Journal of Antimicrobial Chemotherapy (2007) **60**, 1124–1130
doi:10.1093/jac/dkm356
Advance Access publication 20 September 2007

JAC

Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case–control study

Matthew E. Falagas[1,2,3]*, Petros I. Rafailidis[1,3], Diamantis Kofteridis[4], Simona Virtzili[5], Fotini C. Chelvatzoglou[3], Vassiliki Papaioannou[6], Sofia Maraki[7], George Samonis[4] and Argyris Michalopoulos[1,5]

[1]Alfa Institute of Biomedical Sciences (AIBS), Athens, Greece; [2]Department of Medicine, Tufts University School of Medicine, Boston, MA, USA; [3]Department of Medicine, Henry Dunant Hospital, Athens, Greece; [4]Department of Medicine, University Hospital of Heraklion, Heraklion, Greece; [5]Intensive Care Unit, Henry Dunant Hospital, Athens, Greece; [6]Department of Microbiology, Henry Dunant Hospital, Athens, Greece; [7]Department of Microbiology, University Hospital of Heraklion, Heraklion, Greece

Received 7 June 2007; returned 27 July 2007; revised 17 August 2007; accepted 21 August 2007

***Background*: Carbapenems are frequently used to treat infections due to extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*. Thus, the emergence of infections due to carbapenem-resistant *K. pneumoniae* (CRKp) is a major public health concern.**

***Objectives*: To identify risk factors associated with the development of CRKp infections.**

***Methods*: We conducted a matched case–control study in two hospitals (Henry Dunant Hospital, Athens, Greece and University Hospital of Heraklion, Crete, Greece). The controls were selected among patients with carbapenem-susceptible *K. pneumoniae* (CSKp) and were matched with CRKp cases for site of infection.**

***Results*: One hundred and six patients were included in our study (53 cases and 53 controls). Mortality was 30.1% and 33.9% for patients with CRKp and CSKp infections, respectively ($P = 0.83$). Bivariable analysis showed that exposure to anti-*pseudomonas* penicillins ($P = 0.004$), carbapenems ($P = 0.01$), quinolones ($P < 0.001$) and glycopeptides ($P < 0.001$), as well as admission to the intensive care unit ($P = 0.002$), tracheostomy ($P = 0.02$), chronic obstructive pulmonary disease ($P = 0.04$), surgery with use of foreign body ($P = 0.04$) and mechanical ventilation ($P = 0.02$) were associated with CRKp infection. The multivariable analysis showed that exposure to fluoroquinolones [odds ratio (OR) 4.54, 95% confidence intervals (CIs) 1.78–11.54, $P = 0.001$] and exposure to antipseudomonal penicillins (OR 2.57, 95% CI 1.00–6.71, $P = 0.04$) were independent risk factors for CRKp infections.**

***Conclusions*: Our data suggest that prior exposure to fluoroquinolones and antipseudomonal penicillins are independent risk factors for the development of CRKp infections.**

Keywords: imipenem, meropenem, polymyxins, colistin, multidrug-resistant, mortality

Introduction

Klebsiella pneumoniae, one of the most important Gram-negative bacterial pathogens, has caused worldwide concern because of its ability to produce extended-spectrum β-lactamases (ESBLs). Therefore, clinicians have frequently used carbapenems as a tool to treat patients with infections because of ESBL-producing *K. pneumoniae*.[1] Unfortunately, owing to the selective pressure put on the bacterium, *K. pneumoniae* strains resistant to carbapenems have emerged.[2–5] The need for the treatment of patients with infections due to carbapenem-resistant Gram-negative bacteria[6] such as *K. pneumoniae* (but also *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) has led to the revival of polymyxins as a therapeutic solution.[7]

*Correspondence address. Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23 Marousi, Greece. Tel: +30-694-611-0000; Fax: +30-210-683-9605; E-mail: m.falagas@aibs.gr

There are few reports regarding the risk factors for acquisition of carbapenem-resistant *K. pneumoniae* (CRKp).[8,9] We performed a matched case–control study to evaluate potential risk factors for isolation of CRKp infections in patients hospitalized in two tertiary medical centres in Greece.

