EPIDEMIOLOGY AND PROGNOSTIC FACTORS OF CARBAPENEM-RESISTANT *KLEBSIELLA PNEUMONIAE* INFECTION IN WUHAN, HUBEI, CHINA (JANUARY 2015 - JULY 2017)

Meng-Lin Zou, Jing-Feng Zou, Xing-Xing Hu, Chao-Jie Wei and Zhen-Shun Cheng

Department of Respiratory medicine, Zhongnan Hospital of Wuhan University, Wuhan, Hubei Province, PR China

Abstract. Prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has been increasing during the past decades with a high rate of mortality. A retrospective 1:2 case-control study was conducted at Zhongnan Hospital, Wuhan University, Hubei Province, China from January 2015 to July 2017 to identify risk factors associated with CRKP infection, mortality and prognostic factors among adult inpatients (n = 83) with CRKP infection and matched adult inpatients (n = 166) with carbapenem-susceptible *K. pneumoniae* (CSKP) infection at the same site and time of isolation. Univariate and multivariate logistic regression analysis were performed to assess risk factors associated with CRKP infection and predictors of death. Incidence of CRKP in 2015, 2016 and 2017 was 5, 6 and 10%, respectively. Multivariable analysis identified cerebrovascular disease (odds ratio (OR) = 2.10, 95% confidence interval (CI): 1.06-4.13, p-value = 0.032), central venous catheter catheterization (CVC) (OR = 2.03, 95% CI: 1.07-3.85, p-value = 0.029), indwelling gastric tube (OR = 2.00, 95% CI: 1.05-3.79, p-value = 0.034), and exposure to carbapenem (OR = 3.16, 95% CI: 1.58-6.30, p-value =0.001), cefoperazone plus sulbactam (OR = 2.99, 95% CI: 1.59-5.64, p-value = 0.001) or fluoroquinolones (OR = 2.54, 95% CI: 1.23-5.24, p-value = 0.012) as independent risk factors for CRKP infection. Mortality in CRKP (29%) is significantly higher than that of CSKP (11%) group (p-value = 0.001). Cardiac disorders (OR = 5.70, 95% CI: 1.02-32.02, p-value = 0.048), CVC (OR = 13.94, 95% CI: 2.15-90.40, p-value = 0.006), indwelling gastric tube (OR = 43.40, 95% CI: 4.01-470.35, p-value = 0.002), and decrease in absolute lymphocyte counts (OR = 5.49, 95% CI: 1.18-25.46, p-value = 0.030) were predictors for higher mortality rate. These findings should be of value in developing preventive measures to reduce mortality among inpatients with CRKP infection.

Keywords: carbapenem-resistant *Klebsiella pneumoniae*, mortality, prognostic factors, risk factors

Correspondences: Chao-Jie Wei and Zhen-Shun Cheng, Department of Respiratory Medicine, Zhongnan Hospital of Wuhan University, 169 Donghu Ave, Wuhan, Hubei, 430000, People's Republic of China.
Tel: +86 136 2728 8300
Email: zhenshun_cheng@126.com

INTRODUCTION

Klebsiella pneumoniae (*K. pneumoniae*) is a common cause for nosocomial infection (Ahmad *et al*, 2012) presenting a broad spectrum of diseases, such as bacteremia, meningitis, pneumonia, and urinary tract infection (Pitout and Laupland, 2008). As a

result of emergence of extended spectrum beta-lactamase (ESBL)-producing *K. pneumoniae*, carbapenem use has been widespread; however, carbapenem-resistant *K. pneumoniae* (CRKP), first reported in the United States in 2001 (Yigit *et al*, 2001) is now globally widespread (Lautenbach and Perencevich, 2014).

