

Emergence of carbapenem-resistant *Klebsiella* spp. infections in a Turkish university hospital: epidemiology and risk factors

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Abstract

Introduction: Risk factors for nosocomial carbapenem-resistant *Klebsiella* spp. (CRK) infections were analyzed in this study.

Methodology: The incidence, clinical characteristics, risk factors, antimicrobial susceptibility, and outcomes of CRK infections during a seven-year period (2004-2010) were retrospectively analyzed.

Results: A total of 720 patients were included in the study. Carbapenem resistance among *Klebsiella* spp. was significantly increased between 2003 and 2007 ($p < 0.001$). CRK strains were mostly isolated from intensive care units (ICUs) ($p < 0.001$). Using imipenem and cefoperazone-sulbactam within the prior three months, staying in ICU, receiving immunosuppressive therapy, receiving H2 receptor antagonists, having a tracheostomy, using mechanical ventilation, hemodialysis, and having a urinary catheter were found to be significant risk factors for carbapenem-resistant *Klebsiella* spp. infections. In a multivariate analysis, previously using imipenem (OR 3.35; CI 1.675-6.726, $p < 0.001$), staying in ICU (OR 3.36; 95% CI 1.193-9.508; $p = 0.022$), and receiving H2 receptor antagonist (OR 4.49; 95% CI 1.011-19.951; $p = 0.048$) were independently associated with carbapenem resistance. Respiratory tract infections were the most common nosocomial infections. Attack mortality rate was significantly higher in patients infected with CRK strains ($p < 0.001$). CRK strains showed significantly higher resistance rates to other antibiotics.

Conclusions: The emergence and rapid spread of CRK strains in our hospital is worrisome. The patients in the ICU are at the highest risk for the acquisition of CRK strains. High resistant rates to other antibiotics except colistin and tigecycline limit therapeutic options, and increase mortality rates.

Key words: *Klebsiella* spp.; carbapenem resistance; risk factors; nosocomial infection

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Introduction

The increasing prevalence of antimicrobial-resistant bacteria has become a serious worldwide problem. Carbapenems have been the drug of choice for treating such severe infections. However, intensive use of these compounds has resulted in the emergence of carbapenem-resistant isolates, leaving few therapeutic options [1]. Carbapenem resistance among *Klebsiella* spp. has increased in the last decade in many geographical regions of the world, including the USA and Europe. In the USA, the National Healthcare Safety Network (NHSN) reports showed that carbapenem resistance among *Klebsiella* isolates reached 12% in invasive device-related infections in 2009-2010 [2]. In Europe, carbapenem-resistant *Klebsiella* isolates became an important nosocomial pathogen in some countries, particularly in Greece, Italy, and Turkey. Mortality rates of these infections are high because of limited choices of antibiotics. In addition, although there are many reports about

hospital outbreaks of carbapenem-resistant *Klebsiella* spp., only a few of them examine the epidemiological characteristics and risk factors of these infections. Understanding the risk factors of carbapenem-resistant *Klebsiella* infections will be helpful in preventing these infections. Prolonged hospitalization, staying in the intensive care unit, using invasive devices, immunosuppression, and multiple antibiotic agents were reported as risk factors previously [1]. More studies are needed to determine the risk factors for the acquisition of carbapenem-resistant *Klebsiella* spp. infections in hospital settings.

In this study, we aimed to identify risk factors for nosocomial carbapenem-resistant *Klebsiella* spp. infections, and to contrast those factors with those for carbapenem-susceptible *Klebsiella* spp. infections.

Methodology

Patients who had nosocomial *Klebsiella* infections between January 2004 and December 2010 were

included in the study. Nosocomial infection (NI) surveillance was performed prospectively during the period. The data were obtained from infection control committee records. The diagnosis of NI was assessed according to Centers for Diseases Control and Prevention (CDC) criteria [3]. The following data were collected and analyzed from the patients: age, sex, hospital ward, length of hospitalization, prior use of various antibiotics within the last three months, risk factors and underlying diseases of the patients, type of NI, microbiological data, and outcome. To assay the demographic data, each patient was assessed once. More than one isolate of *Klebsiella* related to an individual nosocomial infection attack in patients was included in the study. The data about risk factors for carbapenem-resistant *Klebsiella* spp. infection were given through the number of attacks.

