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Carbapenemase-producing Enterobacteriaceae digestive carriage at hospital readmission and the role of antibiotic exposure

S. Evain [a], C. Bourigault [a,b], M.-E. Juvin [b], S. Corvec [b], D. Lepelletier [a,b,*]

[a] Microbiotas, Host, Antibiotics, Bacterial Resistance (MiHAR Lab), University of Nantes, Nantes, France
[b] Bacteriology and Infection Control Department, Nantes University Hospital, Nantes, France

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SUMMARY

Background: Colonization by carbapenemase-producing Enterobacteriaceae (CPE) may persist for several months after hospital discharge, especially in patients with altered microbiota.

Aim: To identify how many previously OXA-48 CPE-positive patients identified during an outbreak period were readmitted; to evaluate their CPE-positive or -negative digestive tract colonization at hospital readmission and during readmission stay; and to assess the role of antibiotic exposure on their CPE colonization status during readmission.

Methods: All CPE cohort patients from June 2013 to May 2016 ($N = 189$) were registered in a survey database and were systematically identified at readmission by a daily informatics and alert program using specific hospital population number. Each cohort patient was systematically screened for CPE colonization on the day of readmission and then weekly if the length of stay was more than six days.

Findings: In all, 114 (60.3%) patients previously CPE-colonized were readmitted to our hospital. Excluding the 12 patients who were not screened because their period of readmission was <24 h, 88 patients were negative (86.3%) and 14 were positive (13.7%) for CPE colonization at first hospital readmission. The 14 CPE-positive patients did not change their infectious status and remained CPE-positive during the study period. Of the 88 negative patients, 65 remained negative during the study period, and 23 subsequently became CPE-positive after the negative readmission screening. CPE-positive colonization was significantly associated with antibiotic exposure during readmission periods ($P < 0.001$).

Conclusion: Negative screens at hospital readmission did not necessarily predict resolution of CPE carriage. Antibiotic exposure appears to influence the risk of remaining CPE positive.

Introduction

Our hospital experienced a large outbreak caused by *Klebsiella pneumoniae* producing OXA-48 carbapenemase between June 2013 and June 2015 [1]. The first case retrospectively

* Corresponding author. Address: University of Nantes, Nantes, 5 rue du Professeur Yves Boquien, Bât le Tourville, FR-44093, Cedex 1, France. Tel.: +33 611 915 233.
E-mail address: didier.lepelletier@chu-nantes.fr (D. Lepelletier).

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identified was a patient repatriated from Morocco after a quad motor accident. This outbreak involved several healthcare wards, generated more than 180 secondary cases during the outbreak period, and was managed using French guidelines [2]. Colonization by carbapenemase-producing Enterobacteriaceae (CPE) may persist for several months after hospital discharge, especially in patients with altered microbiota [3–5]. These findings closely affect the clinical management and infection control measures at the time of CPE-colonized patients' readmission. The aims of our study were to identify how many prior CPE-positive patients were readmitted, to evaluate their CPE positive or negative colonization at hospital readmission, and to assess the role of antibiotic exposure on their positive CPE colonization during readmission.

Methods

Setting and study design

The study was a single-centre survey performed at the Nantes University Hospital, France. Our hospital is a 3000-bed teaching hospital providing all types of acute care with around 90,000 admissions and 900,000 hospital-days per year. We implemented a retrospective analysis of a cohort of CPE-colonized patients detected during a previous outbreak period when readmitted at the Nantes University Hospital from February 2013 to May 2016 [1].

Patients

All cohort patients were registered in a survey database and were systematically identified at readmission by a daily informatics and alert program. Each cohort patient was systematically screened for CPE colonization on the day of readmission and then weekly if the length of stay was longer than six days. Number of CPE-positive or -negative patients was calculated according to the time between prior admission and first readmission (<3, <6, <12, <18, and >18 months).