The predominant mechanism of resistance to carbapenem is production of plasmid-encoded carbapenemase, which can be horizontally transferred to other *K. pneumoniae* strains (Munoz-Price and Quinn, 2009). Prevalence of CRKP infection has increased during the past two decades (Hu *et al*, 2016a). In Italy, the overall proportion of non-susceptible carbapenem *K. pneumoniae* isolates increased from 2.2% in 2009 to 19.4% in 2012 (Sisto *et al*, 2012). In USA, an overall rate of 24.6% of CRKP was reported among 64 long-term acute care hospitals (LTACHs) from January 2014 to March 2015 (Han *et al*, 2017). In China, according to the China Antimicrobial Surveillance Network (CHINET) surveillance system, carbapenem resistance among *K. pneumoniae* isolates increased from 2.4% in 2005 to 13.4% in 2014 (Hu *et al*, 2016a), but there are significant differences in CRKP rates across geographic regions, being highest in the western region (42.2%) of the country (Han *et al*, 2017). As CRKP growth rate is high and prevalence varies in different regions, an understanding of the evolving regional epidemiology of CRKP is important to regional and national infection prevention and surveillance efforts.

Mortality of hospitalized patients with CRKP infection is exceptionally high, ranging 40-50% (Patel *et al*, 2008; Schwaber *et al*, 2008). Identification of risk factors for CRKP infection can help inform infection prevention programs and guide appropriate empirical clinical therapy. Although several studies have been performed to determine risk factors for CRKP infection, but conclusions are inconsistent (Kofteridis *et al*, 2014; Jiao *et al*, 2015; Hu *et al*, 2016b). Furthermore, a few studies have reported risk factors for mortality in adult inpatients with CRKP infection in mainland China but no unanimous conclusion is reached (Jiao *et al*, 2015; Tian *et al*, 2016).

In order to facilitate the efficacy of empirical therapy for CRKP infection, a retrospective case-control study was conducted to (i) assess incidence of CRKP infection, (ii) identify risk factors associated with CRKP infection, and (iii) assess mortality and factors associated with poor outcome among hospitalized adults in all departments of a large teaching hospital in central China.

MATERIALS AND METHODS

Study subject recruitment and study design

The study was conducted at Zhongnan Hospital, Wuhan University, a 3,000-bed tertiary-care hospital located in Wuhan, Hubei Province, central China between January 2015 and July 2017. Study subject inclusion criteria were (i) *K. pneumoniae* isolated >48 hours after hospital admission, and (ii) >18 years of age. If a patient had multiple episodes of *K. pneumoniae* infection, only the first occurrence was included in the study. For determination of risk factors for CRKP infection, a carbapenem-susceptible *K. pneumoniae* (CSKP) group was randomly selected from a pool of patients with CSKP infection determined at the same site and time as CRKP isolation at a ratio of 2:1 CSKP:CRKP patients.

The research protocol was approved by the Ethics Committee of Zhongnan

Hospital, Wuhan University (approval no. 2019031). As this was a retrospective survey, no prior written consent was required and all data were stripped of patients' identity prior to collection.

Study subjects' demographic profiles and medical records

Data on age, admission date, medical history (lung disease, cardiac disorder, liver disease, renal dysfunction, cerebrovascular disease, diabetes, illness severity requiring admission to intensive care unit (ICU), and prior hospital stay) and laboratory findings (lymphocyte (LYM) numbers) were collected. Acute Physiology and Chronic Health Evaluation (APACHE II) scores were determined on the day or before the day but no more than 72 hours prior to sample collection for *K. pneumoniae* culture. Interventions (central venous and indwelling urinary catheters, mechanical ventilation, indwelling gastric tube and antibiotic use during the 2-month period prior to *K. pneumoniae* culture) and mortality rate were recorded. Antibiotics used were classified into carbapenems (meropenem, biapenem or imipenem), cefoperazone plus sulbactum, cephalosporins (second-, third- and fourth-generation), fluoroquinolones, glycopeptides and piperacillin tazobactam.

Laboratory investigation of CRKP and CSKP cultures

K. pneumoniae from sputum, bronchoalveolar lavage fluid, urine, drainage fluid, wound secretion, blood and bile samples were identified by culturing on standard media (Debby *et al*, 2012). Antimicrobial susceptibility to ertapenem, imipenem or meropenem was carried out using a VITEK 2 system (bioMérieux, Marcy l' Etoile, France). Resistance is defined as such when the minimum inhibitory concentration (MIC) of meropenem or imipenem was $\geq$4 μg/ml, and the MIC of ertapenem was $\geq$2 μg/ml. A strain with intermediate susceptibility to a carbapenem is considered resistant. A *K. pneumoniae* infection is defined as a positive culture together with symptoms and/or signs of infection.