Methods

Design of the study

A matched case–control study was conducted at 'Henry Dunant', a 450 bed tertiary-care hospital in Athens, Greece and the 650 bed University Hospital of Heraklion, Crete, Greece. Data were extracted from patient records by S. V. or F. C. at the Henry Dunant Hospital and D. K. at the University Hospital of Heraklion.

Patient selection

Patients with infections caused by CRKp hospitalized during the period 1 October 2000 to 1 May 2006 and 1 October 2003 to 1 May 2006 at the Henry Dunant Hospital and the University Hospital of Heraklion, respectively, were identified from the databases of the Microbiology Laboratories of the hospitals.

Selection of controls

For each patient with CRKp infection, we selected a matched control patient from the pool of patients with carbapenem-susceptible *K. pneumoniae* (CSKp) infections. We used a stepwise matching technique to identify the appropriate control patient matched to a case for the site of infection, age $\pm$ 5 years and length of hospital stay up to isolation of CRKp $\pm$3 days and year of hospital admission.

Microbiological testing

Identification of CRKp and other pathogens was performed using routine microbiological methods. Susceptibility testing for meropenem and imipenem was performed by both the disc diffusion method and an automated broth microdilution method (bioMerieux, Vitek II, Hazelwood, MO, USA). CRKp was defined as such when the MIC level was $\geq$16 mg/L. Susceptibility testing for ertapenem was not performed.

Definitions of infections and outcomes

Infections were defined based on guidelines from the Centers for Disease Control and Prevention.[10] The primary outcome measure was in-hospital mortality. Secondary outcome was the outcome of the infection and this was assessed as either favourable (cure and improvement) or unfavourable (stable and deterioration).

Data collection

We collected data from all available medical records including site of infection, age, sex, length of hospital stay and hospital admission. Microbiological data included the causative organism isolated from the site of infection, the date of isolation and the *in vitro* susceptibilities to several antibiotics, including colistin. In addition, the type of infection, the causative pathogen and the clinical outcome were determined by two blinded reviewers (P. I. R. and M. E. F.). For patients with more than one episode of infection due to *K. pneumoniae*, only data relevant to the first episode were collected and analysed. The exposure to various risk factors was taken into consideration in the analysis, only if it had occurred prior to the development of the infection. Variables analysed as risk factors included sex, co-morbidity, prior hospitalization and surgery, intensive care unit (ICU) admission, and events and procedures related to ICU (mechanical ventilation, tracheotomy, etc.), severity of illness [assessed with Acute Physiology and Chronic Health Evaluation (APACHE) II score for patients admitted to the ICU], administration of special treatments (defined as administration of steroids, chemotherapy and blood products) and, finally, previous exposure to various antibiotic agents. Exposure to a specific antimicrobial agent was considered significant to be included in our analysis only if (i) that exposure had occurred only during the hospitalization in which infection developed and (ii) the antibiotic had been administered for at least 3 consecutive days prior to the development of the infection.

Data analysis

Discrete variables for the matched case–control pairs were compared by McNemar's test; for continuous variables we used the Wilcoxon test. Variables associated with CRKp infections in the bivariable analysis ($P < 0.05$) were included in a backward, conditional stepwise multivariable logistic regression model. For the analysis of risk factors for mortality, we used Mann–Whitney and *t*-tests for the categorical and continuous variables, respectively. Variables associated with mortality in the bivariable analysis ($P < 0.05$) were included in a backward, stepwise multivariable logistic regression model. All statistical analyses were performed using SPSS 13.0 (SPPS Inc., Chicago, IL, USA).

Results

Study population

From 1 October 2000 to 1 May 2006 and from 1 October 2003 to 1 May 2006, there were 25 patients and 28 patients with CRKp infection at the Henry Dunant Hospital (all 25 were ICU patients) and the University Hospital of Heraklion (14 of these 28 patients were ICU patients), respectively. We selected an equal number of controls from each hospital (25 and 28 controls from the Henry Dunant Hospital and the University Hospital of Heraklion, respectively). Matching was achieved for all 53 cases (100%) for the first criterion of matching (site of infection), for 44 cases (83.01%) for age and only for 3 cases (5.66%) for length of hospital stay up to isolation of the *K. pneumoniae* strain. Hence, the matched analysis included only the site of infection as a matching variable (otherwise one would have to disregard the number of patients that did not match from the analysis or proceed to an unmatched analysis).

