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ORIGINAL ARTICLE

Risk factors for carbapenem-resistant Enterobacteriaceae infections: a French case-control-control study

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Abstract

This study aimed to assess characteristics associated with infections due to carbapenem-resistant Enterobacteriaceae (CRE), producing (CPE) or not producing (non-CPE) carbapenemase, among hospitalised patients in 2014–2016 in France. Case-patients with CRE were compared to two control populations. In multivariate analysis comparing 160 CRE cases to 160 controls C1 (patients with a clinical sample positive for carbapenem-susceptible Enterobacteriaceae), five characteristics were linked to CRE: male gender (OR = 1.9; 95% CI = 1.3–3.4), travel in Asia (OR = 10.0; 95% CI = 1.1–91.2) and hospitalisation in (OR = 2.4; 95% CI = 1.3–4.4) or out of (OR = 4.4; 95% CI = 0.8–24.1) France in the preceding 12 months, infection in the preceding 3 months (OR = 3.0; 95% CI = 1.5–5.9), and antibiotic receipt between admission and inclusion (OR = 1.9; 95% CI = 1.0–3.3). In multivariate analysis comparing 148 CRE cases to 148 controls C2 [patients with culture-negative sample(s)], four characteristics were identified: prior infection (OR = 3.3; 95% CI = 1.6–6.8), urine drainage (OR = 3.0; 95% CI = 1.5–6.1) and mechanical ventilation (OR = 3.7; 95% CI = 1.1–13.0) during the current hospitalisation, and antibiotic receipt between admission and inclusion (OR = 6.6; 95% CI = 2.8–15.5). Univariate analyses comparing separately CPE cases to controls (39 CPE vs C1 and 36 CPE vs C2) and non-CPE cases to controls (121 non-CPE vs C1 and 112 non-CPE vs C2), concomitantly with comparison of CPE to non-CPE cases showed that only CPE cases were at risk of previous travel and hospitalisation abroad. This study shows that, among CRE, risk factors are different for CPE and non-CPE infection, and suggests that question patients about their medical history and lifestyle should help for early identification of patients at risk of CPE among patients with CRE.

Keywords Carbapenem-resistant Enterobacteriaceae (CRE) · Carbapenemase-producing Enterobacteriaceae (CPE) · Risk factors · Case-control-control study · Multicentre study

Introduction

Resistance to extended-spectrum cephalosporins linked to various extended-spectrum β-lactamases (ESBL), notably CTX-M enzymes since the early 2000s, is a global well-known problem among Enterobacteriaceae [1]. As most ESBL-producing Enterobacteriaceae resist multiple antibiotic classes in addition to penicillin and cephalosporin classes,

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carbapenems have widely been regarded as the drugs of choice for the treatment of severe infections caused by these multidrug-resistant isolates [2, 3]. Unfortunately, carbapenem resistance emerged among Enterobacteriaceae in link to two principal mechanisms [4]: acquisition of specific enzymes that hydrolyse carbapenems, called carbapenemases, such as KPC, OXA-48 and NDM, and combination of ESBL and/or AmpC production and alterations of porin synthesis alone or associated with overexpression of genes encoding efflux pumps [5–8]. Recent national and regional surveillances of carbapenem-resistant Enterobacteriaceae (CRE) showed that combination of ESBL and/or AmpC production and membrane permeability alterations is currently the dominant carbapenem resistance mechanism in France [9, 10]. Such a feature was also shown in other countries or regions such as Belgium, Taiwan, Hong Kong, Korea and Lebanon [7, 11–14]. The purpose of the present study was to characterise the factors associated with a clinical sample positive for CRE in patients hospitalised in France and to clarify those factors associated with a sample positive for a carbapenemase-producing CRE (CPE) and a sample positive for a non-CPE CRE. To reach this objective, we performed a prospective case-control-control study in 14 French hospitals located in various regions of France.

Methods

Ethical approval

The study was approved by the Ethics Committee of the Ile de France IV (Institutional Review Board No. IRB 00003835).

Study design and participants

The study was carried out from May 2014 to April 2016 in 13 university hospitals and 1 general hospital located in various French regions: two in the North, two in the South, two in the East, one in the West, one in the Centre and six in the Paris area. Factors associated with a clinical sample positive for CRE in patients hospitalised for at least 24 h were studied by using a case-control-control study. We followed the methodological principles recommended for case-control studies that analyse risk factors for antibiotic resistance, i.e. controls derived from the same source population as cases and selected during the same time periods [15]. Moreover, two different control groups were selected in order to get a better representation of the total base population.

Patients prospectively identified by the microbiological laboratory of each participating hospital with a clinical sample yielding CRE were eligible for the study. To be pre-included (pre-case), eligible patient had to be still hospitalised, able to answer a standardised questionnaire, the single patient with CRE in the concerned ward for several days or the index case of a known CRE outbreak, and to have control-patients. For each pre-case, two controls were selected on the laboratory register of the same hospital. The first control (C1) was the first inpatient with a clinical sample positive for carbapenem-susceptible Enterobacteriaceae (CSE) the same day or within the 3 days following the pre-case detection and without previous CRE detection in the digestive tract. When case was hospitalised in intensive care unit (ICU), his/her C1 had to be hospitalised in the same ICU. When case was hospitalised in a ward other than ICU, his/her C1 had to be hospitalised in a ward of the same type as that of case (medicine, surgery, paediatric, rehabilitation). The second control (C2) was the first inpatient with culture-negative sample(s), and without known carriage of CRE in the digestive tract since admission and until 3 days after the pre-case detection. C2 could be hospitalised in any ward.