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables as percent. Variables showing statistically significance differences (p-value <0.05) in potential risk factors for CRKP infection or mortality by univariate analysis were subsequently subjected to multivariate logistic regression model analysis (Hu *et al*, 2016b). Odds ratios (OR) and 95% confidence intervals (CIs) were calculated to evaluate strength of association. For all statistical analyses, a two-tailed p-value <0.05 is considered significant. Statistical analyses were performed using a Statistical Package for the Social Sciences software, version 21.0 (SPSS, Chicago, IL).

RESULTS

Study subjects' profiles

Incidence of CRKP at Zhongnan Hospital, Wuhan University, Wuhan, Hubei, China rose from 5% in 2015 to 10% in 2017, an average increase of 2% (Fig 1). Inpatients with CRKP infection (n = 83) and matched inpatients (n = 166) were recruited between January 2015 and July 2017. Study subjects were mainly elderly ($\geq$60 years of age) (Table 1). CRKP was most commonly isolated from sputum and bronchoalveolar lavage fluid (58%), followed by urine (21%), drainage fluid (10%), wound secretion (8%), blood (2%), and bile (1%). According clinical departments where they were admitted, CRKP was most commonly isolated

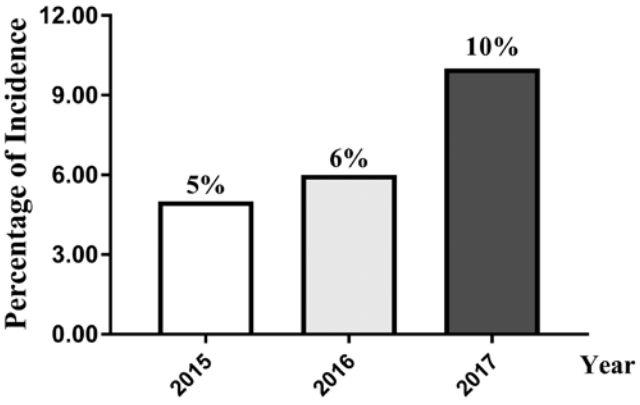

Fig 1-Incidence of carbapenem-resistant *Klebsiella pneumoniae* infection at Zhongnan Hospital, Wuhan University, Wuhan, Hubei, PR China (January 2015 - July 2017).

from intensive care unit (ICU) (36%), followed by units of respiratory medicine (24%,), neurology (10%,), neurosurgery (8%), geriatrics (6%), gastrointestinal surgery (4%), hepatobiliary surgery and orthopedics (3% each), and emergency ward, endocrinology, infectious disease, nephrology, thoracic surgery, and urology (1% each).

Risk factors associated with CRKP infection

Univariable analysis revealed CRKP infection was associated with older age, cerebrovascular disease, central venous catheter catheterization (CVC), presence of indwelling gastric tube, exposure to antibiotics (cefoperazone plus sulbactam, fluoroquinolones, or carbapenem) and stay in intensive care unit (Table 1). Subsequent analysis of these risk factors by multivariable analysis, only cerebrovascular disease, use of central venous catheter catheterization, presence of indwelling gastric tube and exposure to cefoperazone plus sulbactam, fluoroquinolones or carbapenem remained independently associated risk factors for CRKP infection (Table 1).

Prognostic factors and outcome

Mean mortality rate from *Klebsiella pneumonia* infection during the study period was 17%, significantly higher (24/83, 29%) in CRKP compared to CSKP (19/166, 11%) group (p-value = 0.001). Univariate analysis showed cardiac disorders, CVC, presence of indwelling urinary catheter, presence of indwelling gastric tube, and low absolute lymphocyte counts were associated with death from CRKP infection, from which multivariate analysis ruled out the presence of indwelling urinary catheter as independent predictor of mortality from CRKP infection (Table 2).

