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SHORT REPORT
A hospital-based matched case–control study to identify risk factors for clinical infection with OXA-48-producing *Klebsiella pneumoniae* in rectal carriers

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SUMMARY

Asymptomatic colonisation of the gastrointestinal tract by carbapenemase-producing *Enterobacteriaceae* is an important reservoir for transmission, which may precede infection. This retrospective observational case–control study was designed to identify risk factors for developing clinical infection with OXA-48-producing *Klebsiella pneumoniae* in rectal carriers during hospitalisation. Case patients ($n = 76$) had carbapenemase-producing *K. pneumoniae* (CPKP) infection and positive rectal culture for CPKP. Control patients ($n = 174$) were those with rectal colonisation with CPKP but without CPKP infection. Multivariate analysis identified the presence of a central venous catheter (OR 4·38; 95% CI 2·27–8·42; $P = 0·008$), the number of transfers between hospital units (OR 1·27; 95% CI (1·06–1·52); $P < 0·001$) and time at risk (OR 1·02 95% CI 1·01–1·03; $P = 0·01$) as independent risk factors for CPKP infection in rectal carriers. Awareness of these risk factors may help to identify patients at higher risk of developing CPKP infection.

Key words: Antibiotic resistance, hospital-acquired (nosocomial) infections, Klebsiella.

The spread of antimicrobial-resistant bacteria is a major public health issue worldwide, primarily due to associated morbidity and mortality [1]. Among these microorganisms, carbapenemase-producing *Enterobacteriaceae* (CPE) are perhaps the most of clinical concern, since they can cause a broad spectrum of infections that are typically associated with high mortality, particularly in the acute healthcare setting. The impact of CPE in Spain is primarily due to OXA-48-producing and VIM-1-producing *Klebsiella pneumoniae* [2]. The proportion of patients who develop infection following CPE colonisation is influenced by host characteristics and the invasiveness of each type of CPE and although data regarding infection/colonisation ratios are limited, it has been estimated that 10–30% of colonised patients will subsequently develop CPE infection [3] The aim of the present study was to identify risk factors for carbapenemase-producing *K. pneumoniae* (CPKP) infection in rectal carriers of CPKP during hospitalisation.

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This study was conducted at the Hospital Universitario de Canarias (Tenerife, Spain), a 687-bed public tertiary hospital serving the northern area of the islands of Tenerife and La Palma, with a population of 446 253 inhabitants. Since October 2013 our hospital has implemented a CPE surveillance programme based on recommendations by the Autonomous Community of Madrid [4]. Our institution is currently classified as an endemic area for OXA-48-producing CPE to European Society of Clinical Microbiology guidelines [5]. All patients admitted to hospital wards where CPE had previously been detected were screened by rectal cultures once a week until 2 weeks after the last patient with confirmed CPE in that ward had been discharged. In addition, rectal swabs were collected from each patient on admission to the intensive care unit and then weekly until discharge.

Rectal swabs were cultured directly on ChromID® CARBA SMART selective chromogenic media (bioMèrieux, Marcy l'Etoile, France) and incubated at 37 °C for 24–48 h. Species identification and antimicrobial susceptibility tests were carried out with Vitek-II® (bioMèrieux) and reduced susceptibility or resistance to carbapenems was confirmed by Etest (bioMérieux). Carbapenemase production was confirmed with the modified Hodge test [6] and combination disk tests according to the European Committee on Antimicrobial Susceptibility Testing guidelines [7]. The resistance molecular mechanisms were identified by the Spanish Surveillance Programme of Antibiotic Resistance, Centro Nacional de Microbiología (Instituto de Salud Carlos III, Madrid) by polymerase chain reaction with specific primers (blaOXA-48, blaKPC, blaVIM, blaIMP, blaNDM, blaSHV and blaCTX-M) and sequencing.

We conducted a retrospective, observational, case–control study, between October 2013 and December 2015 using the following patient definitions:

- Case: patient with CPKP rectal colonisation (CPKP-RC) who developed CPKP infection (CPKP-IN) (at least one positive culture with demonstrated signs and/or symptoms of infection) during hospitalisation.
- Control: CPKP-RC patient, without isolation of CPKP from any biological sample in the previous 6 months, and no appearance of CPKP infection during hospital stay at the time of study.

A range of patient clinical and demographic variables as well as antibiotic treatment were collected to verify comparability between case and control groups as outlined in Table 1. Time at risk was considered as the number of days from hospital admission to infection for case patients, and to discharge or death for controls. The source of infection was established according to the Centers for Disease Control and Prevention criteria [8]. The authors waived the need for approval of the present study by Clinical Research Ethics Committee of our hospital, given its non-interventional and retrospective design.

Statistical analyses were performed using SPSS 21.0 (IBM, Armonk, NY: IBM Corp.).