Written informed consent was obtained from all adult cases and controls and from parents for child cases and controls. Each pre-case was included (case) as soon as the standardised questionnaire was filled out for him/herself and his/her controls. This study was registered on ClinicalTrials.gov (Identifier: NCT02127450).

Variables

Data were prospectively collected by one investigator in each countryside hospital and by one investigator in the six Paris area hospitals from inpatients, their family, medical team and the bacteriological and medical files for all cases and controls.

Demographic data

Standard demographic data, including country of birth and place of residence were collected.

Patient's lifestyle

Living arrangement was divided into three categories: individual housing with or without householder(s), collective housing and homeless. If appropriate, hospitalisation in the preceding 6 months and working in a medical centre of household(s) were collected. Patients receiving assistance for daily living before the current hospitalisation were considered functionally dependent. Occupation, unemployment or retirement as well as the presence of companion animals were clarified. Travel abroad during the last 12 months as well the countries visited and the accommodation type were recorded for the patients and, if appropriate, for household(s).

Medical history

The following variables were collected: number of hospitalisations, and location of hospital stay, and surgery during the preceding 12 months; invasive devices during the preceding 6 months; infection in the preceding 3 months; home care and antibiotic treatment during the preceding month.

Current hospitalisation

Date of admission in the hospital and in the ward in which cases and controls were pre-included, type of admission (direct admission or transfer from another hospital located in or outside of France), and stay in another hospital ward before inclusion were recorded. A patient was considered immunocompromised if he/she was under immunosuppressive drugs, i.e. chemotherapy, radiotherapy or corticosteroids (≥ 30 days or > 5 mg/kg for 5 days); he/she had haematological disease, metastatic cancer or HIV-related CD4 < 500 mm^3. Presence of invasive devices within the last week, and antibacterial treatment between hospital admission and inclusion in the study were documented. Date of sampling and type of clinical specimens positive for CRE (case), positive for Enterobacteriaceae susceptible to carbapenems (C1) or culture-negative sample(s) (C2) were collected.

Microbiological analyses

Enterobacteriaceae isolates were locally identified by the system used in each laboratory [API 20E or Vitek® 2 systems (bioMérieux, Marcy l'Etoile, France), MALDI-TOF MS (Bruker Daltonics, Bremen, Germany) or Vitek® MS (bioMérieux)].

Susceptibility to antibiotics was determined by the method used in each laboratory [Vitek2 ® (bioMérieux) and the agar disk diffusion method] and interpreted according to the 2014–2016 recommendations of the French Antibiogram Committee/European Committee on Antimicrobial susceptibility testing/(http://www.sfm.asso.fr/nouv/general.php?pa=2). Isolates were considered resistant to carbapenems when they were categorised intermediate susceptible or resistant to at least one of the carbapenems tested: ertapenem and imipenem or meropenem. Ertapenem non-susceptibility was systematically determined in each laboratory by using the ETEST® system (bioMérieux) whereas imipenem or meropenem susceptibility was determined by an inhibition zone diameter < 22 mm or a MIC > 2 mg/L when the Vitek2 ® system was used. Non-susceptibility to carbapenems of the Proteae tribe isolates had to be assessed on the susceptibility to ertapenem and meropenem, but not to imipenem because of the natural reduced susceptibility of this bacterial group to imipenem. Searching for carbapenemase production was locally performed on each CRE isolate by PCR with primers aimed at identifying the genes encoding the main carbapenemases described in Enterobacteriaceae: $bla_{\text{OXA-48 like}}$, bla_{NDM}, bla_{KPC}, bla_{VIM} and bla_{IMP}.

Study size

The study size was derived from the total number of patients with CRE clinical samples available through a surveillance study implemented in 71 French laboratories between May 2011 and April 2012 [10]. Therefore, 300 eligible patients (patients with a clinical sample positive for CRE) were expected during the study period, resulting in the inclusion of 160 cases. With regard to a risk factor present in 20% of controls, this number of included cases and controls will allow to detect an odds ratio of at least 2.0 with a power of 80% and a type 1 error of 5%. For a risk factor present in 10% of controls, an odds ratio of 2.4 would be detected.

Statistical analysis

Comparisons were analysed between cases and C1 and then between cases and C2. Variables associated with cases were analysed using conditional logistic regression on the pairs of cases and C1 and the pairs of cases and C2. Odds ratios (OR) and 95% confidence intervals (95% CI) were first estimated in univariate analyses. Variables with a p value < 0.1 were introduced into multivariate models and were selected thereafter by using a backward selection method. A final model in which all variables had a p value < 0.05 was obtained. For subpopulation of cases who had CPE, comparisons were analysed between 39 cases and 39 C1, and 36 cases and 36 C2 using only univariate analyses. Due to low number of CPE cases and risk of overfitting, multivariate analyses were not conducted for this subpopulation. For reasons of homogenisation, comparisons between the subpopulation of non-CPE cases and controls (121 cases vs 121 C1, and 112 cases vs 112 C2) were also performed by using univariate analyses. Comparisons between CPE and non-CPE were performed by Fisher exact tests. All statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC). Two-sided p-values were assessed at the 0.05 level.

