can be used to identify patients at increased risk for CRE colonization at admission and to target active surveillance programs in healthcare settings [27].

The relationship between carbapenem resistance and mortality is not definitive. In the study by Bhargava et al., mortality was not statistically different between carbapenem-resistant and susceptible strains (p=0.084), which was similar to our study [27]. In the study by Hussein et al., although mortality rates of CRKP patients were significantly higher than those of CSKP patients, mortality was not connected to carbapenem resistance. In multivariate analyses, bedridden status, chronic liver disease, Charlson comorbidity index ≥5, mechanical ventilation, and hemodialysis were still associated with mortality [14]. But in another study investigating the relationship between mortality and carbapenem resistance in elderly in-patients, UTI from carbapenem-resistant pathogens was an independent risk factor for 6-month mortality, irrespective of the etiologic agent, and further studies were needed to reveal the mechanisms underlying this association [28]. In the study of Liu et al., 14-day mortality of ertapenem-susceptible KP bacteremia was lower than ertapenem non-susceptible KP bacteremia (44.0% *vs.* 22.0%, p=0.049) but the overall in-hospital mortality rates for these two groups were 60.0% and 40.0%, respectively (p=0.102) [16]. Mortality was also higher for patients with carbapenem-resistant *K. pneumoniae* infections compared with susceptible ones in another study (50.0% *vs.* 25.7%) [11]. KPC-producing *K. pneumoniae* was also found to be independently associated with in-hospital mortality (AOR 3.60, 95% CI 1.87–6.91) [21]. In a study investigating attributable-mortality of CRKP; crude mortality rate was 71.9% *vs.* 21.9% in case and controls, respectively (P<0.001), and attributable mortality was 50% (95% CI 15.3–98.6%). The mortality risk ratio was 3.3 (95% CI 2.9–28.5) for CRKP bacteremia cases. The control patients were similar except for not having bacteriemia and different controls were thought to be the reason for higher mortality [29].

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In low-income countries where there is trouble in infection control practices and antibiotic use policies, high prevalence of ESBL and carbapenem resistance seems inevitable. This causes a vicious cycle of wide-spectrum antibiotic use and consequent resistance. It is very hard to restrict the use of carbapenems because they are only option for infections caused by ESBL-positive microorganisms. At present there is no solution to this dilemma. It seems that, especially in these settings, the only solution is compliance to infection control precautions such as hand-washing, sterilization, and disinfection, as well as standard and contact precautions.

The limitations of our study are that it was performed at a single medical center, thus the results may not be representative. In addition, because it was retrospective, disease severity indexes could not be used and further evaluation of mortality could not be done.

Conclusions

The high prevalence of CRKP and the risk factors revealed in our study highlight the urgent need to develop effective strategies. Prior use of antibiotics is the main risk factor found at the majority of the studies and relevant precautions should be a priority. Limiting use of certain antimicrobials, specifically fluoroquinolones, cephalosporins, and carbapenems, along with infection control practices, may be effective strategies.

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