The characteristics of the sample are described summarising the nominal variables with the relative frequency of their component categories and scale variables with the median (P_5–P_{95}) due to their non-normal distribution shown by the Kolmogorov–Smirnov test. Simple comparisons of variables between infected and non-infected groups were made in the first case with Pearson's χ^2 test and in the second with the Mann–Whitney test. The Kaplan–Meier method was used to investigate the role of patient length of stay on the risk of infection. All factors with a significance level of $P < 0{\cdot}10$ in simple comparisons were introduced as potential predictors of infection in binary logistic regression multivariable models to estimate their odds ratios using the full model and backward stepwise method of adjustment with Wald criterion. All tests of the study hypothesis were bilateral; differences with a $P < 0{\cdot}05$ were considered statistically significant.

During the study period, 272 CRKP-RC patients were detected, of whom 83 (30·5%) developed CPKP infection. All isolates were confirmed as CTX-M-15 ESBL and OXA-48-producing *K. pneumoniae* ST15. Of the 83 patients, 76 met the inclusion criteria for the study case group and among patients with positive rectal swabs, 174 constituted the control group. Median age was 72 years (interquartile range, 25–90 years) in the CPKP-RC group and 73 years (interquartile range, 28–92 years) in the CPKP-IN group. The sources of infection urinary tract (28, 37%), surgical site (17, 22%), secondary bloodstream (13, 17%), primary and central line bloodstream (10, 13%), pneumonia (6, 8%) and soft tissue and skin (2, 3%) A quarter (25%) of CPKP-IN patients died during these episodes.

The clinical and epidemiological characteristics of the two groups are shown in Table 1. Controls had significantly longer hospital stays (time at risk), but cases were more often transferred between hospital

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Table 1. *Comparison of potential predictive factors for CPKP infection between hospitalised cases (infected rectal carriers) and controls (non-infected rectal carriers)*

Variable	Cases ($n = 76$)	Controls ($n = 174$)	P
Age (years)[a]	72 (25–90)	73 (28–92)	0·598
Male sex[b]	42 (55)	115 (66)	0·103
Time at risk (days)[a,c]	23 (1–82)	32 (8–115)	0·013
Death during hospitalisation[b]	19 (25)	25 (14)	0·042
Admission from a long-term care facility[b]	3 (3·9)	15 (9)	0·189
Prior hospital admission within the last 3 months[b,c]	38 (50)	65 (37)	0·062
Transfers between hospital units[a,c]	2 (0–6)	1 (0–4)	<0·001
Surgery during hospitalisation[b]	45 (59)	92 (53)	0·354
Endoscopy[b]	9 (12)	27 (16)	0·446
Charlson comorbidity index[a]	4 (0–11)	5 (0–13)	0·325
Hospitalisation in medical ward[b]	23 (30)	79 (45)	0·002
Hospitalisation in intensive care unit[b,c]	12 (16)	7 (4)	
Hospitalisation in surgical ward[b]	41 (54)	88 (51)	
Neoplasia[b]	22 (29)	45 (26)	0·612
Liver disease[b]	5 (7)	18 (10)	0·343
Chronic obstructive pulmonary disease[b,c]	3 (4)	23 (13)	0·026
Diabetes mellitus[b]	38 (50)	82 (47)	0·676
Moderate or severe kidney disease[b]	10 (13)	35 (20)	0·188
Immunosuppression[b]	2 (3)	7 (4)	0·727
Urinary catheter[b,c]	67 (88)	109 (63)	<0·001
Central venous catheter[b,c]	62 (82)	79 (45)	<0·001
Invasive mechanical ventilation[b,c]	17 (22)	24 (14)	0·092
MDRO infection/colonisation within the last 3 months[b,c]	26 (34)	38 (22)	0·039
Antibiotic treatment[d]			
Antibiotic use [b,c]	69 (91)	139 (80)	0·034
Carbapenems[b]	34 (45)	60 (34)	0·124
Imipenem[b,c]	14 (18)	18 (10)	0·079
Ertapenem[b]	2 (3)	6 (3)	0·999
Meropenem[b]	22 (29)	44 (25)	0·546
Penicillins[b,c]	27 (36)	41 (24)	0·051
Cephalosporins[b]	30 (40)	70 (40)	0·911
Fluoroquinolones[b,c]	37 (49)	55 (32)	0·010
Other antibiotics[b]	33 (43)	70 (40)	0·637

MDRO: multidrug-resistant organisms (Methicillin-resistant *Staphylococcus aureus*, Imipenem – resistant *Acinetobacter baumannii*, Vancomycin – resistant *Enterococcus*, multidrug-resistant *Pseudomoonas aeruginosa* and CPE).
[a] Median (interquartile range) compared with *U* Mann–Whitney test.
[b] *n* (%) compared with Pearson's χ^2 test.
[c] Variables were included in the multivariate analysis.
[d] Administration for more than 3 days within the last 3 months.

units ($P < 0·001$), had prior hospital admissions within the last 3 months ($P < 0·062$), and resident in intensive care unit ($P < 0·002$). In addition, cases underwent more invasive procedures during their hospital stay, including insertion of a central venous and/or urinary catheter and mechanical ventilation. Higher rates of colonisation or infection with other multi-resistant microorganisms were observed in the case group and the use of antibiotics (penicillins and fluoroquinolones) was more frequent in cases compared with the control group. The cumulative infection risk increased progressively during the first 100 days of hospital stay, then stabilised with a risk level around 1.