Results

Participants and clinical samples

Among the 307 consecutively eligible CRE cases obtained during the study period, 180 were pre-included (pre-cases) and 127 excluded (Fig. 1). Among the 180 pre-cases, 17 were secondly excluded because of the following reasons: seven had an isolate susceptible to ertapenem (MIC < 0.5 mg/L),

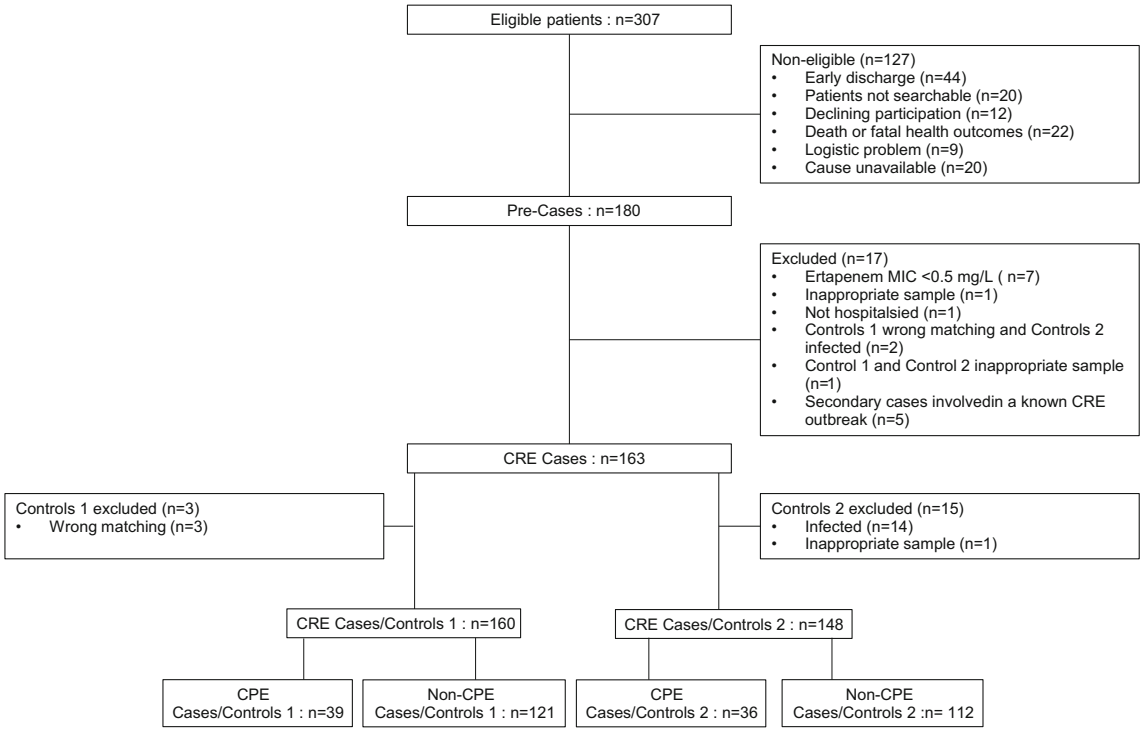

Fig. 1 Flowchart. Cases: patients with a clinical sample positive for carbapenem-resistant Enterobacteriaceae (CRE), controls 1 (patients with a clinical sample positive for carbapenem-susceptible Enterobacteriaceae), controls 2 [patient with culture-negative sample(s)]. CPE, carbapenemase-producing Enterobacteriaceae; non-CPE, non-carbapenemase-producing Enterobacteriaceae

one had an inappropriate sample, one was not hospitalised, three had both C1 and C2 with wrong inclusion criteria and five were secondary cases involved in a known CRE outbreak. Among the 163 cases, 160 could be compared with 160 C1 and 148 with 148 C2 (Fig. 1). Urine was the most common sample for cases (45.1%), C1 (53.1%) and C2 (41.2%) followed by blood sample (13.1, 11.2 and 32.3%, respectively).

Microbiological data

Enterobacter cloacae was the dominant species ($n = 73$: 45.6%) among the 160 CRE, followed by *Klebsiella pneumoniae* ($n = 47$: 29.4%) and *Escherichia coli* ($n = 19$: 11.9%), whereas *E. coli* was the dominant species ($n = 87$: 54.4%) among the 160 CSE isolated from C1, followed by *K. pneumoniae* ($n = 23$: 14.4%) and *E. cloacae* ($n = 12$: 7.5%).

Among the 160 cases, 39 (24.4%) had a clinical sample positive for CPE including 28 (71.8%) OXA-48 like, 8 (20.5%) NDM and 3 (7.7%) KPC (Table 1). Twenty-three (59.0%) of these enzymes were detected among the 47 (48.9%) CRE *K. pneumoniae*, 10 (25.6%) among the 19 (52.6%) CRE *E. coli*, 4 (10.3%) among the 73 (5.5%) CRE *E. cloacae* and 2 (5.1%) among the 21 (9.5%) other CRE isolates (Table 1).

The 160 CRE were resistant to ertapenem but mostly remained susceptible to imipenem or meropenem (diameter > 22 mm): 68% among *E. coli*, 62% among *K. pneumoniae* and 86% among *E. cloacae*. Inversely, most CRE were resistant to the other antibiotics tested except for amikacin (data not shown).

