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Original Article

Risk factors for carbapenemase-producing organisms among inpatients in Scotland: A national matched case–control study

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Abstract

Objective: To determine risk factors for carbapenemase-producing organisms (CPOs) and to determine the prognostic impact of CPOs.

Design: A retrospective matched case–control study.

Patients: Inpatients across Scotland in 2010–2016 were included. Patients with a CPO were matched with 2 control groups by hospital, admission date, specimen type, and bacteria. One group comprised patients either infected or colonized with a non-CPO and the other group were general inpatients.

Methods: Conditional logistic regression models were used to identify risk factors for CPO infection and colonization, respectively. Mortality rates and length of postisolation hospitalization were compared between CPO and non-CPO patients.

Results: In total, 70 CPO infection cases (with 210 general inpatient controls and 121 non-CPO controls) and 34 CPO colonization cases (with 102 general inpatient controls and 60 non-CPO controls) were identified. Risk factors for CPO infection versus general inpatients were prior hospital stay (adjusted odds ratio [aOR], 4.05; 95% confidence interval [CI], 1.52–10.78; $P = .005$), longer hospitalization (aOR, 1.07; 95% CI, 1.04–1.10; $P < .001$), longer intensive care unit (ICU) stay (aOR, 1.41; 95% CI, 1.01–1.98; $P = .045$), and immunodeficiency (aOR, 3.68; 95% CI, 1.16–11.66; $P = .027$). Risk factors for CPO colonization were prior high-dependency unit (HDU) stay (aOR, 11.46; 95% CI, 1.27–103.09; $P = .030$) and endocrine, nutritional, and metabolic (ENM) diseases (aOR, 3.41; 95% CI, 1.02–11.33; $P = .046$). Risk factors for CPO infection versus non-CPO infection were prolonged hospitalization (aOR, 1.02; 95% CI, 1.00–1.03; $P = .038$) and HDU stay (aOR, 1.13; 95% CI, 1.02–1.26; $P = .024$). No differences in mortality rates were detected between CPO and non-CPO patients. CPO infection was associated with longer hospital stay than non-CPO infection ($P = .041$).

Conclusions: A history of (prolonged) hospitalization, prolonged ICU or HDU stay; ENM diseases; and being immunocompromised increased risk for CPO. CPO infection was not associated with increased mortality but was associated with prolonged hospital stay.

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Carbapenem-resistant organisms (CROs) have been gradually increasing worldwide since they were first identified >30 years ago, and they pose a major global public health threat.[1,2] In 2015, CROs accounted for 16.0% of infections caused by antibiotic-resistant bacteria and 26.5% of attributable deaths in Europe.[3] Furthermore, CRO was associated with a 4-fold increased risk of receiving inappropriate empiric antimicrobial treatment, which in turn increased mortality (by 12%), length of hospital stay (by >5.2 days), and healthcare costs (by an extra $10,312).[4] Carbapenemase production is a major mechanism of carbapenem resistance, and carbapenemase-producing organisms (CPOs) have largely been responsible for the rapid worldwide spread of carbapenem resistance.[5]

Many risk factors contribute to CPO acquisition, and they can generally be classified into 2 groups: host-related factors and healthcare-related factors. From both clinical and epidemiological perspectives, a comprehensive understanding of risk factors for acquiring a CPO will help predict an individual's risk of CPO acquisition through early identification of high-risk populations, thus also preventing the spread of CROs. With regard to CPO epidemiology, the United Kingdom was reported as having "regional

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spread," whereas many European countries have an "interregional spread or endemic" situation, such as Italy, Greece, France, Poland and Denmark.[2] In 2017, the prevalence of CPOs in Scotland (0.1 per 100,000 patient days) was lower than that in England and Northern Ireland (0.85 per 100,000 patient days) in healthcare settings.[6] However, there has been a 39% year-by-year increase in the prevalence of reported CPO isolates since 2013 in Scotland, from 0.4 per 100,000 population in 2013 to 2.0 per 100,000 population in 2017.[7] To date, most risk-factor studies have been conducted in regions of high CRO endemicity, and only a few risk-factor studies have been conducted in such a low-prevalence setting.[8–10] The appropriate choice of controls is very important in risk-factor analyses for antimicrobial resistance; otherwise, the association between risk factors and antimicrobial resistance can be either overestimated or underestimated.[11–13]

The aims of this study were 2-fold. First, we aimed to provide more in-depth understanding of underlying factors associated with CPO infection and colonization among inpatients. Second, we aimed to evaluate the impact of carbapenemase production on mortality and length of hospital stay.

Methods

Ethics

All data for analyses in this study were anonymized. The study was reviewed and approved by the Public Benefit and Privacy Panel for Health and Social Care and covered by National Safe Haven generic ethics approval (reference no. 1617-0328). The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

Study design

We conducted a national retrospective matched case–control study among inpatients in Scotland between January 2010 and December 2016. In 2003, Scotland initiated an acute-care hospital admission screening program for carbapenemase-producing Enterobacteriaceae (CPE).[14] In this program, a specimen from clinical indications or surveillance program is cultured onto an agar plate. Identification and susceptibility testing of isolates that grow on the agar plate were performed using VITEK-2 (bioMérieux, Marcy-l'Étoile, France), Etest (bioMérieux), and British Society for Antimicrobial Chemotherapy methods and break points.[15] Isolates nonsusceptible to ≥1 carbapenem (ie, imipenem, meropenem, or ertapenem) were tested using in-house polymerase chain reaction (PCR) for carbapenemase genes.[16]

A case was defined as an inpatient infected with or colonized by a CPO. This study had 2 control groups: The first group (general inpatient control) was randomly selected among inpatients who were not suspected to have any infection but whose colonization status was unknown. The second group (non-CPO control) were randomly selected inpatients with positive cultures of gram-negative bacteria that might be resistant or susceptible to carbapenems but did not produce carbapenemases confirmed by polymerase chain reaction assay (PCR). Each case was matched with up to 3 controls by hospital, admission date, specimen type, and bacteria.