DISCUSSION

The survey shows an overall prevalence of CRKP at a tertiary-care hospital in central China between January 2015 and July 2017 was lower than that (13.4%) reported by CHINET surveillance system in 2014 (Hu *et al*, 2016a); however, the annual rate of increase was higher than (1.10%) of the previous study (Hu *et al*, 2016a). The majority of CRKP

Table 1
Analysis of risk factors associated with carbapenem-resistant *Klebsiella pneumoniae* infection of inpatients at Zhongnan Hospital, Wuhan University, Wuhan,Hubei Province, PR China (January 2015 - July 2017).

Risk factor	Variable		Univariate analysis		Multivariate analysis	
	CRKP Number (%) ($n = 83$)	CSKP Number (%) ($n = 166$)	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Demographic						
Age, years, mean ± SD	70 ± 17	65 ± 17	1.02 (1.00-1.03)	0.044	0.99 (0.97-1.01)	0.447
Concomitant disease						
Lung disease	18 (22)	22 (13)	1.81 (0.91-3.61)	0.090		
Cardiac disorders	54 (65)	99 (60)	1.26 (0.73-2.18)	0.408		
Liver disease	11 (13)	28 (17)	0.75 (0.35-1.60)	0.460		
Renal dysfunction	14 (17)	17 (10)	1.78 (0.83-3.81)	0.139		
Cerebrovascular disease	46 (55)	53 (32)	2.65 (1.54-4.56)	0.000	2.10 (1.06-4.13)	0.032
Diabetes	19 (23)	29 (17)	1.40 (0.73-2.69)	0.308		
Invasive procedure						
Central venous catheter	51 (61)	65 (39)	2.48 (1.44-4.25)	0.001	2.03 (1.07-3.85)	0.029
Indwelling urinary catheter	60 (72)	133 (80)	0.65 (0.35-1.20)	0.165		
Mechanical ventilation	54 (65)	103 (62)	1.14 (0.66-1.97)	0.643		
Indwelling gastric tube	46 (55)	50 (30)	2.88 (1.67-4.98)	0.000	2.00 (1.05-3.79)	0.034
Antibiotics use prior to *Klebsiella pneumoniae* infection						
2nd generation cephalosporins	19 (23)	45 (28)	0.80 (0.43-1.48)	0.473		
3rd generation cephalosporins	8 (10)	26 (16)	0.57 (0.25-1.33)	0.196		
4th generation cephalosporins	6 (7)	13 (8)	0.92 (0.34-2.51)	0.866		
Cefoperazone plus sulbactam	51 (61)	45 (27)	4.29 (2.45-7.50)	<0.001	2.99 (1.59-5.64)	0.001
Fluoroquinolones	33 (40)	25 (15)	3.72 (2.02-6.86)	<0.001	2.54 (1.23-5.24)	0.012

Table 1 (Continued)

Risk factor	Variable		Univariate analysis		Multivariate analysis	
	CRKP Number (%) (n = 83)	CSKP Number (%) (n = 166)	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Carbapenem	45 (54)	28 (17)	5.84 (3.23-10.56)	<0.001	3.16 (1.58-6.30)	0.001
Piperacillin tazobactam	33 (40)	51 (31)	1.49 (0.86-2.58)	0.156		
Glycopeptides	16 (19)	22 (13)	1.56 (0.77-3.17)	0.215		
Prior hospital stay, days, mean ± SD	30 ± 32	34 ± 100	1.00 (1.00-1.01)	0.743		
Absolute lymphocyte counts (10^9/l), mean ± SD	0.9 ± 0.5	0.9 ± 0.6	1.05 (0.66-1.66)	0.849		
ICU stay	35 (42)	42 (25)	2.15 (1.23-3.76)	0.007	1.60 (0.82-3.13)	0.169
APACHEII score among patients in ICU	19 ± 7	21 ± 34	1.00 (0.98-1.02)	0.811		
Death	24 (29)	19 (11)	0.32 (0.16-0.62)	0.001		

*Significance at p<0.050; CI: confidence interval; CRKP: carbapenem-resistant *K. pneumoniae*; CSKP: carbapenem-sensitive *K. pneumoniae*; ICU: intensive care unit; OR: odds ratio; SD: standard deviation.

was isolated from patients in medicine department, followed by ICU and surgery departments, similar to the report from Italy during 2009 to 2012 (Cascio *et al*, 2014). These findings should be of concern to physicians in hospitals across China.