Analyses of CRE cases vs C1 controls

When cases were compared with C1 for demographic and lifestyle-related factors, univariate analysis showed that cases were more likely than C1 to be males (OR = 1.7; 95% CI = 1.1–2.7) and to have travelled in Asia in the preceding 12 months (OR = 4.5; 95% CI = 0.9–20.8) (Table 2). Regarding medical history-related factors (Table 3), cases were more likely than C1 (i) to have been hospitalised in the preceding 12 months: one hospitalisation (OR) = 2.3; 95% CI = 1.2–4.2), two or more hospitalisations (OR = 2.4; 95% CI = 1.4–4.4), location of hospitalisation either in France (OR = 2.3; 95% CI = 1.4–3.8) or outside of France (OR = 4.0; 95% CI = 1.0–16.4), and (ii) to have had intravascular devices in the preceding 6 months (OR = 2.0; 95% CI = 1.2–3.3), infection in the preceding 3 months (OR = 2.4; 95% CI = 1.4–4.2) and antibiotic receipt in the preceding month (OR = 2.0; 95% CI = 1.2–3.4). Regarding the current hospitalisation-related factors (Table 4), cases were more likely than C1 to have been transferred from a hospital located in France (OR = 2.1; 95% CI = 1.1–3.7) and given antibiotics between admission and inclusion (OR = 1.8; 95% CI = 1.1–2.9).

Table 1 CRE isolates producing carbapanemase from 39 of the 160 cases according to species and carbapenemase type

Carbapenemase	Number of isolates (%)				
	E. coli $N = 19$	*K. pneumoniae* $N = 47$	*E. cloacae* $N = 73$	Others[a] $N = 21$	Total $N = 160$
OXA-48 like	8	14	4	2	28
NDM	2	6	0	0	8
KPC	0	3	0	0	3
Total	10 (52.6)	23 (48.9)	4 (5.5)	2 (9.5)	39 (24.3)

CRE carbapenem-resistant Enterobacteriaceae

[a] Species with < 8 isolates: *Klebsiella oxytoca* ($n = 1$ producing OXA-48 like), *Citrobacter koseri* ($n = 1$ producing OXA-48-like), *Morganella morganii* ($n = 1$), *Citrobacter freundii* ($n = 3$), *Serratia marcescens* ($n = 3$), *Hafnia alvei* ($n = 5$), and *Enterobacter aerogenes* ($n = 7$)

In multivariate analysis (Table 5), variables independently associated with a CRE isolate were male gender (OR = 1.9; 95% CI = 1.1–3.4), travel in Asia (OR = 10.0; 95% CI = 1.1–91.2) in the preceding 12 months, hospitalisation either in France (OR = 2.4; 95% CI = 1.3–4.4) or outside of France (OR = 4.4; 95% CI = 0.8–24.1) in the preceding 12 months, infection in the preceding 3 months (OR = 3.0; 95% CI = 1.5–5.9), and antibiotic receipt between admission and inclusion (OR = 1.9; 95% CI = 1.0–3.3).

Analyses of CRE cases vs C2 controls

When cases were compared to C2, univariate analysis showed, once again, that cases were more likely to be males (OR = 1.6; 95% CI = 1.0–2.7) (Table 2). Regarding medical history-related factors, cases were more likely than C2 to have had mechanical ventilation (OR = 4.4; 95% CI = 1.7–11.6) and urine drainage (OR = 2.1; 95% CI = 1.2–3.9) in the preceding 6 months; infection in the preceding 3 months (OR = 2.7; 95% CI = 1.6–4.5); antibiotic receipt (OR = 2.3; 95% CI = 1.3–4.1) and also nursing or physiotherapy (OR = 2.1; 95% CI = 1.2–3.8) in the preceding month (Table 3). The remaining factors were linked to the current hospitalisation (Table 4): intravascular devices (OR = 2.5; 95% CI = 1.2–5.2), urine drainage (OR = 3.5; 95% CI = 2.0–6.1), mechanical ventilation (OR = 3.3; 95% CI = 1.4–7.7), antibiotic receipt between admission and inclusion (OR = 5.9; 95% CI = 3.1–11.2) and hospitalisation ward [intensive care (OR = 9.5; 95% CI = 2.2–41.8) and surgery (OR = 2.2; 95% CI = 0.7–6.5) vs medicine, paediatric or rehabilitation wards].

In multivariate analysis comparing cases and C2 (Table 5), two factors already identified in CRE cases/C1 multivariate analysis remained independently associated with CRE infection, i.e. infection in the preceding 3 months (OR = 3.3; 95% CI = 1.6–6.8) and antibiotic receipt between admission and inclusion (OR = 6.6; 95% CI = 2.8–15.5). Two additional factors were identified: urine drainage (OR = 3.0; 95% CI = 1.5–6.1) and mechanical ventilation (OR = 3.7; 95% CI = 1.1–13.0) in the current hospitalisation.

Subpopulation analyses

In order to analyse differences of factors associated with CPE and non-CPE isolates, we performed two subpopulation analyses.

Subpopulation of CRE cases with a CPE isolate

The 39 cases with a CPE isolate had a control C1 whereas 36 of them had a control C2 (Fig. 1). When comparing CPE cases to controls in univariate analysis (Table S1, S2 and S3), cases were more likely than C1 to have had hospitalisation in the preceding 12 months: one hospitalisation (OR = 5.5; 95% CI = 1.4–20.7), two or more hospitalisations (OR = 2.2; 95% CI = 0.7–7.2) and mechanical ventilation in the preceding 6 months (OR = 4.5; 95% CI = 0.9–20.8), whereas CPE cases were more likely than C2 to have had antibiotic receipt both in the previous month (OR = 4.0; 95% CI = 1.1–14.2) and between admission and inclusion (OR = 7.5; 95% CI = 1.7–32.8), and urine drainage during the current hospitalisation (OR = 3.7; 95% CI = 1.0–13.1).