Microorganisms were identified by the BBL Crystal Enteric/Nonfermenter ID Kit (Becton Dickinson, Franklin Lakes, USA). The *in vitro* activities of antimicrobial agents were tested against the clinical isolates of *Klebsiella* spp. using the disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) criteria [4].

The statistical analysis of the data was performed using the SPSS version 17.0 software package. Categorical variables were analyzed using Chi-square or Fisher's exact test when appropriate. To test the independence of the risk factors for carbapenem resistance, a multivariate analysis was performed by logistic regression. Statistical significance was set at a *p* value of < 0.05.

Results

Klebsiella spp. was isolated from 840 attacks in 720 patients as a causative agent of nosocomial infection. During the study period, *Klebsiella* spp. was the etiological agent in 10.1% of NI isolates, and in 14.9% of Gram-negative microorganisms hospital wide during the study period. Its incidence and percentage among Gram negatives did not significantly change over the years. Even though the incidence of *Klebsiella* spp. infection did not change, carbapenem resistance among *Klebsiella* spp.

significantly increased between 2003 and 2007 (*p* < 0.001). The increase in carbapenem resistance was evident between the periods 2004-2008 and 2009-2010 (Table 1).

The male/female ratio was 1.24; mean age was 45.40 years (SD ± 28.68 years, median 54 years). In total, 41.1% of *Klebsiella* spp. infections occurred in intensive care units (ICUs). Carbapenem-resistant strains were more frequent (78.57%) than carbapenem-susceptible strains (39.1%) in ICUs (*p* < 0.001). Using imipenem and cefoperazone-sulbactam within the prior three months, staying in the ICU, receiving immunosuppressive therapy, receiving H2 receptor antagonists, having a tracheostomy, using mechanical ventilation, having hemodialysis, and having a urinary catheter were found to be significant risk factors for carbapenem-resistant *Klebsiella* spp. infections. Patient characteristics are shown in Table 2. In a multivariate analysis, prior use of imipenem (OR 3.35; CI 1.675-6.726, *p* < 0.001), staying in the ICU (OR 3.36; 95% CI 1.193-9.508; *p* = 0.022), and receiving H2 receptor antagonist (OR 4.49; 95% CI 1.011-19.951; *p* = 0.048) were independently associated with carbapenem resistance (Table 2).

The percentage of carbapenem-resistant *Klebsiella* spp. was significantly higher in respiratory tract infections (*p* < 0.001). There was no statistical difference among other infections related to carbapenem resistance. Of the isolates, 63.1% were *K. pneumoniae*, 17.9% were *K. oxytoca*, and 19% of them were not typed. Carbapenem resistance was not different among the subtypes of *Klebsiella* strains.

The attack mortality rate was higher in patients infected with carbapenem-resistant strains (57.1%) than in those infected with carbapenem-susceptible strains (27.4%) (*p* < 0.001).

Carbapenem-resistant *Klebsiella* strains showed significantly higher resistance rates to other antibiotics (Table 3). Tigecycline was tested in only 144 strains and the resistance rates to tigecycline were not different between carbapenem-resistant and carbapenem-susceptible strains. Colistin was tested in 100 strains and no resistance was detected.