Definitions of infection and colonization for cases and non-CPO controls were based on the source of specimen and diagnosis.[17] If a patient with a positive culture of either CPO or non-CPO isolate met any of the following criteria, the patient was identified as an infection case: (1) the isolate was isolated from normally sterile sites; (2) the specimen matched an infection diagnosis, for example, the isolate was isolated from urine and with a diagnosis of urinary tract infection; (3) the primary diagnosis was sepsis with no source specified. If a patient with a positive culture of either a CPO or non-CPO isolate met either of the following criteria, the patient was identified as a colonization case: (1) there was no infection diagnosis or (2) there was an infection diagnosis but caused by a different organism(s) at a different site from CPO or non-CPO isolates.

To determine the risk factors for CPO infection and colonization, infection cases were compared with infection non-CPO controls and general inpatients controls, respectively, and colonization cases were compared with colonization non-CPO controls and general inpatient controls, respectively. The impact of carbapenemase production on clinical outcomes was estimated using mortality rates (all-cause 30-day and 1-year mortality rates) and length of postisolation hospital stay.

Data collection

The data used in this study were extracted from several national data sets. Laboratory records were extracted from the Electronic Communication of Surveillance in Scotland, including organism, specimen date, specimen site and hospital. Medical records were extracted from the General Acute Inpatient and Day Case-Scottish Morbidity Record. Mortality data were extracted from the National Records of Scotland Deaths, including date and causes of death. Data extraction and linkage of these data sets were performed by Public Health Scotland electronically by the Data Research and Innovation Service. All patients were anonymized in the file made available for analysis. The potential risk factors of interest associated with CPO infection and colonization were placed in 1 of 4 categories: (1) demographics, including age and sex; (2) comorbidities; (3) healthcare exposure in the prior 90 days; and (4) invasive procedures in the prior 90 days. Definitions of each potential risk factor of interest are listed in Supplementary Table 1 (online).

Statistical analyses

The Pearson χ^2 test or the Fisher exact test was used as appropriate to compare mortality rates between cases and non-CPO controls. Univariate conditional logistic regression analyses were performed to compare length between bacteria isolation and hospital discharge. Conditional logistic regression modeling was used to determine risk factors.[18,19] Univariate analysis was performed first. Correlation and interactions between variables with $P < .10$ in univariate analysis were checked. After removing variables with high-level correlation (correlation coefficient ≥ 0.70), the remaining variables were considered to be included in the multivariate model and were selected using lease absolute shrinkage and selection operator (LASSO) penalty (λ was used to choose variables = λ.1SE, the λ that minimizes cross-validation error plus 1 standard error).[20] Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to determine the strengths of association. A P value <.05 was considered significant. To test the stability of the final multivariate model, variables in the model were removed in turn, and the significance levels of the remaining variables were checked. Analyses were carried out using the package 'clogitL1' in R version 3.5.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 116 consecutive inpatients with CPO infection and colonization were identified during 2010–2016. During this period, the prevalence of CPO infection was 0.06–0.33 per 100,000 population

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Table 1. Carbapenemase-Producing Organisms (CPOs) Included in This Study (Family, Genus, and Species)

Family	Genus	Species	CPO Infections (N=70), No.	CPO Colonization (N=34), No.
Enterobacteriaceae	*Citrobacter*	*Citrobacter freundii*	2	2
	Enterobacter	*Enterobacter cloacae*	26	5
	Escherichia	*Escherichia coli*	10	4
	Klebsiella	*Klebsiella pneumonia*	20	16
		Klebsiella oxytoca	0	1
	Proteus	*Proteus mirabilis*	1	0
	Providencia	*Providencia stuartii*	0	2
Nonfermenters	*Pseudomonas*	*Pseudomonas aeruginosa*	8	4
		Pseudomonas fluorescens	3	0