Subpopulation of CRE cases with a non-CPE isolate

The 121 cases with a non-CPE isolate had a control C1 whereas 112 of them had a control C2 (Fig. 1). Through univariate analysis (Table S4, S5 and S6), non-CPE cases were more likely than C1 to be males (OR = 1.9; 95% CI = 1.1–3.3) and to have been exposed to healthcare factors, i.e. prior hospitalisation in the preceding 12 months (one hospitalisation (OR = 1.7; 95% CI = 0.8–3.5), two or more hospitalisations (OR = 2.4; 95% CI = 1.2–4.6), especially in France (OR = 2.2; 95% CI = 1.2–4.0), prior intravascular devices (OR = 2.2; 95% CI = 1.2–3.9), prior infection (OR = 2.9; 95% CI = 1.5–5.8), and receipt of antibiotics prior (OR = 2.1; 95% CI = 1.1–4.0) and during (OR = 1.8; 95% CI = 1.0–3.0) the current hospitalisation. On the contrary, non-CPE cases were less likely than C1 to have travelled in Africa (OR = 0.4; 95% CI = 0.1–1.0) and to have stayed in their family

Table 2 Univariate analysis of demographic and lifestyle-related factors associated with a carbapenem-resistant Enterobacteriaceae (CRE) isolate through a case (patient with a CRE isolate)-control (C1: patient with a carbapenem-susceptible Enterobacteriaceae isolate)-control (C2: patient with culture-negative sample) study

Factor	Case: $N = 160$ No. (%)	C1: $N = 160$ No. (%)	Odds ratio (95% CI)	p value	Case: $N = 148$ No. (%)	C2: $N = 148$ No. (%)	Odds ratio (95% CI)	p value
Demographic data								
Age (mean ± SD) in years	62 ± 18.4	64 ± 18.6	1.0 (0.98–1.0)	0.4	61 ± 18.6	61 ± 16.5	1.0 (0.99–1.0)	1
Male gender	109 (68)	90 (56)	1.7 (1.1–2.7)	0.03	105 (71)	89 (60)	1.6 (1.0–2.7)	0.05
Country of birth								
- France	121 (76)	128 (80)	1	0.6	110 (74)	113 (76)	1	0.5
- Other Europe country	12 (7)	9 (6)	1.4 (0.6–3.4)		12 (8)	7 (5)	1.7 (0.7–4.4)	
- Country outside Europe	27 (17)	23 (14)	1.3 (0.7–2.5)		26 (18)	28 (19)	1.0 (0.5–1.8)	
Living in France	153 (96)	156 (98)	0.5 (0.1–2.0)	0.3	141 (95)	144 (97)	0.6 (0.2–2.0)	0.4
Lifestyle								
Housing								
- Individual housing	150 (94)	150 (94)	1	0.9	138 (93)	146 (99)	1	0.9
- Collective housing	7 (4)	6 (4)	1.2 (0.4–3.5)		7 (5)	0	–	
- Homeless	3 (2)	4 (3)	0.8 (0.2–3.4)		3 (2)	2 (1)	1.5 (0.3–0.9)	
Live alone	35 (23)	40 (26)	0.9 (0.5–1.4)	0.6	33 (23)	39 (27)	0.8 (0.5–1.4)	0.5
Household hospitalisation in the preceding 6 months	11 (9)	9 (10)	0.7 (0.2–1.9)	0.4	10 (9)	7 (7)	1.6 (0.5–4.9)	0.4
Household working in a medical centre	9 (8)	7 (6)	2.3 (0.6–9.0)	0.2	9 (7)	5 (5)	2.3 (0.6–9.0)	0.2
Functionally independent before hospitalisation	131 (82)	126 (79)	1.3 (0.7–2.3)	0.5	123 (83)	135(89)	0.6 (0.3–1.1)	0.1
Occupational status								
- Working	46 (29)	36 (23)	1	0.2	49 (33)	48 (33)	1	0.5
- Student	5 (3)	3 (2)	1.6 (0.3–9.8)		5 (3)	3 (2)	2.1 (0.4–12.7)	
- Unemployed	21 (13)	16 (10)	1.1 (0.5–2.4)		19 (13)	14 (10)	1.4 (0.6–3.1)	
- Retirement	83 (52)	94 (59)	0.7 (0.4–1.2)		72 (49)	74 (50)	0.9 (0.6–1.6)	
- Others	5 (3)	11 (7)	0.3 (0.1–1.2)		3 (2)	8 (5)	0.4 (0.1–1.5)	
With pets	57 (36)	65 (41)	0.8 (0.5–1.3)	0.4	48 (32)	54 (36)	0.8 (0.5–1.4)	0.4
Patient travel abroad in the preceding 12 months								
- Yes, in Europe	19 (12)	19 (12)	1.0 (0.5–2.0)	1	20 (14)	20 (14)	1.0 (0.2–2.0)	1
- Yes, in Asia	10 (6)	3 (2)	4.5 (0.9–20.8)	0.05	11 (7)	3 (2)	3.7 (1.0–13.1)	0.3
- Yes, in Africa	13 (8)	20 (13)	0.6 (0.3–1.3)	0.2	13 (9)	18 (12)	0.7 (0.3–1.4)	0.3
- Yes, in America	3 (2)	2 (1)	1.5 (0.3–9.0)	0.7	3 (2)	2 (1)	1.5 (0.3–9.0)	0.7
If travel, accommodation								
- In the family/home stay	22 (14)	27 (17)	0.7 (0.4–1.4)	0.3	23 (16)	24 (17)	0.9 (0.5–1.7)	0.7
- In hotel	16 (10)	13 (8)	1.3 (0.6–2.8)	0.5	17 (12)	15 (10)	1.2 (0.5–2.6)	0.7
Household travel abroad in the preceding 12 months								
- Yes, in Europe	16 (10)	17 (11)	0.9 (0.5–1.9)	0.9	14 (10)	24 (16)	0.5 (0.3–1.1)	0.09
- Yes, in Asia	9 (6)	4 (3)	2.3 (0.7–7.3)	0.2	9 (6)	5 (3)	2.0 (0.6–6.6)	0.3
- Yes, in Africa	8 (5)	14 (9)	0.5 (0.2–1.3)	0.2	7 (5)	13 (9)	0.5 (0.2–1.4)	0.2
- Yes, in America	4 (3)	7 (4)	0.6 (0.2–2.0)	0.4	4 (3)	2 (1)	2.0 (0.4–10.9)	0.4
If travel, accommodation								
- In the family/home stay	16 (10)	20 (13)	0.7 (0.3–1.5)	0.4	16 (11)	19 (13)	0.8 (0.4–1.7)	0.6
- In hotel	16 (10)	13 (8)	1.3 (0.6–2.8)	0.5	14 (10)	21 (14)	0.6 (0.3–1.3)	0.2