Table 1. Incidence of *Klebsiella* spp. infections and isolation percentages by year

	2004	2005	2006	2007	2008	2009	2010	Total
Number of <i>Klebsiella</i> spp. isolates	122	127	145	118	104	100	124	840
% of <i>Klebsiella</i> spp. among NI isolates	11.7	10.3	9.3	8.2	7.5	8.5	9.2	10.1
% of <i>Klebsiella</i> spp. among Gram-negative isolates	17.1	16.8	14.4	13.1	11.8	13.5	13.8	14.9
% of carbapenem resistance	1.6	3.1	2.7	3.3	4.8	10	10.4	5

Table 2. Risk factors of 840 attacks of *Klebsiella* spp. infections according to carbapenem resistance

Characteristic	No. (%) of <i>Klebsiella</i> spp. infections			p
	CPM R ^a 42 (5)	CPM S ^b 798 (95)	Total 840 (100)	
Setting, ICU ^c	33 (78.57)	312 (39.1)	345 (41.1)	< 0.001
Male/female	21/21	446/352	463/373	0.553
Age	52.05 ± 26.82	45.02 ± 28.75	45.40 ± 28.68	0.149
Prior duration of hospitalization	28.17 ± 25.20	31.27 ± 57.86		0.727
Underlying diseases / risk factors				
Malignancy	11 (26.2)	219 (27.4)	230 (27.3)	0.999
Diabetes mellitus	5 (11.1)	111 (13.9)	116 (13.8)	0.930
Trauma	2 (4.7)	32 (4.01)	34 (4.04)	0.999
Immunosuppressive therapy	18 (42.8)	161 (20.1)	279 (33.2)	0.002
H2 antagonist	40 (95.2)	519 (65)	559 (66.5)	< 0.001
Neutropenia	2 (4.7)	53 (6.6)	55 (6.54)	0.941
Tracheostomy	10 (23.8)	70 (8.7)	80 (9.5)	0.008
Hemodialysis	8 (19)	65 (8.0)	73(8.7)	0.046
Mechanical ventilation	30 (71.4)	291 (36.4)	321 (38.2)	< 0.001
Central venous catheter	30 (71.4)	466 (58.3)	496 (59.0)	0.126
Urinary catheter	31 (73.8)	430 (53.8)	461 (54.9)	0.015
Kidney failure	4 (9.5)	44 (5.5)	48 (5.7)	0.427
Transfusion	10 (23.8)	166 (20.8)	176 (20.1)	0.61
Endoscopy	12 (28.5)	196 (24.5)	208 (24.7)	0.669
Drainage catheter	12 (28.5)	244 (30.5)	256 (30.4)	0.934
Prior use antibiotics	36 (85.7)	572 (71.7)	608 (72.4)	0.06
Prior use of imipenem	24 (57.1)	147 (18.4)	171 (20.3)	< 0.001
Prior use of cefoperazone-sulbactam	16 (38)	110 (13.8)	126 (15)	< 0.001
Type of infection				
Bloodstream infection	11 (26.1)	189 (23.6)	200 (22.6)	0.830
Respiratory tract infection	21 (50)	192 (24.0)	213 (25.35)	< 0.001
Urinary tract infection	6 (14.3)	212 (26.6)	218 (25.95)	0.100
Skin-soft tissue infection	4 (9.52)	166 (20.80)	170 (20.23)	0.099
Other infections	0	39 (4.87)	39 (4.6)	

^aCPM R: carbapenem resistant; ^bCPM S: carbapenem susceptible; ^cICU: intensive care unit

Table 3. Antibiotic resistance rates of *Klebsiella* spp. according to carbapenem resistance

Antibiotics	No. (%) of <i>Klebsiella</i> spp infections			p
	CPM R ^a (n = 42)	CPM S ^b (n = 798)	Total (n = 840)	
Amikacin	25 (59.5)	78 (9.7)	103 (12.2)	< 0.0001
Amoxicillin clavulanate	42 (100)	601 (75.3)	643 (80.5)	< 0.0001
Gentamycin	30 (71.4)	203 (25.4)	233 (27.7)	< 0.0001
Piperacillin-tazobactam	34 (80.9)	281 (35.2)	311 (37.0)	< 0.0001
Cefotaxime	40 (95.2)	394 (49.3)	434 (51.6)	< 0.0001
Ceftazidime	33 (78.5)	371 (46.4)	404 (48.1)	< 0.0001
Ciprofloxacin	31 (73.8)	279 (34.9)	310 (36.9)	< 0.0001
Cefoperazone-sulbactam	26 (61.9)	253 (31.7)	279 (33.2)	< 0.0001
Trimethoprim-sulfamethoxazole	37 (88.1)	515 (64.5)	552 (65.7)	0.001
Cefepime	36 (85.7)	334 (41.8)	370 (44.0)	< 0.0001
Tigecycline ^c	3/17 (17.6)	17/127 (13.4)	20/144 (13.9)	0.861
Colistin ^c	10 (100)	60 (100)	70 (100)	