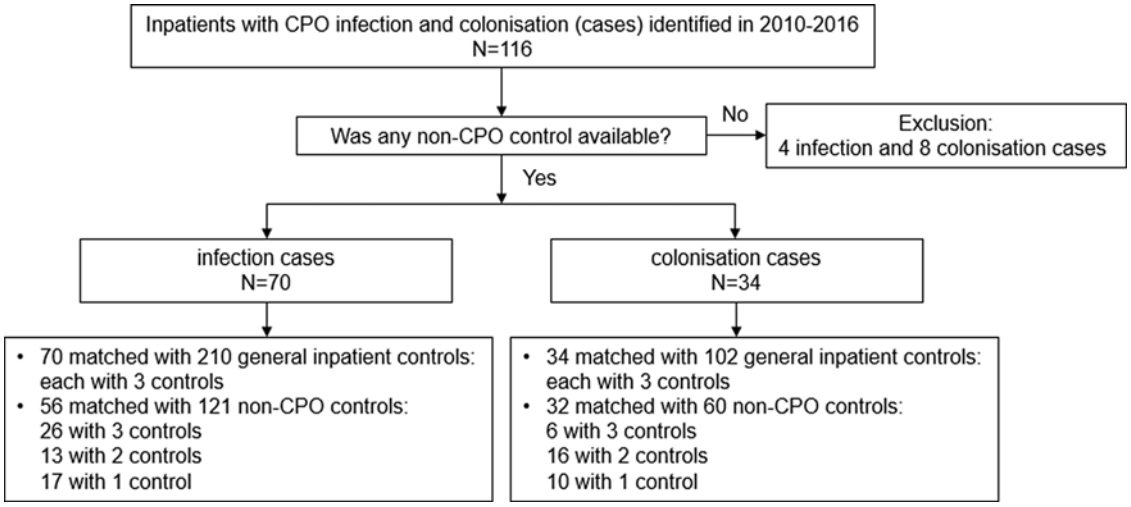

Fig. 1. Flowchart of case and control selection.

and the prevalence of colonization was 0.04–0.39 per 100,000 population. However, 12 inpatients without any available non-CPO control were excluded; therefore, 70 inpatients infected with CPO and 34 inpatients colonized by CPO remained in the study (Fig. 1). The 104 CPO isolates comprised 89 Enterobacteriaceae and 15 nonfermenter isolates. The species distribution of CPO isolates is listed in Table 1. All of the cases were matched with 3 general inpatient controls. Of the 70 infection cases, 56 (80.0%) could be matched with at least 1 infection non-CPO control, and 32 of the 34 colonization cases (94.1%) could be matched with at least 1 colonization non-CPO control (Fig. 1). All of the cases and controls were from 11 tertiary-care hospitals and 10 secondary-care hospitals. The distribution of patients and the care levels of the 21 hospitals are listed in Supplementary Table 2 (online).

Risk factors associated with CPO infection

When cases were compared with general inpatient controls, the univariate analysis showed that a range of variables were associated with CPO infection, including all demographic variables, most healthcare exposure variables, some comorbidities, and some invasive procedures (Table 2 and Supplementary Fig. 1 online). The multivariate analysis indicated that hospitalization, length of hospitalization, length of intensive care unit (ICU) stay in the prior 90 days, and being immunocompromised were independently associated with CPO infection (Table 4). When cases were compared with non-CPO controls, at the univariate level, fewer variables were associated with CPO infection than for general inpatient controls, including sex, some healthcare exposure variables, hematologic malignancy, 'injury, poisoning, and certain other consequences of external causes and surgical procedures (Table 2 and Supplementary Fig. 1 online). The multivariate analysis showed that length of hospitalization, and length of high-dependency unit (HDU) stay in the prior 90 days were independently associated with CPO infection (Table 4).

Risk factors associated with CPO colonization

The univariate analysis comparing cases and general inpatient controls indicated that CPO colonization was associated with age; endocrine, nutritional, and metabolic (ENM) diseases including diabetes mellitus; endoscopic operation; and most healthcare-exposure variables (Table 3 and Supplementary Fig. 2 online). The multivariate analysis showed that HDU stay in the prior 90 days and ENM diseases were independent risk factors for CPO

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Table 2. Univariate Analysis of Risk Factors Associated With Carbapenemase-Producing Organism (CPO) Infection