Microbiology

Stool samples were collected with rectal swab and cultured on selective chromogenic media (chromID Carba-Smart ID®; bioMérieux, Marcy l'Etoile, France). Mastdiscs ESBL-E and Mastdisc-carbapenemase (CARB/OXA48) were used to confirm the suspected resistance phenotype.

Collection of data

Demographic, clinical, microbiological (result of systematic screening for CPE colonization at each readmission, characterization of CPE), antibiotic exposure during readmission periods and intra-hospital death were collected from the electronic medical records. Each patient could be readmitted several times in our hospital during the study period (i.e. cares for chronic diseases). Each patient was studied to assess the CPE colonization status at readmission and antibiotic exposure. Patients were classified as those without change in their CPE infectious status (negative or positive) and those with CPE infectious status that had changed during readmission periods (negative to positive). Data according to demographic characteristics and to CPE carriage at first hospital readmission were related to each readmitted patient; data according to the length of stay, antibiotic exposure, and to CPE carriage classification (positive/positive or negative/positive) were related to each hospital readmission.

Statistics

Data were collected using Excel software (Microsoft, Redmond, CA, USA). Data were described using the mean with standard deviation (SD) for continuous variables and proportions (%) for qualitative variables. Comparisons relied on the Kruskal–Wallis test for continuous variables and on the χ^2-test or Fisher's exact test, as appropriate, for qualitative variables. All *P*-values were two sided, and $P < 0.05$ was considered significant.

We used the STROB (STrengthening the Reporting of OBservational studies in Epidemiology) criteria for transparent reporting [6].

Results

In total, 189 patients were detected positive for CPE digestive carriage during the outbreak period (June 2013 to June 2015) with the clonal strain. The median age was 66.6 years ($\pm$16.6 SD) and 58% were male. The microbiological analysis showed monobacterial results in 142 cases: the most common Enterobacteriaceae producing OXA-48 were *K. pneumoniae* (61/142, 43%) and *E. coli* (58/142, 40.8%). Among other samples ($N = 47$), two different OXA-48 were detected, mainly *E. coli* and *K. pneumoniae* (Figure 1). Molecular analysis showed a clonal spread of both strains and plasmids. The majority of these identifications were made by systematic epidemiological rectal screening for EPC OXA-48 colonization with culture exam (166/189, 87.8%). In the other cases, they were performed from clinical specimens such as cytological and bacteriological urinary exam (11/189, 5.8%), blood culture (5/189, 2.6%), the combination of two (1/189, 0.5%), rapid real-time PCR screening (4/189, 2.1%), cytological and bacteriological sputum test (1/189, 0.5%), or surgical wound (1/189, 0.5%).

During this study period, 47/189 (24.9%) CPE-positive carriers died. Among them, 19 (40.4%) deaths occurred during the first hospitalization (detection of the first CPE colonization). Around 3000 contact patients were detected during the outbreak period and were included in a specific alert database in order to screen them if readmitted in our hospital. During the study period, 500 contact patients were readmitted (17%) and five of them were found to be positive for OXA-48 CPE colonization, suggesting cross-transmission during their hospitalization (1%).

During this study period, 114 (60.3%) patients previously CPE-colonized were readmitted to our hospital. Of these 114 CPE-colonized patients, 67.5% were readmitted more than once. In total, 359 readmissions were analysed, with a median number of 2 (range: 1–13). The median time between two readmissions was 36 days (range: 0–712). Patients were mainly readmitted in three healthcare wards: infectious diseases (33.9%), immunology–nephrology (19.6%) and internal medicine (17.5%), respectively. Among the 359 readmissions, the length of stay varied from <5 days (21.4%), 5–10 days (39.3%), 11–20 days (25.9%), and >21 days (13.6%).