Types of infection

In the group of the 53 cases, the following sites of infection were identified: bacteraemia was present in 14 patients (8 and 6 patients in the Henry Dunant Hospital and the University of Heraklion hospital, respectively), pneumonia in 12 (8 and 4), urinary tract infections in 12 (1 and 11), surgical site infection in 8 (4 and 4), catheter-related infection in 4 (4 and 0) and genital tract infections in 3 patients (0 and 3). The risk of acquisition of *K. pneumoniae* for different types of infections varies (as genital tract infections due to *K. pneumoniae* are relatively rare).

Risk factors

In Table 1, we present the results of the bivariable analysis of matched data regarding risk factors associated with CRKp infections. Statistically significant differences between cases and controls were observed for history of COPD ($P = 0.04$), admission to the ICU ($P = 0.002$), need for mechanical ventilation ($P = 0.02$), prior use of anti-*pseudomonas* penicillins ($P = 0.004$), fluoroquinolones ($P < 0.0001$), glycopeptides ($P < 0.001$), carbapenems ($P = 0.01$), presence of tracheostomy ($P = 0.02$) and surgery with use of foreign body ($P = 0.04$). The multivariable analysis for matched data showed that prior use of fluoroquinolones [odds ratio (OR) 4.54, 95% OR 1.78–11.54, $P = 0.001$] and antipseudomonal penicillins [OR 2.60, 95% confidence interval (CI) 1.00–6.71, $P = 0.04$] were independent risk factors for CRKp infections.

In Table 2, we present the results of the bivariable analysis of risk factors associated with death (in-hospital mortality) (comparators in this analysis are the survivors and the deceased patients). Age, admission to the ICU, APACHE II score at ICU admission, use of carbapenems, special treatments and rhinogastric tube in place were identified as risk factors for hospital mortality because of *K. pneumoniae* infections (irrespective of whether this was carbapenem-susceptible or carbapenem-resistant). The multivariable analysis showed that APACHE II score was the only independent risk factor for mortality in the studied group of patients (OR 1.15, 95% CI 1.04–1.28, $P = 0.007$).

Outcome

In our study, 16 of 53 patients (30.1%) with an infection due to CRKp died during hospitalization when compared with 18 of 53 (33.9%) of their matched controls ($P = 0.83$). Favourable outcomes of infection in the cases and their matched control group were achieved in 62.2% and 58.4%, respectively ($P = 0.83$). In a subset analysis of 14 patients with CRKp bacteraemia and their matched controls, no statistical difference was found regarding patient outcome and infection outcome. Thirty-seven of the 53 patients with CRKp infections received appropriate antibiotic treatment (according to the results of the *in vitro* susceptibility testing), whereas 16 received inappropriate antibiotic treatment. In the group that received appropriate antibiotic treatment, intravenous colistin was the antibiotic used in 36 out of the 37 patients (97.2%), whereas one patient received intravenous tetracycline. In the group that received antibiotics discordant from the *in vitro* results, 8 out of the 16 patients (50%) received a carbapenem combination [4 meropenem (2 of them received additionally an aminoglycoside, 1 additionally tetracycline and 1 a fluoroquinolone) and 4 imipenem/cilastatin (1 of them additionally an aminoglycoside)], 4 (25%) received other β-lactams (2 received ampicillin/sulbactam plus fluoroquinolone and one piperacillin/tazobactam plus doxycycline) and 4 (25%) received fluoroquinolones (1 of them in addition to doxycycline). Eleven out of 37 patients who received appropriate antibiotic treatment died, whereas 5 out of the 16 patients who received inappropriate antibiotics died ($P = 0.9$).

Discussion

The main finding of our analysis is that prior use of quinolones and antipseudomonal penicillins was an independent risk factor associated with the development of CRKp infections. In addition, the APACHE II score at ICU admission was associated with death among the studied patients (cases and controls). Methodological principles suggest that the appropriate control group, for the majority of studies in the field of antibiotic resistance, that ideally represents the source or base population is, for studies of hospital-acquired pathogens, the cohort of all hospitalized patients. One exception is if the specific question is, 'What are the risk factors for developing antibiotic-resistant pathogen X among patients with antibiotic-susceptible pathogen X?'.[11] The selection of controls in our study was in accordance to the question 'What are the risk factors for developing CRKp among patients with CSKp?' The appropriate control group for this research question is patients who previously had a susceptible organism isolated.