Table 3 Univariate analysis of medical history-related factors associated with a carbapenem-resistant Enterobacteriaceae (CRE) isolate through a case (patient with a CRE isolate)-control (C1: patient with a carbapenem-susceptible Enterobacteriaceae isolate)-control (C2: patient with culture-negative samples) study

Factor	Case $N = 160$ No. (%)	C1 $N = 160$ No. (%)	Odds ratio (95% CI)	p value	Case $N = 148$ No. (%)	C2 $N = 148$ No. (%)	Odds ratio (95% CI)	p value
Medical history								
Number of hospitalisations in the preceding 12 months								
- 0	42 (27)	72 (45)	1	0.004	41 (29)	58 (41)	1	0.1
- 1	50 (33)	42 (26	2.3 (1.2–4.2)		44 (31)	45 (31)	1.4 (0.7–2.5)	
- > 2	62 (40)	45 (28)	2.4 (1.4–4.4)		56 (40)	40 (28)	1.9 (1.0–3.6)	
Hospitalisation location in the preceding 12 months								
- No hospitalisation	42 (26)	72 (45)	1	0.003	41 (28)	58 (40)	1	0.06
- In France	110 (69)	84 (52)	2.3 (1.4–3.8)		99 (67)	85 (58)	1.7 (1.0–2.8)	
- Outside of France	8 (5)	4 (3)	4.0 (1.0–16.4)		8 (5)	4 (3)	3.4 (0.8–14.1)	
In the preceding 6 months								
- Mechanical ventilation	26 (17)	19 (12)	2.0 (0.9–4.5)	0.09	23 (16)	7 (5)	4.4 (1.7–11.6)	0.003
- Urine drainage	41 (26)	38 (24)	1.1 (0.6–2.0)	0.7	40 (28)	24 (16)	2.1 (1.2–3.9)	0.02
- Intravascular devices	94 (59)	69 (44)	2.0 (1.2–3.3)	0.006	85 (58)	76 (51)	1.3 (0.8–2.2)	0.3
- Colonoscopy, endoscopy	65 (42)	56 (35)	1.5 (0.8–2.6)	0.2	65 (45)	68 (39)	1.3 (0.8–2.2)	0.3
Surgery during the preceding 12 months	46 (29)	38 (24)	1.5 (0.8–2.6)	0.19	39 (27)	31 (21)	1.5 (0.8–2.6)	0.2
Infection in the preceding 3 months	84 (53)	58 (37)	2.4 (1.4–4.2)	0.001	78 (53)	44 (30)	2.7 (1.6–4.5)	0.0001
Antibiotics in the month preceding hospitalisation	60 (39)	41 (26)	2.0 (1.2–3.4)	0.01	57 (40)	34 (24)	2.3 (1.3–4.1)	0.003
Nursing or physiotherapy in the month preceding hospitalisation	63 (41)	56 (36)	1.3 (0.8–2.1)	0.4	57 (40)	40 (28)	2.1 (1.2–3.8)	0.01

when travelling (OR = 0.4; 95% CI = 0.2–1.0). When non-CPE cases were compared with C2, cases were more likely to be male (OR = 1.9; 95% CI = 1.0–3.4), to have had infection (OR = 2.7; 95% CI = 1.5–4.9), antibiotic receipt (OR = 2.0; 95% CI = 1.1–3.7) and nursing (OR = 2.2; 95% CI = 1.1–4.2), all before the current hospitalisation, and to have been exposed to multiple healthcare factors during the current hospitalisation: urine drainage (OR = 3.5; 95% CI = 1.9–6.4), mechanical ventilation (OR = 4.0; 95% CI = 1.5–10.7) and antibiotic receipt (OR = 5.6; 95% CI = 2.7–11.3).