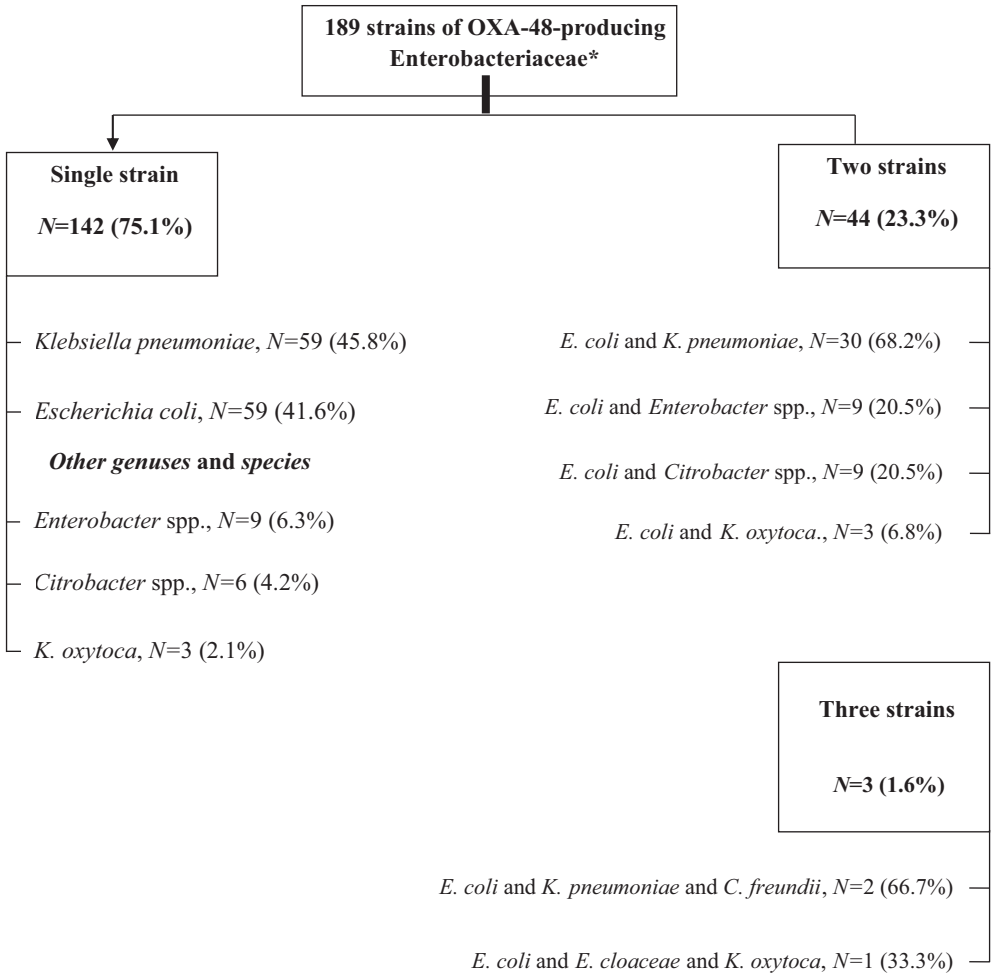

Figure 1. Distribution and number of strains per specimen of the different OXA-48-producing Enterobacteriaceae isolated from the 189 positive patients ($N = 189$).

Twelve patients were not screened despite (or within) the protocol (readmission <24 h), 88/102 (86.3%) patients were negative and 14 (13.7%) were positive for CPE colonization at first hospital readmission, respectively. Those 14 CPE-positive patients did not change their infectious status and remained CPE positive during the study period. Of the 88 negative patients, 65 remained negative during the study period and 23 were detected CPE positive after the negative readmission screening (Figures 2 and 3). A total of 472 swabs were made for all the 359 readmissions during the study period and 65.5% were negative for CPE colonization (309/472).

Forty-four per cent of patients were exposed to antibiotics during readmission (50/114). The rate of readmission with antibiotic exposure was 24.8% (89/359). The median duration of antibiotic exposure was 6.5 days (range: 1–55). The median number of antibiotics per patient was 2 (1–9): 43 antibiotics of 25 different classes were prescribed including carbapenems and trimethoprim–sulfamethoxazole (31/89, 34.8%, respectively), amoxicillin–clavulanic acid (29/89, 32.6%), and cephalosporins (26/89, 29.0%). Sixteen cohort patients (14.0%) were never exposed to antibiotics during readmissions and 13 always (11.4%).