	Cases vs General Inpatient Controls		Cases vs Non-CPO Controls		Cases vs General Inpatient Controls		Cases vs Non-CPO Controls	
Variables	Cases[a] (N=70), No. (%)	Controls [a] (N=210), No. (%)	Cases [a] (N=56), No. (%)	Controls[a] (N=121), No. (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Demographics								
Age, median y (IQR) [range]	64.5 (53–77.75) [1–92]	53 (35–72) [2–93]	65.5 (53–77.25) [1–92]	68 (52–78) [0–96]	1.03 (1.01–1.05)	<.001	1.00 (0.98–1.02)	.916
Age > 60 y	44 (62.9)	91 (43.3)	35 (62.5)	81 (66.9)	2.55 (1.37–4.77)	.003	0.74 (0.37–1.47)	.394
Sex, male	43 (61.4)	91 (43.3)	38 (67.9)	64 (52.9)	2.11 (1.20–3.70)	.009	2.16 (1.06–4.37)	.033
Comorbidities								
Neoplasms and diseases of the blood and blood-forming organs	24 (34.3)	30 (14.3)	19 (33.9)	32 (26.4)	3.28 (1.70–6.32)	<.001	1.58 (0.75–3.34)	.231
Malignancy	15 (21.4)	20 (9.5)	12 (21.4)	24 (19.8)	2.86 (1.30–6.28)	.009	1.37 (0.53–3.50)	.516
Solid	5 (7.1)	16 (7.6)	3 (5.4	15 (12.4)	0.93 (0.33–2.63)	.896	0.42 (0.11–1.57)	.195
Hematologic	10 (14.3)	3 (1.4)	9 (16.1)	9 (7.4)	26.15 (3.32–205.92)	.002	4.73 (1.20–18.71)	.027
Anemia	6 (8.6)	2 (1.0)	6 (10.7)	3 (2.5)	9.00 (1.82–44.59)	.007	3.42 (0.82–14.34)	.093
ENM diseases	14 (20.0)	23 (11.0)	10 (17.9)	18 (14.9)	1.93 (0.96–3.90)	.065	1.13 (0.46–2.81)	.785
Diabetes mellitus	7 (10.0)	10 (4.8)	6 (10.7)	12 (9.9)	2.18 (0.81–5.91)	.125	1.02 (0.37–2.85)	.965
With complications	1 (1.4)	0 (0.0)	1 (1.8)	3 (2.5)	. . .	.250[a]	0.60 (0.06–5.95)	.660
Diseases of the circulatory system	17 (24.3)	41 (19.5)	14 (25.0)	35 (28.9)	1.41 (0.69–2.87)	.350	0.84 (0.41–1.72)	.632
Heart failure	1 (1.4)	1 (0.5)	1 (1.8)	3 (2.5)	3.00 (0.19–47.96)	.437	0.69 (0.06–8.04)	.764
Diseases of the respiratory system	20 (28.6)	28 (13.3)	16 (28.6)	38 (31.4)	2.56 (1.33–4.94)	.005	0.65 (0.28–1.53)	.326
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	. . .	1.000[b]	. . .	1.000[b]
Diseases of the digestive system	13 (18.6)	39 (18.6)	13 (23.2)	30 (24.8)	1.00 (0.50–1.99)	1.000	0.90 (0.36–2.22)	.818
Diseases of the genitourinary system	33 (47.1)	27 (12.9)	24 (42.9)	51 (42.1)	8.38 (3.81–18.47)	<.001	0.81 (0.36–1.83)	.613
Renal failure	9 (12.9)	7 (3.3)	7 (12.5)	13 (10.7)	5.48 (1.65–18.16)	.005	1.09 (0.40–2.94)	.865
Diseases of the nervous system	10 (14.3)	12 (5.7)	7 (12.5)	11 (9.1)	2.84 (1.14–7.10)	.026	1.39 (0.52–3.77)	.512
Diseases of the skin and subcutaneous tissue	4 (5.7)	9 (4.3)	3 (5.4)	10 (8.3)	1.36 (0.40–4.57)	.623	0.39 (0.08–1.92)	.245
Diseases of the musculoskeletal system and connective tissue	8 (11.4)	17 (8.1)	5 (8.9)	10 (8.3)	1.50 (0.60–3.77)	.388	1.15 (0.38–3.51)	.808
External causes of morbidity	21 (30.0)	32 (15.2)	18 (32.1)	15 (12.4)	2.31 (1.23–4.34)	.009	2.96 (1.40–6.26)	.005
Injury, poisoning and certain other consequences of external causes	19 (27.1)	29 (13.8)	16 (28.6)	13 (10.7)	2.27 (1.18–4.36)	.014	3.38 (1.50–7.60)	.003
Immunocompromised status	21 (30.0)	20 (9.5)	17 (30.4)	25 (20.7)	4.53 (2.14–9.58)	<.001	2.07 (0.91–4.71)	.081
Healthcare exposure								
Emergency admission	51 (72.9)	117 (55.7)	39 (69.6)	98 (81.0)	2.15 (1.19–3.91)	.012	0.46 (0.20–1.06)	.070
Admission from healthcare facilities	6 (8.6)	10 (4.8)	5 (8.9)	9 (7.4)	1.92 (0.65–5.65)	.235	1.65 (0.49–5.58)	.419

(*Continued*)

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Table 2. (*Continued*)