Additional analyses

Additional analyses were performed because travel in Asia and prior hospitalisation out of France found independently related to CRE in the CRE/C1 comparison were not associated with non-CPE cases (Table S4 and S5), whereas they tended to be associated to CPE cases (OR = 6.0; 95% CI = 0.7–49.8; $p = 0.1$) (Tables S1 and S2). Therefore, we compared CPE and non-CPE cases with regard to both characteristics (Table 6). Through this comparison, we found that CPE cases were more likely than non-CPE cases (i) to have travelled in Asia (15.4 vs 3.3%; $p = 0.01$), in Africa (17.9 vs 5.0%; $p = 0.02$) and in America (7.7 vs 0%; $p = 0.01$) but not in Europe (15.4 vs 10.8%; $p = 0.56$) and (ii) to have had prior hospitalisation abroad (17.9 vs 0.8%; $p = 0.0005$).

Discussion

Globally, CRE are major health care-associated pathogens and responsible for both sporadic and grouped hospital-acquired infections [16]. CRE incidence rate varies according to regions (https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf.) [17–19]. We recently showed, through a 2011–2012 national survey, in which 71 hospital and community laboratories had participated, that CRE incidence rate was 0.63% in France and that of CPE was fortunately low, i.e. < 0.1% [10]. Therefore, this low endemicity of both CRE and CPE encourages implementation of aggressive and comprehensive procedures to prevent the spread of CRE, including CPE. As identifying factors associated with CRE infections is a key component of control efforts, we conducted a prospective, multicentre and case-control-control study to assess risk factors with regard to CRE, including CPE and non-CPE.

Our results are in line with previous findings reported in France in terms of microbiology: predominance of non-CPE

Table 4 Univariate analysis of current hospitalisation-related factors associated with a carbapenem-resistant Enterobacteriaceae (CRE) isolate through a case (patient with a CRE isolate)-control (C1: patient with a carbapenem-susceptible Enterobacteriaceae isolate)-control (C2: patient with culture-negative samples) study

Factor	Case $N = 160$ No. (%)	C1 $N = 160$ No. (%)	Odds ratio (95% CI)	p value	Case $N = 148$ No. (%)	C2 $N = 148$ No. (%)	Odds ratio (95% CI)	p value
Current hospitalisation								
Transferred from a hospital located in France	48 (30)	31 (19)	2.1 (1.1–3.7)	0.02	46 (31)	35 (24)	1.6 (0.9–2.7)	0.1
Transferred from a hospital located outside of France	4 (3)	2 (1)	2.0 (0.4–10.9)	0.4	4 (3)	4 (3)	0.8 (0.2–3.4)	0.7
Stay in another hospital ward before the current ward								
- None	82 (52)	96 (61)	1	0.3	79 (55)	84 (60)	1	0.6
- Medicine, paediatric, rehabilitation	37 (24)	27 (17)	1.8 (1.0–3.3)		33 (23)	28 (20)	1.2 (0.6–2.3)	
- Surgery	15 (10)	16 (10)	1.1 (0.4–2.8)		11 (7)	13 (9)	0.9 (0.3–2.2)	
- Intensive care	23 (15)	19 (12)	1.6 (0.7–3.5)		22 (15)	15 (11)	1.6 (0.7–3.5)	
Intravascular devices	142 (89)	131 (82)	1.8 (0.9–3.5)	0.1	132 (89)	116 (79)	2.5 (1.2–5.2)	0.02
Urine drainage	100 (63)	92 (58)	1.3 (0.8–2.2)	0.4	94 (64)	54 (36)	3.5 (2.0–6.1)	< 0.0001
Mechanical ventilation	38 (24)	41 (26)	0.9 (0.5–1.9)	0.9	36 (25)	21 (14)	3.3 (1.4–7.7)	0.006
Immunocompromised	48 (30)	48 (30)	1.0 (0.6–1.6)	0.9	44 (30)	56 (38)	0.6 (0.4–1.1)	0.1
Antibiotic receipt between admission and inclusion	104 (66)	83 (52)	1.8 (1.1–2.9)	0.02	96 (66)	39 (27)	5.9 (3.1–11.2)	< 0.0001
Hospitalisation ward								
- Medicine, paediatric, rehabilitation	85 (53)	84 (53)	1	0.6	74 (50)	93 (63)	1	0.007
- Surgery	30 (19)	31 (19)	0.5 (0.05–5.5)		29 (20)	25 (17)	2.2 (0.7–6.5)	
- Intensive care	45 (28)	45 (28)	–		45 (30)	30 (20)	9.5 (2.2–41.8)	

isolates among all CRE isolates (66%), a majority of OXA-48 like carbapenemase among detected carbapenemases (72%) and of *K. pneumoniae* among species producing CPE (59%) [9, 10]. We identified four factors associated with CRE, namely male gender, mechanical ventilation and urine drainage in the current hospitalisation, and recent antibiotic exposure. These factors also were previously found in the review and meta-analyses recently published by van Loon et al. from

Table 5 Multivariate analysis of factors associated with a CRE clinical isolate

Independent variable	Odds ratio (95% CI)	p value
Comparison with controls C1: patients with a CSE isolate ($N = 160$)		
Male gender	1.9 (1.1–3.4)	0.03
Patient travel abroad in the preceding 12 months, Yes in Asia	10.0 (1.1–91.2)	0.04
Hospitalisation/location in the preceding 12 months		0.009
- No hospitalisation	1	
- In France	2.4 (1.3–4.4)	
- Outside of France	4.4 (0.8–24.1)	
Infection in the preceding 3 months	3.0 (1.5–5.9)	0.002
Antibiotic receipt between admission and inclusion	1.9 (1.0–3.3)	0.04
Comparison with controls C2: patients with culture-negative samples ($N = 148$)		
Infection in the preceding 3 months	3.3 (1.6–6.8)	0.002
Urine drainage in current hospitalisation	3.0 (1.5–6.1)	0.003
Mechanical ventilation in current hospitalisation	3.7 (1.1–13.0)	0.04
Antibiotic receipt between admission and inclusion	6.6 (2.8–15.5)	< 0.0001