It is interesting that in the only other relevant study in the literature, the previous use of carbapenems and cephalosporins were identified as independent risk factors for acquisition of CRKp, whereas the use of fluoroquinolones was negatively associated with the isolation of CRKp.[8] However, in that study, the controls were randomly selected; this methodological approach may explain the difference of the findings regarding the role of fluoroquinolones as a potential risk factor for CRKp. Special attention is always required when interpreting the results of a case–control study focusing on infections due to multidrug-resistant bacteria.[11,12] Increased fluoroquinolone use has been associated with increased fluoroquinolone resistance among Gram-negative bacilli in a large US study.[13] In the same study, ciprofloxacin-resistant *K. pneumoniae* and ciprofloxacin-susceptible *K. pneumoniae* were associated with a 3.2% and 0.5% imipenem resistance, respectively.

It is noteworthy that fluoroquinolone use has also been associated with the acquisition of multidrug-resistant (including carbapenem resistance) *P. aeruginosa* and polymyxin-only-susceptible *A. baumannii*.[14] Even though case–control studies only attempt to highlight associations and by no means can imply causality, we can speculate that previous administration of fluoroquinolones either results in a selective pressure and overgrowth of non-susceptible strains or facilitates the activation of intrinsic mechanisms that confer resistance to multiple antibiotic drug classes (e.g. drug-efflux mechanisms).

In our study, prior use of an antipseudomonal penicillin (only combinations of an antipseudomonal penicillin with an inhibitor were studied) was found to be an independent risk factor for the development of CRKp. There are no previous studies in the literature reporting antipseudomonal penicillins as a risk factor for CRKp. In a study examining the acquisition of multidrug-resistant (including imipenem-resistant) *P. aeruginosa* in ICU patients, the use of piperacillin (but not piperacillin/tazobactam) was found to be a risk factor in the univariate analysis only.[15] A stepwise manner of evolution of resistance is associated with the exposure to a variety of antipseudomonal antibiotics (including piperacillin/tazobactam) in the case of imipenem-resistant *P. aeruginosa*.[16]

There is a scarcity of information about risk factors and outcome for CRKp infections, despite the universal concern regarding the emergence of outbreaks because of CRKp.[17–22] In a case series describing the outcome of eight patients with CRKp infections in the surgical intensive care setting, six of eight patients died (mortality 75%).[9] One of the two patients who survived in that study received quinolone, whereas the

Table 1. Bivariable analysis of risk factors associated with carbapenem-resistant *K. pneumoniae* infections

Variable name	CR ($n = 53$) mean ± SD or n (%)	CS ($n = 53$) mean ± SD or n (%)	P value
Demographic			
age (years)	61.5 ± 18.8	61.9 ± 17.2	0.60
sex (male)	38/53 (71.6)	39/53 (73.5)	1.00
length of hospital stay[a]	21.4 ± 23.9	15.3 ± 19.9	0.09
Co-morbidity			
heart disorders	23/53 (43.3)	28/53 (52.8)	0.38
malignancy	12/53 (22.6)	15/53 (28.3)	0.67
COPD	25/53 (47.1)	15/53 (28.3)	0.04
diabetes mellitus	13/53 (24.5)	19/53 (35.8)	0.32
acute renal failure	9/53 (16.9)	8/53 (15.0)	1.00
chronic renal failure	3/53 (5.6)	3/53 (5.6)	1.00
liver disorders	4/53 (7.5)	5/53 (9.4)	1.00
haematological disorders	3/53 (5.6)	2/53 (3.7)	1.00
neurological disorders	15/53 (28.3)	13/53 (24.5)	0.83
prior hospitalization	31/53 (58.4)	23/53 (43.3)	0.18
prior surgery	16/53 (30.1)	11/53 (20.7)	0.33
admission to the ICU	38/53 (71.6)	26/53 (49.0)	0.002
mechanical ventilation	35/53 (66.0)	26/53 (49.0)	0.02
APACHE II score on ICU admission	14.4 ± 8.8	12.4 ± 6.1	0.42
Prior antibiotic use	24/53 (45.2)	10/53 (18.8)	0.07
anti-*Pseudomonas* penicillins	25/44 (56.8)	12/44 (27.2)	0.004
second-generation cephalosporins	6/44 (13.6)	4/44 (9.0)	0.72
third-generation cephalosporins	12/44 (27.2)	5/44 (11.3)	0.06
aminoglycosides	9/44 (20.4)	3/44 (6.8)	0.28
quinolones	29/44 (65.9)	12/44 (27.2)	<0.001
metronidazole	11/44 (25.0)	12/44 (27.2)	1.00
clindamycin	6/44 (13.6)	1/44 (2.2)	0.12
glycopeptides	27/44 (61.3)	11/44 (25.0)	<0.001
carbapenems	22/44 (50.0)	10/44 (22.7)	0.01
Special treatments total	30/53 (56.6)	26/53 (49.0)	0.45
Invasive procedures and devices			
central venous catheter	24/25 (96.0)	24/25 (96.0)	1.00
Foley catheter	26/53 (49.0)	25/53 (47.1)	1.00
nasogastric tube	22/53 (41.5)	23/51 (45.0)	1.00
foreign material in the body	17/53 (32.0)	7/53 (13.2)	0.04
colostomy	2/53 (3.7)	0/53 (0.0)	0.50
gastrostomy	2/53 (3.7)	1/53 (1.8)	1.00
surgical operations after admission	27/53 (50.9)	25/53 (47.1)	0.83
tracheostomy	18/53 (33.9)	7/53 (13.2)	0.02
Outcome			
infection outcome: favourable	33/53 (62.2)	31/53 (58.4)	0.83
patient outcome: mortality	16/53 (30.1)	18/53 (33.9)	0.83