	Cases vs General Inpatient Controls		Cases vs Non-CPO Controls		Cases vs General Inpatient Controls		Cases vs Non-CPO Controls	
Variables	Cases[a] (N=70), No. (%)	Controls [a] (N=210), No. (%)	Cases [a] (N=56), No. (%)	Controls[a] (N=121), No. (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Surgical Specialty	35 (50.0)	97 (46.2)	30 (53.6)	46 (38.0)	1.16 (0.68–1.99)	.583	1.87 (0.96–3.64)	.068
TAR, median d (IQR) [range]	11 (1–32.5) [0–88]	1 (0–4) [0–69]	7 (0.75–37) [0–85]	1 (0–12) [0–142]	1.07 (1.04–1.09)	<.001	1.02 (1.00–1.03)	.042
Prior HDU stay	28 (40.0)	9 (4.3)	20 (35.7)	19 (15.7)	18.92 (6.60–54.20)	<.001	2.95 (1.35–6.48)	.007
Duration of prior HDU stay, median d (IQR) [range]	0 (0–2) [0–28]	0 (0–0) [0–6]	0 (0–2) [0–28]	0 (0–0) [0–14]	1.82 (1.26–2.64)	.001	1.16 (1.04–1.28)	.006
Prior ICU stay	21 (30.0)	6 (2.9)	16 (28.6)	15 (12.4)	19.10 (5.67–64.32)	<.001	2.67 (1.18–6.06)	.019
Duration of prior ICU stay, days, median (IQR, range)	0 (0–0) [0–39]	0 (0–0) [0–7]	0 (0–0) [0–39]	0 (0–0) [0–27]	1.49 (1.09–2.04)	.012	1.06 (0.97–1.15)	.176
Prior hospitalization	34 (48.6)	29 (13.8)	28 (50.0)	38 (31.4)	6.14 (3.13–12.04)	<.001	3.08 (1.42–6.70)	.004
Duration of prior hospitalization, median d (IQR) [range]	19 (8–44) [0–85]	1 (0–4) [0–69]	17.5 (5.5–47.5) [0–85]	5 (0–15) [0–142]	1.08 (1.05–1.11)	<.001	1.02 (1.01–1.04)	.003
Hospital transfer	13 (18.6)	5 (2.4)	9 (16.1)	5 (4.1)	11.77 (3.33–41.60)	<.001	5.57 (1.44–21.48)	.013
Ward transfer	40 (57.1)	41 (19.5)	31 (55.4)	49 (40.5)	6.59 (3.38–12.85)	<.001	1.65 (0.86–3.14)	.131
Invasive procedures								
Any	35 (50.0)	57 (27.1)	28 (50.0)	45 (37.2)	2.65 (1.51–4.65)	.001	1.78 (0.92–3.43)	.087
Transplantation	4 (5.7)	0 (0.0)	4 (7.1)	1 (0.8)	. . .	.004[b]	7.67 (0.82–71.32)	.073
Centesis	5 (7.1)	5 (2.4)	3 (5.4)	4 (3.3)	3.36 (0.89–12.73)	.074	2.35 (0.46–12.02)	.304
Ectomy	10 (14.3)	17 (8.1)	9 (16.1)	8 (6.6)	1.95 (0.82–4.61)	.129	2.72 (1.04–7.15)	.042
Catheterisation	9 (12.9)	3 (1.4)	6 (10.7)	10 (8.3)	9.00 (2.44–33.24)	.001	1.46 (0.49–4.35)	.501
Urinary catheter	1 (1.4)	1 (0.5)	1 (1.8)	1 (0.8)	3.00 (0.19–47.96)	.437	1.73 (0.10–30.76)	.708
CVC	8 (11.4)	2 (1.0)	5 (8.9)	9 (7.4)	12.00 (2.55–56.51)	.002	1.41 (0.43–4.62)	.566
Dialysis or drainage	5 (7.1)	1 (0.5)	5 (8.9)	4 (3.3)	15.00 (1.75–128.39)	.013	3.21 (0.85–12.18)	.086
Endoscopic operation	7 (10.0)	10 (4.8)	6 (10.7)	12 (9.9)	2.18 (0.81–5.91)	.125	1.00 (0.33–3.03)	1.000
Invasive ventilation	4 (5.7)	2 (1.0)	3 (5.4)	8 (6.6)	6.00 (1.10–32.76)	.039	0.84 (0.20–3.51)	.813
Other surgical procedures	9 (12.9)	24 (11.4)	6 (10.7)	19 (15.7)	1.15 (0.50–2.63)	.745	0.60 (0.21–1.67)	.328

Note. OR, odds ratio; CI, confidence interval; IQR, interquartile range; ICU, intensive care unit; HDU, high-dependency unit; TAR, time at risk; CVC, central venous catheter; ENM, endocrine, nutritional, and metabolic.
[a]No. of cases/controls with exposure to the variable (%), unless stated otherwise.
[b]Fisher exact test.

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Table 3. Univariate Analysis of Risk Factors Associated With Carbapenemase-Producing Organism (CPO) Colonization