^aCPM R: carbapenem resistant; ^bCPM S: carbapenem susceptible; ^ccalculated by the number of tested strains

Discussion

In recent years, carbapenem resistance in *Klebsiella* spp. has become a major problem in Turkey as well as the rest of the world. Outbreaks due to carbapenem-resistant *Klebsiella* spp. have been reported worldwide with increasing frequency [1,5,6,7]. In the SENTRY antimicrobial surveillance program (2007-2009), carbapenem resistance was found in 5.3% of *Klebsiella* spp., and 3.8% of the isolates were found to produce a carbapenemase [8].

Carbapenem resistance may occur because of the reduced permeability or carbapenemases. Carbapenemase production is a major resistance mechanism between Enterobacteriaceae. Carbapenemases have been placed in three group of beta-lactamases: class A beta-lactamases such as KPC, class B metallo beta-lactamases such as IMP, VIM, and class D OXA-type beta-lactamases such as OXA-48; class D are clinically and epidemiologically the most important enzymes [1]. KPC-type enzymes in carbapenem-resistant *K. pneumoniae* strains were first reported in 2001 in North Carolina [9]. The first outbreak of KPC-producing *K. pneumoniae* outside the USA was in Israel [6]. Almost all European countries are affected by the expansion of carbapenem-resistant *Klebsiella* spp. In some hospitals in Greece and Italy, carbapenem-resistant *Klebsiella* spp. has become endemic [7,10].

Although KPC-type carbapenemases are endemic in the countries near Turkey, this enzyme was not described in Turkey until now. However, OXA-type enzymes seem to be primarily a carbapenem resistance mechanism, especially OXA-48, in Turkey. This enzyme was first described in Turkey during an outbreak of *K. pneumoniae* in Istanbul [11]. OXA-48 producing *K. pneumoniae* was reported from different hospitals in Turkey, as well as in the Middle East, India, and Europe [7,12,13]. In our hospital, the frequency of nosocomial *Klebsiella* isolates did not change during the study period; however, the frequency of carbapenem-resistant *Klebsiella* isolates significantly increased. This may be due to an outbreak by the clonal spread of a resistant strain. We found an OXA-48 enzyme in some of the *Klebsiella* strains, but we could not perform a molecular analysis in all strains. This was a limitation of our study. We focused on analyzing the risk factors of carbapenem-resistant *Klebsiella* spp. infections in our study.

Several risk factors for the acquisition of carbapenem-resistant *Klebsiella* spp. have been described in the literature. Falagas *et al.* reported that prior use of quinolones and antipseudomonal

penicillins was an independent risk factor associated with the development of carbapenem-resistant *K. pneumoniae* infections [14]. Hussein *et al.* found an independent association between previous exposure to carbapenems or fluoroquinolones and subsequent development of carbapenem-resistant *K. pneumoniae* (CRKP) infections [5]. Independent risk factors for continued CRKP carriage were antibiotic exposure during the prior three months, receipt of amoxicillin-clavulanate, and screening within 90 days of the first culture growing CRKP [15]. Prolonged hospitalization, staying in intensive care unit, using invasive devices, immunosuppression, and multiple antibiotic agents before initial culture were found to be associated with the acquisition of KPC-producing bacteria [1,16]. Our results, similar to other studies, showed that prior use of antibiotics within three months, especially carbapenems and cefoperazone-sulbactams, which are commonly used in our country, was significantly associated with higher carbapenem resistance among nosocomial *Klebsiella* isolates. Prior use imipenem was found to be an independent risk factor for CRK infections in a multivariate analysis. No significant relationship was detected between other antibiotics and CRK infections.