CR, carbapenem-resistant; CS, carbapenem-susceptible; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; APACHE II score, Acute Physiology and Health Evaluation II score.
[a]Days of hospital stay prior to isolation of *K. pneumoniae*.

other patient received imipenem. Faecal surveillance specimens put into broth containing an imipenem disc have been used to screen samples for carbapenem-resistant nosocomial pathogens including *K. pneumoniae*.[23] In another reported outbreak, the outcome of carbapenemase KPC-3 *K. pneumoniae* infections in 24 patients in ICUs was reported. Eight out of 24 patients died (mortality 33%).[18] In an outbreak due to carbapenemase KPC-2 *K. pneumoniae*, three out of four patients with true infection survived (hospital mortality 25%).[19] Two of these patients had a urinary tract infection: one patient was successfully treated with a regimen that included piperacillin/tazobactam and imipenem and the other was successfully treated with imipenem and amikacin. One patient with bacteraemia was successfully treated with imipenem and amikacin. One patient with respiratory tract infection in this group died despite receiving treatment with ciprofloxacin and polymyxin.

Our patient population with CRKp nosocomial infection showed an overall mortality that was not different from the

Table 2. Bivariable analysis of risk factors associated with death

Variable name	Died ($n = 34$) mean ± SD or n (%)	Survived ($n = 72$[a]) mean ± SD or n (%)	P value
Demographic			
age (years)	71.4 ± 9.6	57.2 ± 19.2	<0.001
sex (male)	23/34 (67.6)	54/72 (75)	0.49
length of hospital stay[b]	21.6 ± 22.9	16.9 ± 21.8	0.31
Co-morbidity			
heart disorders	21/34 (61.8)	30/72 (41.7)	0.06
malignancy	12/34 (35.3)	15/72 (20.8)	0.15
COPD	14/34 (41.2)	26/72 (36.1)	0.67
diabetes mellitus	10/34 (29.4)	22/72 (30.6)	1.00
acute renal failure	5/34 (14.7)	12/72 (16.7)	1.00
chronic renal failure	1/34 (2.9)	5/72 (6.9)	0.66
liver disorders	4/34 (11.8)	5/72 (6.9)	0.46
haematological disorders	3/33 (9.1)	2/71 (2.8)	0.32
neurological disorders	8/34 (23.5)	20/72 (27.8)	0.81
prior hospitalization	20/34 (58.8)	34/72 (47.2)	0.30
prior surgery	10/34 (29.4)	17/72 (23.6)	0.63
admission to the ICU	26/34 (76.5)	38/72 (52.8)	0.03
intubation/mechanical ventilation	24/34 (70.6)	37/72 (51.4)	0.09
APACHE II score on ICU admission	17.19 ± 8.0	10.72 ± 6.0	0.002
Prior antibiotic use			
anti-*Pseudomonas* penicillins	14/34 (41.2)	20/72 (27.8)	0.18
second-generation cephalosporins	16/31 (51.6)	22/66 (33.3)	0.11
third-generation cephalosporins	3/31 (9.7)	7/66 (10.6)	1.00
aminoglycosides	5/31 (16.1)	12/66 (18.2)	1.00
quinolones	5/31 (16.1)	7/66 (10.6)	0.51
metronidazole	16/31 (51.6)	26/66 (39.4)	0.27
clindamycin	11/31 (35.5)	12/66 (18.2)	0.07
glycopeptides	2/31 (6.5)	6/66 (9.1)	0.72
carbapenems	16/31 (51.6)	18/66 (27.3)	0.02
Special treatments total	24/34 (70.6)	32/72 (44.4)	0.013
Invasive procedures and devices			
central venous catheter	21/28 (75.0)	27/39 (69.2)	0.78
Foley catheter	21/34 (61.8)	30/72 (41.7)	0.06
nasogastric tube	20/34 (58.8)	25/72 (34.7)	0.02
foreign material in the body	7/34 (20.6)	17/72 (23.6)	0.80
colostomy	0/34 (0)	2/72 (2.8)	0.56
gastrostomy	1/34 (2.9)	2/71 (2.8)	1.00
surgical operations after admission	17/34 (50.0)	35/72 (48.6)	1.00
tracheostomy	11/34 (32.4)	14/72 (19.4)	0.22
Outcome			
infection outcome: favourable	1/34 (2.9)	63/72 (87.5)	<0.001

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; APACHE II score, Acute Physiology and Health Evaluation II score.