	Cases vs General Inpatient Controls		Cases vs Non-CPO Controls		Cases vs General Inpatient Controls		Cases vs Non-CPO Controls	
Variables	Cases[a] (N=34), No. (%)	Controls [a] (N=102), No. (%)	Cases [a] (N=32), No. (%)	Controls [a] (N=60), No. (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Demographics								
Age, median y (IQR) [range]	64.5 (58–78) [19–91]	51.5 (33.25–63) [0–95]	65 (58.75–78) [19–91]	73 (59–81.25) [0–94]	1.03 (1.01–1.06)	.002	0.99 (0.96–1.01)	.318
Age > 60 y	21 (61.8)	67 (65.7)	21 (65.6)	43 (71.7)	0.85 (0.38–1.88)	.680	0.71 (0.27–1.85)	.482
Sex, male	15 (44.1)	50 (49.0)	15 (46.9)	28 (46.7)	0.83 (0.39–1.77)	.629	0.98 (0.40–2.39)	.970
Comorbidities								
Neoplasms and diseases of the blood and blood-forming organs	7 (20.6)	14 (13.7)	7 (21.9)	8 (13.3)	1.61 (0.60–4.34)	.349	2.00 (0.59–6.73)	.263
Malignancy	5 (14.7)	8 (7.8)	5 (15.6)	4 (6.7)	1.95 (0.61–6.24)	.258	2.90 (0.66–12.83)	.160
Solid	3 (8.8)	7 (6.9)	3 (9.4)	4 (6.7)	1.31 (0.32–5.36)	.706	1.45 (0.27–7.81)	.665
Hematologic	2 (5.9)	1 (1.0)	2 (6.3)	0 (0.0)	6.00 (0.54–66.17)	.143	. . .	.119[b]
Anemia	2 (5.9)	2 (2.0)	2 (6.3)	1 (1.67)	3.00 (0.42–21.30)	.272	4.00 (0.36–44.11)	.258
ENM diseases	12 (35.3)	11 (10.8)	12 (37.5)	8 (13.3)	5.52 (1.89–16.14)	.002	4.08 (1.40–11.92)	.010
Diabetes mellitus	5 (14.7)	4 (3.9)	5 (15.6)	3 (5.0)	5.79 (1.09–30.83)	.039	3.62 (0.85–15.41)	.082
With complications	3 (8.8)	0 (0.0)	3 (9.4)	1 (1.7)	. . .	.015[b]	6.69 (0.69–67.78)	.101
Diseases of the circulatory system	14 (41.2)	26 (25.5)	13 (40.6)	24 (40.0)	2.29 (0.93–5.64)	.071	1.02 (0.39–2.64)	.968
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	. . .	1.000[b]	. . .	1.000[b]
Diseases of the respiratory system	5 (14.7)	17 (16.7)	5 (15.6)	12 (20.0)	0.87 (0.30–2.51)	.793	0.66 (0.21–2.08)	.475
Respiratory failure	2 (5.9)	0 (0.0)	2 (6.3)	3 (5.0)	. . .	.061[b]	1.00 (0.16–6.14)	1.000
Diseases of the digestive system	1 (2.9)	11 (10.8)	1 (3.1)	16 (26.7)	0.26 (0.03–2.06)	.201	0.10 (0.01–0.80)	.030
Diseases of the genitourinary system	8 (23.5)	10 (9.8)	8 (25.0)	13 (21.7)	2.64 (0.98–7.13)	.056	1.28 (0.44–3.73)	.651
Renal failure	4 (11.8)	4 (3.9)	4 (12.5)	3 (5.0)	3.00 (0.75–12.00)	.120	3.35 (0.59–18.88)	.171
Diseases of the nervous system	2 (5.9)	5 (4.9)	2 (6.3)	3 (5.0)	1.20 (0.23–6.19)	.827	1.15 (0.19–7.03)	.876
Diseases of the skin and subcutaneous tissue	3 (8.8)	8 (7.8)	3 (9.4)	2 (3.3)	1.13 (0.30–4.24)	.862	3.54 (0.59–21.38)	.168
Diseases of the musculoskeletal system and connective tissue	3 (8.8)	7 (6.9)	3 (9.4)	7 (11.7)	1.31 (0.32–5.36)	.706	0.95 (0.21–4.26)	.949
External causes of morbidity	10 (29.4)	20 (19.6)	9 (28.1)	14 (23.3)	1.61 (0.70–3.72)	.261	1.19 (0.44–3.26)	.731
Injury, poisoning and certain other consequences of external causes	10 (29.4)	15 (14.7)	9 (28.1)	12 (20.0)	2.10 (0.91–4.83)	.081	1.48 (0.53–4.12)	.453
Immunocompromised status	5 (14.7)	8 (7.8)	5 (15.6)	5 (8.3)	1.95 (0.61–6.24)	.258	2.17 (0.55–8.48)	.266
Healthcare exposure								
Emergency admission	23 (67.6)	59 (57.8)	22 (68.8)	45 (75.0)	1.61 (0.67–3.92)	.290	0.84 (0.29–2.44)	.750
Admission from healthcare facilities	2 (5.9)	3 (2.9)	1 (3.1)	2 (3.3)	2.00 (0.33–11.97)	.448	0.62 (0.05–7.00)	.697

(*Continued*)

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Table 3. (*Continued*)

	Cases vs General Inpatient Controls		Cases vs Non-CPO Controls		Cases vs General Inpatient Controls		Cases vs Non-CPO Controls	
Variables	Cases[a] (N=34), No. (%)	Controls [a] (N=102), No. (%)	Cases [a] (N=32), No. (%)	Controls [a] (N=60), No. (%)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Surgical specialty	18 (52.9)	39 (38.2)	16 (50.0)	28 (46.7)	1.70 (0.81–3.55)	.158	1.00 (0.36–2.76)	1.000
TAR, median d (IQR) [range]	4 (0–22.75) [0–91]	1 (0–2) [0–81]	3 (0–23) [0–91]	3 (0–16) [0–139]	1.03 (1.01–1.06)	.007	1.01 (0.99–1.03)	.499
Prior HDU stay	7 (20.6)	2 (2.0)	7 (21.9)	6 (10.0)	19.1 (2.33–156.45)	.006	2.62 (0.64–10.77)	.183
Duration of prior HDU stay, median d (IQR) [range]	0 (0–0) [0–5]	0 (0–0) [0–5]	0 (0–0) [0–5]	0 (0–0) [0–20]	2.01 (1.16–3.51)	.014	0.97 (0.81–1.17)	.762
Prior ICU stay	9 (26.5)	0 (0.0)	8 (25.0)	8 (13.3)	. . .	<.001[b]	2.22 (0.65–7.57)	.203
Duration of prior ICU stay, median d (IQR) [range]	0 (0–0) [0–9]	. . .	0 (0–0) [0–9]	0 (0–0) [0–28]	. . .	<.001[b]	0.90 (0.69–1.16)	.409
Prior Hospitalization	10 (29.4)	13 (12.7)	10 (31.3)	21 (35.0)	2.89 (1.11–7.56)	.030	0.87 (0.37–2.03)	.748
Duration of prior hospitalization, median d (IQR) [range]	6 (0–24.75) [0–91]	1 (0–2) [0–81]	7.5 (0–27) [0–91]	7 (1–24) [0–139]	1.04 (1.01–1.06)	.003	1.01 (0.99–1.02)	.529
Hospital transfer	6 (17.6)	3 (2.9)	6 (18.8)	14 (23.3)	6.00 (1.50–23.99)	.011	0.86 (0.29–2.55)	.783
Ward transfer	19 (55.9)	20 (19.6)	19 (59.4)	26 (43.3)	4.84 (2.06–11.37)	<.001	2.00 (0.78–5.13)	.147
Invasive procedures								
Any	14 (41.2)	30 (29.4)	14 (43.8)	26 (43.3)	1.62 (0.74–3.54)	.224	1.04 (0.41–2.60)	.938
Transplantation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	. . .	1.000[b]	. . .	1.000[b]
Centesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	. . .	1.000[b]	. . .	1.000[b]
Ectomy	3 (8.8)	8 (7.8)	3 (9.4)	9 (15.0)	1.13 (0.29–4.47)	.858	0.53 (0.12–2.24)	.385
Catheterization	1 (2.9)	0 (0.0)	1 (3.1)	3 (5.0)	. . .	.250[b]	0.71 (0.04–11.79)	.809
Urinary catheter	1 (2.9)	0 (0.0)	1 (3.1)	0 (0.0)	. . .	.250[b]	. . .	.348[b]
CVC	1 (2.9)	0 (0.0)	1 (3.1)	2 (3.3)	. . .	.250[b]	1.41 (0.08–23.57)	.809
Dialysis or drainage	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	. . .	1.000[b]	. . .	1.000[b]
Endoscopic operation	6 (17.6)	3 (2.9)	6 (18.8)	6 (10.0)	8.11 (1.62–40.67)	.011	1.97 (0.58–6.68)	.274
Invasive ventilation	1 (2.9)	0 (0.0)	1 (3.1)	2 (3.3)	. . .	.250[b]	1.14 (0.10–12.66)	.917
Other surgical procedures	7 (20.6)	21 (20.6)	7 (21.9)	10 (16.7)	1.00 (0.40–2.52)	1.000	1.41 (0.45–4.36)	.555