CPE-positive colonization was significantly associated with antibiotic exposure during readmission periods ($P < 0.001$) (Figure 2).

Discussion

This study demonstrated the low proportion of CPE-positive patients at hospital readmission and the role of antibiotic exposure. Only 14% of patients with past history of CPE colonization remained positive at the time of the first hospital readmission. But 20% of patients detected negative at readmission were again positive for CPE gastrointestinal carriage either during the first readmission if longer than six days or during new readmissions. When the relationship between CPE-positive/negative gastrointestinal colonization and the antibiotic exposure was examined, there was a significant association between antibiotic exposure and the CPE positivity in patients identified as testing CPE negative at the first readmission. This finding highlights the role of antibiotics in the microbiota modification and the ability to detect CPE carriage. Antibiotics with high activity against anaerobes that were mostly used in our study population potently affect the capacity of the microbiota to prevent colonization by exogenous micro-organisms with an increase in relative abundance of resistant enterobacteria [7]. All CPE-positive patients are at risk of transmitting CPE to patients hospitalized in the same ward by cross-transmission through healthcare and environment [8]. In this situation, barrier

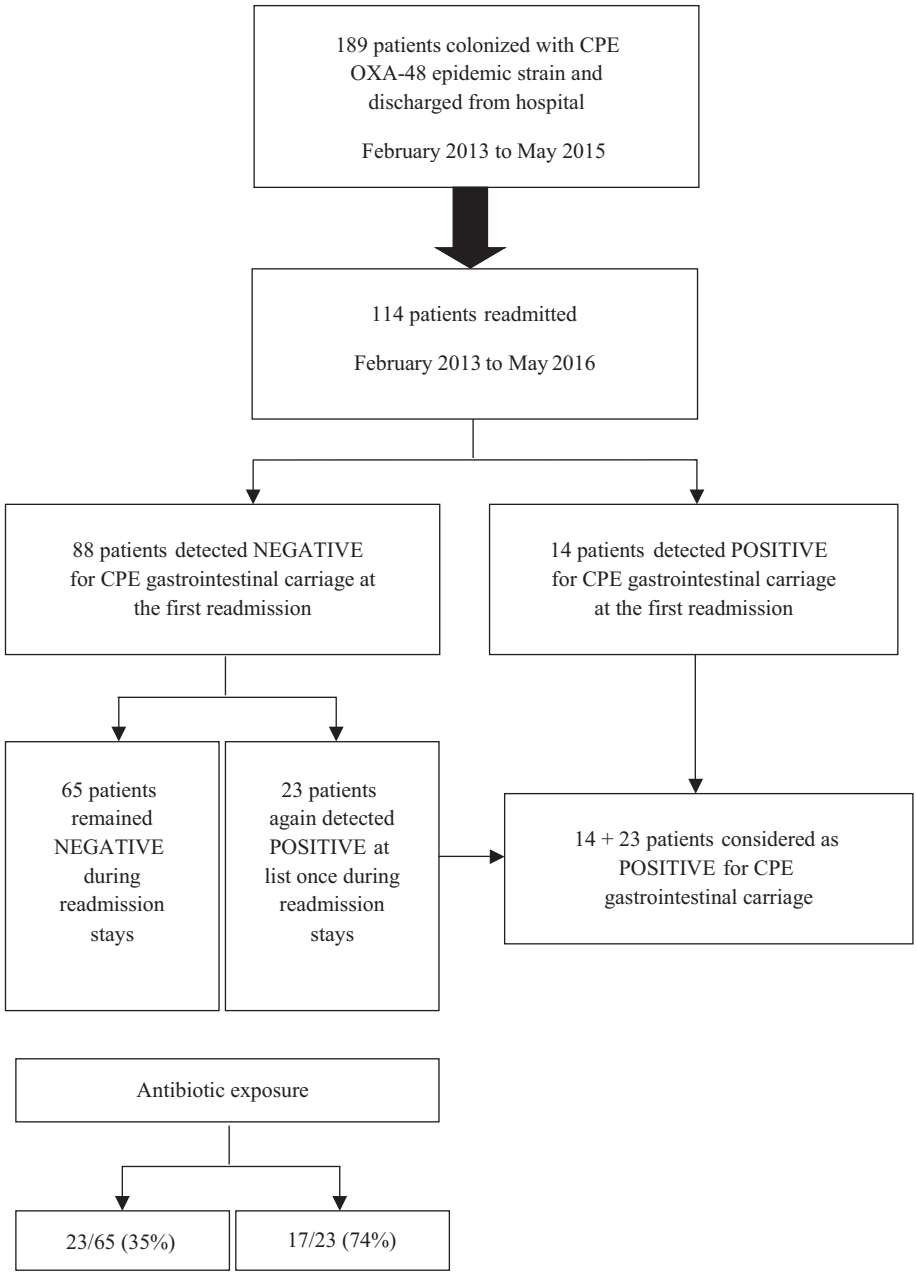

Figure 2. Flow chart related to the carbapenemase-producing Enterobacteriaceae (CPE) infectious status at hospital readmission and during readmission stay among patients with past history of CPE colonization.

precautions and systematic gastrointestinal screening are needed among contact patients to evaluate the possible cross-transmission during the entire hospitalization of CPE-positive patients [2].

Patients were mostly detected CPE positive at hospital readmission within a period of three or 12 months after their initial hospitalization and rarely after 12 months. By contrast, most of the patients (60%) were CPE negative at hospital readmission. Without antibiotic exposure, these patients with previous history of positive CPE gastrointestinal carriage may be considered at lower risk for CPE transmission as they mostly remained negative. This non-detection of CPE gastrointestinal carriage at readmission is probably related to the low rectal CPE concentrations of these patients, as a weak linear correlation between the degree of gastrointestinal carriage of CPE and environmental contamination has been previously described [8]. Those results allow us to propose to survey those low-risk patients without isolation precaution after two negative screenings during the same hospital stay of more than six days. We recommend therefore performance of an additional rectal swab 48 or 72 h after a new antibiotic exposure. We also recommend systematic screening of them again at each readmission time, as microbiota modification may occur between two hospitalizations (community healthcare or antibiotic exposure). But we do not know for how much time and after how many successive negative screenings we need to survey (one year, or the remaining lifetimes for patients with multiple readmissions for chronic diseases), as