[a]The 72 survivors are the aggregate of 37/53 patients with carbapenem-resistant *K. pneumoniae* plus 35/53 patients with carbapenem-susceptible *K. pneumoniae*.
[b]Days of hospital stay prior to isolation of *K. pneumoniae*.

mortality of the control group (APACHE II score in the CRKp group was comparable with that of controls). This may be explained by the fact that in both hospitals participating in the study, there is a significant use of polymyxins for the treatment of severe multidrug-resistant infections. This means that the mortality of the CRKp could be possibly higher, if polymyxins were not used. There was no statistical difference regarding hospital mortality between patients with CRKp who received appropriate (colistin in the vast majority) versus inappropriate treatment.

By further examining the characteristics of patients who died (with either CRKp or CSKp) versus those characteristics of the survivors, mortality was associated in the bivariable analysis with increased age, APACHE II score, admission to the ICU, use of carbapenems and special treatments. APACHE II score, a well-known prognostic factor, was the only independent risk factor for mortality in the studied group of patients. The issue of whether infections due to multidrug-resistant Gram-negative bacteria are associated with increased mortality is controversial;[24,25] however, recent data

show that attributable mortality is associated with these infections.[26]

Unfortunately, the presence of enterobacteria with ESBL activity in a variety of environments (patients, animals and food) probably constitutes an important event that is sometimes associated with the development of further mechanisms of resistance, including carbapenem resistance.[27] In addition, molecular mechanisms enhance this potential.[28,29] Crosstalk between strains of enterobacteria of the same and different species makes the dissemination of multidrug resistance even worse.[30,31]

On the basis of the results of our study, the all-cause in-hospital mortality was not statistically different between cases with CRKp and matched controls with CSKp. Despite the lack of attributable mortality to CRKp infections, at least in the relatively small sample size of our study and in the context of the empirical treatment our patients received, i.e. common use of polymyxins,[32–34] one has to acknowledge that emerging CRKp infections constitute a significant evolution of antimicrobial resistance. Judicious use of antibiotics complementary to strict infection control measures seems to be mandatory in order to minimize or at least delay the widespread presence of multiresistant bacteria.

Our study has limitations. First, we should acknowledge that the number of patients included in this study is relatively small, although this is a common problem in studies assessing risk factors of infections because of multidrug-resistant microorganisms.[35] Secondly, molecular epidemiology investigations using PFGE patterns and PCR for resistance genes and sequencing of PCR products were not performed in our study; thus details on the kind of carbapenemase are not available. The importance of identifying each specific carbapenemase must be acknowledged, as the MICs vary with the type of carbapenemase and may have an impact on treatment results. However, we thought that we should present our experience with this emerging type of infection and designed this retrospective study to assess possible risk factors for the development of CRKp infections and describe the outcome of patients with such infections.