Note. OR, odds ratio; CI, confidence interval; IQR, interquartile range; ICU, intensive care unit; HDU, high dependency unit; TAR, time at risk; CVC, central venous catheter; ENM, endocrine, nutritional, and metabolic.
[a]No. of cases/controls with exposure to the variable (%), unless stated otherwise.
[b]Fisher exact test.

Table 4. Multivariate Analysis of Risk Factors Associated With Carbapenemase-Producing Organism (CPO) Infection and Colonization

	Infection				Colonization			
	Cases vs General Inpatient Controls		Cases vs Non-CPO Controls		Cases vs General Inpatient Controls		Cases vs Non-CPO Controls	
Variables	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Demographics								
Age, y					1.02 (1.00–1.05)	.114		
Comorbidities								
Immunocompromised status	3.68 (1.16–11.66)	.027						
ENM diseases					3.41 (1.02–11.33)	.046	3.03 (0.69–13.31)	.142
Diabetes mellitus							1.24 (0.16–9.61)	.836
Diseases of the digestive system							0.12 (0.01–1.04)	.054
Healthcare exposure								
Prior hospitalization	4.05 (1.52–10.78)	.005						
Duration of prior hospitalization, d	1.07 (1.04–1.10)	<.001	1.02 (1.00–1.03)	.038	1.01 (0.99–1.04)	.306		
Duration of ICU stay, d	1.41 (1.01–1.98)	.045						
HDU stay, d					11.46 (1.27–103.09)	.030		
Duration of HDU stay, d			1.13 (1.02–1.26)	.024				

Note. aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; HDU, high-dependency unit; ENM, endocrine, nutritional, and metabolic.

Table 5. Comparison of Outcomes Between Infection and Colonization for Carbapenemase-Producing Organism (CPO) Cases and Non-CPO Controls

	Infection			Colonization		
Outcomes	CPO (N=56), No. (%)	Non-CPO (N=121), No. (%)	*P* Value[a]	CPO (N=32), No. (%)	Non-CPO (N=60), No. (%)	*P* Value[a]
All-cause 30-d mortality rate[b]	10 (17.86)	17 (14.05)	.667	3 (9.38)	5 (8.33)	1.000[c]
All cause 1-year mortality rate[b]	24 (42.86)	37 (30.58)	.153	7 (21.88)	16 (26.67)	.801
Isolation to discharge, median d (IQR) [range]	17.5 (8.75–34) [2–551]	8 (2–15) [0–155]	.041[d]	12.5 (4.5–28.25) [0–236]	4.5 (1–18.25) [0–219]	.266[d]

Note. IQR, interquartile range; CPO, carbapenemase-producing organisms; non-CPO, organisms that do not yield carbapenemases.
[a]Pearson χ^2 test, unless stated otherwise.
[b]No. of cases/controls with the outcomes (%), unless stated otherwise.
[c]Fisher exact test.
[d]Univariate conditional logistic regression.

colonization (Table 4). Compared with non-CPO controls, cases were more likely to have ENM diseases (Table 3). However, no independent risk factors were detected (Table 4).

Outcome comparison between cases and non-CPO controls

For infection, there were no significant differences regarding all-cause 30-day and 1-year mortality rates ($P = .667$ and .153) (Table 5) between cases and non-CPO controls, nor by infection type (Supplementary Table 3 online). However, lengths of postisolation hospital stay of patients with CPO infections were significantly longer than postisolation stays of patients with non-CPO infections ($P = .041$) (Table 5). For colonization, no differences were noted between cases and non-CPO controls regarding mortality rates or length of postisolation hospital stay (Table 5).

Discussion

To the best of our knowledge, this is the first national risk-factor study of CPOs in a low-prevalence setting. This study will help inform screening and infection control policies for CPOs in both Scotland and other countries with a similar prevalence situation.