In order to limit the spread of CRKP and improve empirical therapy efficacy, it is critical to understand the risk factors for CRKP infection. One independent risk factor was previous exposure to carbapenems, cefoperazone plus sulbactam or fluoroquinolones. Previous studies (Falagas *et al*, 2007; Hussein *et al*, 2009; Kritsotakis *et al*, 2011; Bart *et al*; 2015; Hu *et al*, 2016b) showed prior use of carbapenems is a risk factor for CRKP infection. Third generation cephalosporins alone did not emerge as significant predictors, consistent with the results of Kritsotakis *et al* (2011) but not those of Falagas *et al* (2007); however, third generation cephalosporin plus β-lactamase (cefoperazone plus sulbactam) was a CRKP infection predictor. β-Lactam/β-lactamase combinations were reported to be associated with ESBL-CRKP infection (Kritsotakis *et al*, 2011), although the precise antibiotics used was not indicated. Previous use of fluoroquinolones is negatively associated with isolation of CRKP (Kwak *et al*, 2005); however, this contradicts prior studies (Falagas *et al*, 2007; Schwaber *et al*, 2008; Kritsotakis

Table 2
Predictors of mortality in carbapenem-resistant *Klebsiella pneumoniae*-infected inpatients at Zhongnan Hospital, Wuhan University, Wuhan, Hubei, PR China (January 2015 - July 2017).

Risk factor[#]	Variable		Univariate analysis		Multivariate analysis	
	Death Number (%) ($n = 24$)	Survival Number (%) ($n = 59$)	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Cardiac disorders	20 (83)	34 (58)	3.68 (1.12-12.10)	0.032	5.70 (1.02-32.02)	0.048
Central venous catheter	22 (92)	29 (49)	11.38 (2.45-52.81)	0.002	13.94 (2.15-90.40)	0.006
Indwelling urinary catheter	22 (92)	38 (64)	6.08 (1.30-28.43)	0.022	2.74 (0.36-20.96)	0.332
Indwelling gastric tube	23 (96)	23 (39)	36.00 (4.55-285.11)	0.001	43.40 (4.01-470.35)	0.002
Absolute lymphocyte counts $<0.9\times10^9/1$	17 (71)	26 (44)	3.08 (1.11-8.54)	0.030	5.49 (1.18-25.46)	0.030

[#]Those with p-value <0.050 in univariate analysis; *Significance at $p < 0.05$; CI: confidence interval; OR: odds ratio.

et al, 2011; Bart *et al*, 2015). Prior exposure to glycopeptides was considered to be a risk factor for CRKP infection (Wu *et al*, 2011; Jiao *et al*, 2015), but this was not observed in the present study.

The presence of indwelling gastric tube as a risk factor for CRKP infection is a controversial issue. No association with CRKP infection has been reported (Wu *et al*, 2011; Bart *et al*, 2015; Jiao *et al*, 2015), but the present study showed presence of indwelling gastric tube was as an independent risk factor. Similarly, it is still controversial whether CVC is associated with CRKP infection; Falagas *et al* (2007), Correa *et al* (2013) and Bart *et al* (2015) found no association, but Kritsotakis *et al* (2011) and Jiao *et al* (2015) did. The present finding of association of neurologic disease with CRKP infection is in agreement with the study of Schwaber *et al* (2008) but not those of Falagas *et al* (2007) and Hu *et al* (2016b). These discrepancies could be due to such factors as study subject selection, hospital settings and clinical practices.