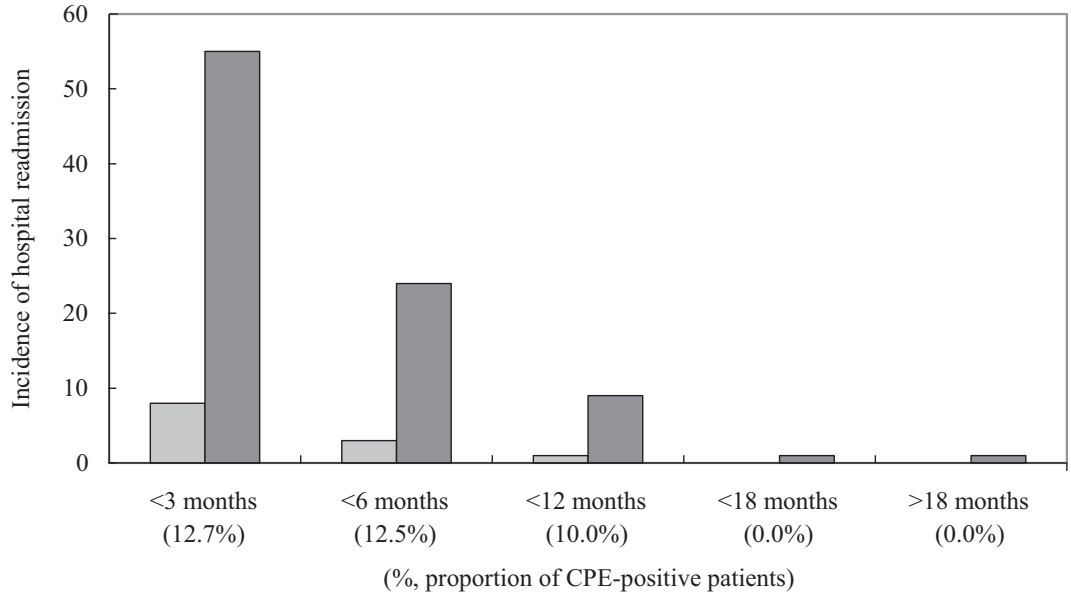

Figure 3. Incidence of carbapenemase-producing Enterobacteriaceae (CPE)-negative (dark grey bars; $N = 65$) or -positive (light grey bars; $N = 14$) patients at hospital readmission among patients with past history of CPE colonization according to the interval time between the first hospitalization (CPE acquisition) and readmission.

negative patients were again detected positive for CPE colonization after five negative screenings [9,10]. Accurate and reliable determination of definitive negativity of CPE gastrointestinal carriage is important for patients and healthcare settings, especially when an active strategy of carrier surveillance is performed. Our results show that a single negative rectal swab is probably not sufficient to determine definitively the negative status of previous CPE-colonized patients, as 23 negative patients at the time of readmission with more than two tests did have a subsequent positive screening. However, the total number of tests per patient and the duration of follow-up in our study are probably not sufficient to determine the exact number of tests that are required for defining CPE clearance according to the discontinuing carrier follow-up [3]. However, our risk factor analyses may identify patients who are less likely to remain carriers (patients with several negative screenings and without antibiotic exposure).

By the cohort contact patient's follow-up during our study period, it was found that very few readmitted contact patients were at risk of carriage, as only 1% of them were detected positive for CPE gastrointestinal carriage (unpublished data). The risk of positive carriage among contacts is probably related to the initial outbreak situation with secondary cases, the antibiotic exposure during hospital stay, and the time between the CPE acquisition and the readmission. Also, no data are available to let us know when we can stop surveillance and screening and when we can exclude contact patients from the database.

The results of the present study are relevant in this field as few data are available, but this study has some limitations. This retrospective analysis of CPE patient cohort is a single-centre study. The time between the previous hospitalization and the first readmission was heterogeneous, and patients and contacts not studied may have been hospitalized in other hospitals of the region and results may have been over- or underestimated. Patients readmitted to our university hospital may represent a population with higher risk of CPE carriage because of chronic underlying diseases and more frequent antibiotic exposures, and some previous CPE-colonized patients may have not been detected at hospital readmission for microbiological features [11].

Since the implementation of this survey, no secondary cases were detected in our hospital from readmitted at-risk patients (contact patients or previous positive colonized patients) (unpublished data). The key factors for this successful control were the daily detection program by the hospital informatics system, the infection control team automatic alert, and the awareness of each healthcare professional in our hospital in implementing isolation and in screening suspected patients immediately at the readmission time. Given the current global menace, this surveillance strategy needs daily risk assessment to implement the best preventive precaution to control the CPE spread [12–14].

In conclusion, CPE-positive patients are frequently readmitted. Negative screenings at hospital readmission did not necessarily predict resolution of CPE carriage. Antibiotic exposure appears to influence the risk of remaining positive for CPE gastrointestinal colonization. Negative carriers at hospital readmission with several negative tests could be defined as at low risk of transmission, especially when they are not exposed to antibiotics. Prevention policies could take into account this remaining negative CPE colonization status for the indication to screen systematically all contact patients. Further studies are needed to better understand and assess the duration and resolution of CPE carriage.

Conflict of interest statement
None declared.

Funding sources
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