In conclusion, this matched case–control study identified previous exposure to fluoroquinolones and antipseudomonal penicillins as independent risk factors for acquisition of infections due to CRKp. Hospital mortality in the general setting of patients with CRKp infections in this study was not different from that of patients with CSKp infections.

Acknowledgements

We thank Alex Spanos for his help in the statistical analysis of the data.

Funding

None.

Transparency declarations

None to declare.

References

1. Endimiani A, Luzzaro F, Perilli M *et al.* Bacteremia due to *Klebsiella pneumoniae* isolates producing the TEM-52 extended-spectrum β-lactamase: treatment outcome of patients receiving imipenem or ciprofloxacin. *Clin Infect Dis* 2004; **38**: 243–51.

2. MacKenzie FM, Forbes KJ, Dorai-John *et al.* Emergence of a carbapenem-resistant *Klebsiella pneumoniae*. *Lancet* 1997; **350**: 783.

3. Koh TH, Babini GS, Woodford N *et al.* Carbapenem hydrolyzing IMP-1 β-lactamase in *Klebsiella pneumoniae* from Singapore. *Lancet* 1999; **353**: 2162.

4. Tortola MT, Lavilla S, Miro E *et al.* First detection of a carbapenem-hydrolyzing metalloenzyme in two Enterobacteriaceae isolates in Spain. *Antimicrob Agents Chemother* 2005; **49**: 3492–5.

5. Lincopan N, McCulloch JA, Reinert C *et al.* First isolation of metallo-β-lactamase-producing multiresistant *Klebsiella pneumoniae* from a patient in Brazil. *J Clin Microbiol* 2005; **43**: 516–9.

6. Thomson JM, Bonomo RA. The threat of antibiotic resistance in Gram-negative pathogenic bacteria: β-lactams in peril! *Curr Opin Microbiol* 2005; **8**: 518–24.

7. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis* 2005; **40**: 1333–41.

8. 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.

9. Ahmad M, Urban C, Mariano N *et al.* Clinical characteristics and molecular epidemiology associated with imipenem-resistant *Klebsiella pneumoniae*. *Clin Infect Dis* 1999; **29**: 352–5.

10. Gaynes RP, Horan TC. Surveillance of nosocomial infections. Appendix A: CDC definitions of nosocomial infections. In: Mayhall CG. *Hospital Epidemiology and Infection Control*. Baltimore: Williams & Wilkins, 1996; 1–14.

11. Harris AD, Karchmer TB, Carmeli Y *et al.* Methodological principles of case–control studies that analysed risk factors for antibiotic resistance: a systematic review. *Clin Infect Dis* 2001; **32**: 1055–61.

12. Harris AD, Samore MH, Lipsitch M *et al.* Control-group selection importance in studies of antimicrobial resistance: examples applied to *Pseudomonas aeruginosa*, enterococci, and *Escherichia coli*. *Clin Infect Dis* 2002; **34**: 1558–63.

13. Neuhauser MM, Weinstein RA, Rydman R *et al.* Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA* 2003; **289**: 885–8.

14. Kopterides P, Koletsi PK, Michalopoulos A *et al.* Exposure to quinolones is associated with carbapenem resistance among colistin-susceptible *Acinetobacter baumannii* blood isolates. *Int J Antimicrob Agents*, in press.

15. Paramythiotou E, Lucet JC, Timsit JF *et al.* Acquisition of multidrug-resistant *Pseudomonas aeruginosa* in patients in intensive care units: role of antibiotics with antipseudomonal activity. *Clin Infect Dis* 2004; **3**: 670–7.

16. Harris A, Torres-Viera C, Venkataraman L *et al.* Epidemiology and clinical outcomes of patients with multiresistant *Pseudomonas aeruginosa*. *Clin Infect Dis* 1999; **28**: 1128–33.

17. Peleg AY, Franklin C, Bell JM *et al.* Dissemination of the metallo-β-lactamase gene bla_{IMP-4} among gram-negative pathogens in a clinical setting in Australia. *Clin Infect Dis* 2005; **41**: 1549–56.