In our study, staying in the ICU was found to be an independent risk factor for the acquisition of carbapenem-resistant *Klebsiella* isolates. Serious underlying diseases of the patients, intensive use of invasive devices such as a mechanical ventilator and urinary catheter, use of broad-spectrum antibiotics, and the lack of proper infection control measures may be an explanation for the high incidence of carbapenem resistance in ICUs. Another independent risk factor in the multivariate analysis was the receipt of H2 receptor antagonist. We did not see this finding in other articles in the literature. Recently, Borer *et al.* reported from Israel that the presence of a gastric ulcer was associated with the carbapenem-resistant *Klebsiella pneumoniae* infection [17]. It can be speculated that the use of H2 receptor antagonists decreases gastric acidity and leads to colonization of carbapenem-resistant *Klebsiella* spp. in the gut. This is an important mechanism for the acquisition of ventilator-associated pneumonia (VAP) in ICU patients. Respiratory tract infections, including VAP, were the most frequent infections caused by carbapenem-resistant *Klebsiella* spp. in our study. Tracheostomy, mechanical ventilation, hemodialysis, urinary catheter, and immunosuppressive therapy, which were found to be significant risk factors in a univariate

analysis, were similar to the findings of other studies [14,17,18].

Carbapenems are usually the antibiotics of choice for treating serious infections in the ICU. The emergence of carbapenem resistance among *Klebsiella* spp. limits the therapeutic options for these infections. Resistance rates to other class antibiotics such as penicillins, cephalosporins, quinolones, and aminoglycosides were significantly higher among carbapenem-resistant *Klebsiella* isolates. In our study, resistance rates to penicillins, cephalosporins, quinolones, and aminoglycosides were found to be significantly higher among carbapenem-resistant *Klebsiella* strains. Colistin resistance was not detected, and susceptibility rates to tigecycline were comparable in both carbapenem-resistant and carbapenem-susceptible *Klebsiella* isolates. Our results were similar to those of other studies in the literature. Us *et al.* reported that carbapenem-resistant *Klebsiella pneumoniae* isolates were resistant to all antimicrobial agents except polymyxins and tigecycline [19]. Won *et al.* reported that KPC-producing *Klebsiella* isolates were also resistant to other beta-lactam antibiotics, amikacin, and ciprofloxacin. Colistin and gentamycin were most effective antibiotics in this study [20]. In Italy, Gaibani *et al.* found that susceptibility to gentamicin, tigecycline, and colistin retained 47 of 52 KPC strains [10]. Patel *et al.* detected 99 carbapenem-resistant *Klebsiella* isolates between 2004 and 2006. *In vitro* susceptibility rates were the highest for polymyxin B (90%) and tigecycline (92%) [21]. This antimicrobial resistance pattern leads to problems in the treatment of serious infections, especially in the ICU. Tigecycline has limited use in the treatment of respiratory tract, bloodstream, and urinary tract infections because of its pharmacokinetic properties. Therefore, colistin remains an only therapeutic option for these infections. Although we did not detect resistance to colistin in our study, some studies showed lower resistance rates to colistin. Colistin resistance rates should be monitored closely.

Limited therapeutic options for these infections may cause an increase in mortality. Several reports have shown that carbapenem resistance was independently associated with an increase in mortality [21-23]. In our study, attack mortality rate was significantly higher in patients infected with carbapenem-resistant strains.

Conclusion

The emergence and rapid spread of carbapenem-resistant *Klebsiella* spp. in our hospital is worrisome. The patients in the ICU are at the highest risk for acquiring carbapenem-resistant strains. High resistant rates to other antibiotics except colistin and tigecycline limits therapeutic options and increases mortality rates. Limitations of carbapenem overuse, active surveillance, and application of strict infection control measures are necessary for combating these infections.

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