As expected, the overall mortality rate was higher in CRKP than in CSKP group, consistent with previous studies (Tumbarello *et al*, 2015; Xu *et al*, 2017; Zhang *et al*, 2018). It was suggested isolation of CRKP itself is a risk factor for worst outcome (Zhang *et al*, 2018) as is severity of disease, defined by APACHE II score (Zarkotou *et al*, 2011). However, in the present study, no correlation was observed between APACHE II score among CRKP infected-patients in ICU and death rate, but cardiac disorder was an independent risk factor for such outcome. Although mechanical ventilation (Zhang *et al*, 2018) and previous cefoperazone plus sulbactam medication (Jiao *et al*, 2015)

were independent risk factors poor outcome, these phenomena were not observed in the present study. This might be due to the small sample size and high rate of ventilator use and long exposure to cefoperazone plus sulbactam in the previous studies. The present study noted CVC and presence of indwelling gastric tube were independent risk factors for high mortality rate among CRKP-infected patients, which were not seen in other reports (Zarkotou *et al*, 2011; Vardakas *et al*, 2015; Hoxha *et al*, 2016; Zhang *et al*, 2108). Lymphocytopenia is implicated with immunosuppression in severe infection and is associated with poor outcome in septic shock patients (Drewry *et al*, 2014), possibly accounting for a similar outcome of the CRKP group in the present study.

The study suffers from several limitations. Firstly, although the case-control group was designed to help in identifying risk factors for CRKP infection, it was problematic to analyze certain important variables, *eg* location and time of risk. Secondly, the study was performed at a single tertiary-care hospital and the results might not be applicable to other hospitals, and could only provide data for that study region. Thirdly, although the predominant mechanism of resistance to carbapenems is the production of carbapenemase enzymes (Chen *et al,* 2014), the types of carbapenemases or other mechanisms of carbapenem resistance in the CRKP isolates were not investigated.

In summary, the study demonstrates that prior exposure to carbapenems, cefoperazone plus sulbactam or fluoroquinolones, underlying cerebrovascular disease, use of central venous catheter catheterization and presence of indwelling gastric tube were independent risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection among inpatients. Low lymphocyte counts, underlying cardiac disorders, use of central venous catheter catheterization and presence of indwelling gastric tube were independent predictor of mortality from CRKP infection. These findings should provide guidance in devising precautionary measures to minimize death among such patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

Ahmad TA, Haroun M, Hussein AA, El Ashry el SH, El-Sayed LH. Development of a new trend conjugate vaccine for the prevention of *Klebsiella pneumoniae*. *Infect Dis Rep* 2012; 4:e33.

Bart Y, Paul M, Eluk O, Geffen Y, Rabino G, Hussein K. Risk factors for recurrence of carbapenem-resistant *enterobacteriaceae* carriage: case-control study. *Infect Control Hosp Epidemiol* 2015; 36: 936-41.

Cascio GL, Soldani F, Mazzariol A, Lleo MM. The high incidence of carbapenem-resistant *Klebsiella pneumoniae* in urine from elderly hospital patients may facilitate the spread of resistant strains to the community. *Microb Drug Resist* 2014; 20: 67-72.

Chen L, Mathema B, Chavda KD, DeLeo FR, Bonomo RA, Kreiswirth BN. Carbapenemase producing *Klebsiella pneumoniae*: molecular and genetic decoding. *Trends Microbiol* 2014; 22: 686-96.

Correa L, Martino MD, Siqueira I, *et al*. A hospital-based matched case-control study to identify clinical outcome and risk factors associated with carbapenem-resistant *Klebsiella pneumoniae* infection. *BMC Infect Dis* 2013; 13: 80.

Debby BD, Ganor O, Yasmin M, *et al*. Epidemiology of carbapenem resistant *Klebsiella pneumoniae* colonization in an intensive care unit. *Eur J Clin Microbiol Infect Dis* 2012; 31: 1811-7.

Drewry AM, Samra N, Skrupky LP, Fuller BM, Compton SM, Hotchkiss RS. Persistent lymphopenia after diagnosis of sepsis predicts mortality. *Shock* 2014; 42: 383-91.

Falagas ME, Rafailidis PI, Kofteridis D, *et al*. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case control study. *J Antimicrob Chemother* 2007; 60: 1124-30.

Han JH, Goldstein EJ, Wise J, Bilker WB, Tolomeo P, Lautenbach E. Epidemiology of Carbapenem-Resistant *Klebsiella pneumoniae* in a network of long-term acute care hospitals. *Clin Infect Dis* 2017; 64: 839-44.