The only variables retained by the model as independent risk factors for infection by CPKP were the presence of a central venous catheter (OR 4·38; 95% CI 2·27–8·42; $P = 0·008$), the number of transfers between hospital units (OR 1·27; 95% CI 1·06–1·52; $P < 0·001$) and time at risk (OR 1·02; 95% CI 1·01–1·3; $P = 0·010$).

This study investigated risk factors for the development of CPKP infection in patients who were initially

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only rectally colonised with these organisms. Previous colonisation with *K. pneumoniae* has often been shown to be preceded its appearance in nosocomial infection [9]. To date, no published studies have investigated risk factors for developing nosocomial infection with OXA-48-producing *K. pneumoniae* in rectal carriers. In our study group, the rate of CPKP infection was 30·5% in initially colonised patients which likely reflects the rate of infection in the general adult inpatient population in our tertiary hospital. As independent risk factors for infection by CPKP, multivariate analysis identified the presence of a central venous catheter, the number of transfers between hospital units and time at risk.

Invasive procedures [2, 9, 10] and medical devices commonly play a far more important role in increasing susceptibility to nosocomial infections than underlying diseases and likely provide a portal of entry or even a source of infection in previously colonised patients. Poor compliance with aseptic techniques and hand hygiene, as well as more aggressive and intensive nursing care, could facilitate the transmission of CPKP from dirty to clean surfaces [2]. As in other studies, prior insertion of a central venous catheter was associated with CPKP infection, and such procedures have been shown to be constituted an independent predictor of CPKP infection in initially colonised patients [9].

Few studies [11] have identified transfers of patients between hospital units as an independent risk factor of CPKP infection but more generally hospital-associated infections have been linked to such transfers [12]. It is therefore not surprising that this proved to be an independent risk factor for CPKP infection in this study, since patients with more transfers inevitably have more direct contact with a contaminated environment, CPE rectal carriers, health workers or hospital equipment.

Extended hospital stay is a major risk factor for CPE colonisation [11]. However, few studies have related length of hospital stay specifically with the development of CPKP infection. Here, we defined time at risk as the number of days from hospital admission to infection for case patients, and to discharge/death for controls, considering that the reservoir is unknown, thus exposure could either be direct and/or indirect. By logistic regression analysis, Vergara-Lopez *et al.* [13] demonstrated that time at risk was the only variable associated with infection by clonal multidrug-resistant *Klebsiella oxytoca* in the context of a four-wave outbreak which occurred in a Spanish intensive care unit. In our study, surprisingly, non-infected controls were significantly more likely than cases to have longer hospital stay and among infected patients, the number of transfers between hospital units outweighed the influence of hospital stay time.

French *et al.* [14] concluded in their review on the control of CPE that there is limited evidence to support the use of multi-component measures, but it is difficult to disaggregate the effectiveness of individual components, or which components are best used together. However, the diminution of hospital stay and the creation of a CPKP patient unit in order to reduce transfers within the hospital could help to decrease CPKP infections in our hospital, apart from emphasis on compliance with aseptic techniques in central venous catheter use.

CPE can produce a broad spectrum of infections usually in the acute healthcare setting [2]. In our study group, the most common type of CPKP infections was urinary tract infection followed by bacteraemia and surgical site infection. Likewise CPE infection is typically a late complication of hospitalisation generally occurring approximately 2–4 weeks from patient admission [15]. Our CPKP-IN cases developed infection at a median of 23 days after admission and the cumulative risk of infection increased progressively during the first 100 days of hospital stay, then stabilised with a risk level around 1.

The present study has some limitations. First, we were unable to obtain reliable information on exposures outside the study centre, so outpatient antibiotic therapy may have influenced our results. Second, because the study was limited to a single centre, these results may not necessarily be extrapolated to other hospital situations.

In conclusion, this case–control study confirmed that use of central venous catheters, number of transfers between hospital units, and time at risk are independent risk factors for CPKP infection in rectal carriers. Awareness of these risk factors would help identify which high-risk patients to target for the prevention of CPKP infection and underline the importance of implementing strict infection control measures.

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DECLARATION OF INTEREST

All authors report no conflicts of interest relevant to this article.

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