18. Woodford N, Tierno PM, Young K *et al.* Outbreak of *Klebsiella pneumoniae* producing a new carbapenem-hydrolyzing class A β-lactamase, KPC-3, in a New York medical center. *Antimicrob Agents Chemother* 2004; **48**: 4793–9.

19. Bradford PA, Bratu S, Urban C *et al.* Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem hydrolyzing KPC-2 and inhibitor-resistant TEM-30 β-lactamases in New York City. *Clin Infect Dis* 2004; **39**: 55–60.

20. Bratu S, Landman D, Haag R *et al*. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. *Arch Intern Med* 2005; **165**: 1430–5.

21. Bratu S, Tolaney P, Karumudi U *et al*. Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and *in vitro* activity of polymyxin B and other agents. *J Antimicrob Chemother* 2005; **56**: 128–32.

22. Ikonomidis A, Tokatlidou D, Kristo I *et al*. Outbreaks in distinct regions due to a single *Klebsiella pneumoniae* clone carrying a bla_{VIM-1} metallo-β-lactamase gene. *J Clin Microbiol* 2005; **43**: 5344–7.

23. Landman D, Salvani JK, Bratu S *et al*. Evaluation of techniques for detection of carbapenem-resistant *Klebsiella pneumoniae* in stool surveillance cultures. *J Clin Microbiol* 2005; **43**: 5639–41.

24. Fournier PE, Richet H. The epidemiology and control of *Acinetobacter baumannii* in health care facilities. *Clin Infect Dis* 2006; **42**: 692–9.

25. Falagas ME, Kopterides P, Siempos , II. Attributable mortality of *Acinetobacter baumannii* infection among critically ill patients. *Clin Infect Dis* 2006; **43**: 389.

26. Falagas ME, Rafailidis PI. Attributable mortality of *Acinetobacter baumannii*: no longer a controversial issue. *Crit Care* 2007; **11**: 134.

27. Mesa RJ, Blanc V, Blanch AR *et al*. Extended-spectrum β-lactamase-producing Enterobacteriaceae in different environments (humans, food, animal farms and sewage). *J Antimicrob Chemother* 2006; **58**: 211–5.

28. Crowley B, Benedí VJ, Doménech-Sánchez A. Expression of SHV-2 β-lactamase and of reduced amounts of OmpK36 porin in *Klebsiella pneumoniae* results in increased resistance to cephalosporins and carbapenems. *Antimicrob Agents Chemother* 2002; **46**: 3679–82.

29. Vourli S, Giakkoupi P, Miriagou V *et al*. Novel GES/IBC extended-spectrum β-lactamase variants with carbapenemase activity in clinical enterobacteria. *FEMS Microbiol Lett* 2004; **234**: 209–13.

30. Bidet P, Burghoffer B, Gautier V *et al*. *In vivo* transfer of plasmid-encoded ACC-1 AmpC from *Klebsiella pneumoniae* to *Escherichia coli* in an infant and selection of impermeability to imipenem in *K. pneumoniae*. *Antimicrob Agents Chemother* 2005; **49**: 3562–5.

31. Luzzaro F, Docquier JD, Colinon C *et al*. Emergence in *Klebsiella pneumoniae* and *Enterobacter cloacae* clinical isolates of the VIM-4 metallo-β-lactamase encoded by a conjugative plasmid. *Antimicrob Agents Chemother* 2004; **48**: 648–50.

32. Michalopoulos AS, Tsiodras S, Rellos K *et al*. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic. *Clin Microbiol Infect* 2005; **11**: 115–21.

33. Falagas ME, Kasiakou SK, Kofteridis DP *et al*. Effectiveness and nephrotoxicity of intravenous colistin for treatment of patients with infections due to polymyxin-only-susceptible (POS) gram-negative bacteria. *Eur J Clin Microbiol Infect Dis* 2006; **25**: 596–9.

34. Falagas ME, Rafailidis PI. When to include polymyxins in the empirical antibiotic regimen in critically ill patients with fever? a decision analysis approach. *Shock* 2007; **27**: 605–9.

35. Falagas ME, Kopterides P. Risk factors for the isolation of multi-drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: a systematic review of the literature. *J Hosp Infect* 2006; **64**: 7–15.