CRE carbapenem-resistant Enterobacteriaceae, *CSE* carbapenem-susceptible Enterobacteriaceae

Table 6 Comparison of CRE cases with a carbapenemase-producing CRE (CPE) and a non-carbapenemase-producing CRE (non-CPE) about travel abroad and prior hospitalisation

Factor	CPE $N = 39$ No. (%)	Non-CPE $N = 121$ No. (%)	p value
Patient with travel abroad in the preceding 12 months			
- In Europe	6 (15.4)	13 (10.8)	0.6
- In Asia	6 (15.4)	4 (3.3)	0.01
- In Africa	7 (17.9)	6 (5.0)	0.02
- In America	3 (7.7)	0 (0.0)	0.01
Hospitalisation location in the preceding 12 months			
- No hospitalisation	8 (20.5)	34 (28.1)	0.0005
- In France	24 (61.5)	86 (71.1)	
- Outside of France	7 (17.9)	1 (0.8)	

CRE carbapenem-resistant Enterobacteriaceae

69 studied [20]. In addition, we identified three factors not reported in van Loon's study. These factors that refer patients' lifestyle and medical history comprise travel in Asia and region of hospitalisations in the preceding 12 months as well as infection in the preceding 3 months. Hospitalisation outside of France displayed an OR higher (4.4; 95% CI = 0.8–24.1) than that of hospitalisation in France (2.4; 95% CI = 1.3–4.4) compared to no hospitalisation. We hypothesised that such factors were not looked for in the 69 studies reviewed by van Loon et al. Therefore, we suggest systematically including questions about patient's medical history and lifestyle in the standard medical questionnaire for early identification of patients at risk of CRE.

Some factors independently associated with CRE were found in univariate analyses performed on the subpopulation of cases infected by CPE whose size was too small to perform multivariate analysis. Three of these factors were found with statistically significant differences: hospitalisation in the preceding 12 months, urine drainage in the current hospitalisation and antibiotic receipt between admission and inclusion. Inversely, travel in Asia and prior hospitalisation out of France did not reach statistical significance. However, CPE cases were more likely to have travelled in Asia when compared with C1 (15 vs 3%) and with C2 (17 vs 0%) and to have been hospitalised out of France when compared with C1 (18 vs 3%) and with C2 (19 vs 6%). Of note, these tendencies were not observed for non-CPE cases when compared with C1 and C2. In our additional analysis comparing CPE and non-CPE cases, we found that CPE cases were significantly more likely to have travelled in Asia than non-CPE cases (15.4 vs 3.3%; $p = 0.01$) and to have been hospitalised abroad (17.9 vs 0.8%; $p = 0.0005$). All these results support the fact that travelling in Asia and having been hospitalised abroad are risk factors of CPE infection. Thus, our case-control-control study re-enforces previously suggestions provided by case reports or case series on the risk of CPE carriage or infection after travelling abroad, notably in Asia with and without hospitalisation abroad [21–27]. Hence, Asia, already known as a reservoir for ESBL-producing Enterobacteriaceae, appears now as a region at risk of CPE acquisition during travel [28, 29].

Among non-CPE, *Enterobacter* spp. and other hospital species (*S. marcescens*, *C. freundii*, *M. morganii*, etc.) accounted for more than 50% of the isolates. In addition, in our study and in France, these species seldom harbour carbapenemases [30]. Therefore, it is not surprising to found as risk factors associated with non-CPE, only factors related to healthcare, including prior hospitalisation in France. Travel abroad was not associated with non-CPE infection.

Overall, because our study included all types of CRE in the same settings, we were able to decipher the differences in risk factors linked to CPE and to non-CPE CRE infections, which is a strength of our study. One of the weaknesses of our study is the limited number of CPE cases preventing the ability to reach statistical significance in subpopulation analyses. This is the result of the French CPE epidemiology. Indeed, CPE are mostly found in asymptomatic digestive carriers and not in infections [30]. As including digestive carriers makes impossible to select C1-type controls, we chose to focus on CRE responsible for infections in the design of the study.

In conclusion, to our knowledge, the present study is the first one reporting in the same settings on risk factors of CRE, including CPE and non-CPE, in France. Beyond finding the most commonly described health care-associated risk factors, it evidences, for the first time, factors associated with the patients' hospitalisation history and travel in Asia for CPE cases. Thus, our study suggests that question patients about their medical history and lifestyle should help for early identification of patients at risk of CPE among patients with CRE.

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Authors' contributions Marie-Hélène Nicolas-Chanoine and Jérôme Robert designed the study, got funding, analysed the data and drafted the manuscript. Marie-Hélène Nicolas-Chanoine coordinated the study, organised meetings with all members of the E-carb study group and reviewed all case-control-control files. Marie Vigan and Cédric Laouénan performed the statistical analyses, participated in the different meetings required to prepare the MS and revised the MS. Members of the E-carb study group implemented the study in their own hospital, participated in the meetings organised to follow this implementation and gave their agreement for MS submission.

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Compliance with ethical standards

Conflict of interest None declare

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