Hoxha A, Karki T, Giambi C, *et al*. Attributable mortality of carbapenem-resistant *Klebsiella pneumoniae* infections in a prospective matched cohort study in Italy, 2012-2013. *J Hosp Infect* 2016; 92: 61-6.

Hu FP, Guo Y, Zhu DM, *et al*. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. *Clin Microbiol Infect* 2016a; 22 (Suppl 1): S9-14.

Hu Y, Ping Y, Li L, Xu H, Yan X, Dai H. A retrospective study of risk factors for carbapenem-resistant *Klebsiella pneumoniae* acquisition among ICU patients. *J Infect Dev Ctries* 2016b; 10: 208-13.

Hussein K, Sprecher H, Mashiach T, Oren I, Kassis I, Finkelstein R. Carbapenem resistance among *Klebsiella pneumoniae* isolates: risk factors, molecular characteristics, and susceptibility patterns. *Infect Control Hosp Epidemiol* 2009; 30: 666-71.

Jiao Y, Qin Y, Liu J, *et al*. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization and predictors of mortality: a retrospective study. *Pathog Glob Health* 2015; 109: 68-74.

Kofteridis DP, Valachis A, Dimopoulou D, *et al*. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection/colonization: a case-case-control study. *J Infect Chemother* 2014; 20: 293-7.

Kritsotakis EI, Tsioutis C, Roumbelaki M, Christidou A, Gikas A. Antibiotic use and the risk of carbapenem-resistant extended-spectrum-{beta}-lactamase-producing *Klebsiella pneumoniae* infection in hospitalized patients: results of a double case-control study. *J Antimicrob Chemother* 2011; 66: 1383-91.

Kwak YG, Choi SH, Choo EJ, *et al*. Risk Factors for the acquisition of carbapenem-resistant *Klebsiella pneumoniae* among hospitalized patients. *Microb Drug Resist* 2005; 11: 165-9.

Lautenbach E, Perencevich EN. Addressing the emergence and impact of multidrug-resistant gram-negative organisms: a critical focus for the next decade. *Infect Control Hosp Epidemiol* 2014; 35: 333-5.

Munoz-Price LS, Quinn JP. The spread of *Klebsiella pneumoniae* carbapenemases: a tale of strains, plasmids, and transposons. *Clin Infect Dis* 2009; 49: 1739-41.

Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect Control Hosp Epidemiol* 2008; 29:1099-106.

Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis* 2008; 8:159-66.

Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrob Agents Chemother* 2008; 52: 1028-33.

Sisto A, D'Ancona F, Meledandri M, et al. Carbapenem non-susceptible *Klebsiella*

pneumoniae from Micronet network hospitals, Italy, 2009 to 2012. *Euro Surveill* 2012; 17: 20247.

Tian L, Tan R, Chen Y, *et al*. Epidemiology of *Klebsiella pneumoniae* bloodstream infections in a teaching hospital: factors related to the carbapenem resistance and patient mortality. *Antimicrob Resist Infect Control* 2016; 5: 48.

Tumbarello M, Trecarichi EM, De Rosa FG, *et al*. Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study. *J Antimicrob Chemother* 2015; 70: 2133-43.

Vardakas KZ, Matthaiou DK, Falagas ME, Antypa E, Koteli A, Antoniadou E. Characteristics, risk factors and outcomes of carbapenem-resistant *Klebsiella pneumoniae* infections in the intensive care unit. *J Infect* 2015; 70: 592-9.

Wu D, Cai J, Liu J. Risk factors for the acquisition of nosocomial infection with carbapenem-resistant *Klebsiella pneumoniae*. *South Med J* 2011; 104: 106-10.

Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*. *Ann Clin Microbiol Antimicrob* 2017; 16: 18.

Yigit H, Queenan AM, Anderson GJ, *et al*. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2001; 45: 1151-61.

Zarkotou O, Pournaras S, Tselioti P, *et al*. Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment. *Clin Microbiol Infect* 2011; 17: 1798-803.

Zhang Y, Guo LY, Song WQ, Wang Y, Dong F, Liu G. Risk factors for carbapenem-resistant *K. pneumoniae* bloodstream infection and predictors of mortality in Chinese paediatric patients. *BMC Infect Dis* 2018; 18 :248.