Debate regarding control group selection is ongoing.[11,21–23] However, the main principles remain the same; choice of controls should depend on the questions being asked and should be representative of the same source population.[11–13] Therefore, we chose general inpatient controls to address risk factors for the bacteria (ie, CPO), and we chose non-CPO controls to address risk factors for the resistance mechanism (ie, carbapenemase production), respectively. Infection and colonization represent different medical conditions with different implications for both clinical therapy and infection control and prevention strategies. Therefore, risk-factor analyses were conducted for CPO infection and colonization separately.

The number of patients enrolled is still relatively low compared with the number of variables of interest; therefore, variable selection is necessary for multivariate analyses that attempt to find a simple and appropriate model. LASSO has several advantages over other methods. First, it can provide a very good prediction

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accuracy because shrinkage and removal of the coefficients can reduce variance without increasing substantial bias. Second, it helps to increase the model interpretability by eliminating irrelevant variables and thereby reduce overfitting.[24] Moreover, we used a liberal criterion of $P < .10$ in univariate analysis to make it more likely that truly important predictors and confounders were retained in the model.

Non-CPO controls tended to be more debilitated than general inpatient controls, more likely to be treated with antibiotics, intensive care, or invasive procedures, which were similar to cases. Therefore, a weaker association (ie, smaller OR) was identified using non-CPO controls than using general inpatient controls for most of the same factors (Tables 2 and 3 and Supplementary Figs. 1 and 2 online). Additionally, more risk factors were identified using general inpatient controls than using non-CPO controls, implying that some of the risk factors identified were associated with acquiring infections in general.

The independent risk factors for CPO infection determined by comparing cases and both control groups were mainly healthcare exposure variables, including prior hospital stay, length of prior hospital stay, and length of HDU/ICU stay. For both general inpatients and patients with infections, the risk of being infected by CPO increased by 7% and 2%, respectively, for each additional day of hospital stay. On one hand, prior hospital stay and longer duration of hospital stay means more healthcare exposure and, therefore, more opportunities to be colonized or subsequently infected by a CPO. On the other hand, this may reflect the selection of resistant strains under antimicrobial pressure due to the body flora changes over time during a longer hospitalization period. Prolonged ICU stay is a well-documented risk factor for multidrug-resistant organisms (MDROs) because these patients have multiple comorbidities and are subject to invasive life-support devices or procedures. Hence, they are at higher risk of acquiring an MDRO due to cross transmission mediated by these factors.[25,26] Patients in the HDU usually require more intensive observation, treatment, and nursing care than can be provided on a general ward and have a single-organ failure, whereas patients in the ICU usually have multiple-organ failure.[27] No previous studies reported (prolonged) HDU stay as a risk factor for CPO, so patient and unit characteristics and their association with CPO warrant more research.

Several studies have reported that CRO including CPO were likely to be pathogenic in those patients who were more immunocompromised.[28–30] Furthermore, immunocompromised patients are subject to multiple readmissions to hospitals and to treatment with broad-spectrum antibiotics and chemotherapy agents that may disrupt the gastrointestinal microbiota, thus rendering them prone to resistant pathogens.[31,32] Our study supports these findings: being immunocompromised independently increased the risk of CPO infection.

A unique risk factor for CPO colonization was ENM disease—diabetes mellitus (with complications) in particular. ENM diseases including diabetes mellitus with complications as an independent risk factor might come from the effects of such disorders on the immune system.[33,34] Interestingly, non–CPO-colonized patients were more likely to have digestive-system diseases than patients colonized by CPO, but this was not independently protective for CPO colonization (Table 4). This finding agrees with some studies reporting that digestive system diseases were more common in patients with carbapenem-susceptible organisms (CSOs) but they were not independent protective factors for CRO.[35,36]

Some researchers have argued that advanced age is associated with severity of illness and thus represents a surrogate marker of such conditions.[10,37] Our results are consistent with this finding: higher age was a risk factor for infection but not specifically for carbapenem resistance (Tables 2 and 3). Interestingly, no invasive-procedure–related factors were independent risk factors for CPO.

The prognostic impact of CPO remains controversial and conflicting. It has been reported that CPO infection was associated with 4 times the risk of 14-day mortality compared with non-CPO infection.[38] However, we detected no differences of all-cause 30-day or 1-year mortality rates between inpatients infected or colonized by bacterial pathogens regardless of carbapenemase production (Table 5). This finding could be explained by more severe comorbid conditions of patients who might die not because of CPO infections but due to complications developed during the hospital stay, such as hematologic malignancies associated with CPO infection (Table 2). Also, this finding could be explained by antimicrobial susceptibility. Compared with other antibiotics, CPO isolates had lower rates of resistance to aminoglycosides (33.3%–37.0%, unpublished data), which could be an alternative but effective therapeutic option. Another concern is the prolonged hospitalization following CPO isolation compared with both control groups (Table 5), which gives opportunities for further CPO transmission and highlights the economic and healthcare burden of this group of patients.

This study has some limitations. First, whether general inpatient controls were colonized by pathogens including a CPO remained unknown because we were not able to screen for all bacteria flora. Second, data on antimicrobial susceptibility, antimicrobial treatment, and travel history were not available. These factors might have had an impact on mortality and risk factors for CPO. Future research should address these points.

Our study sheds light on which inpatients are at high risk of acquiring CPO, which is in turn associated with prolongation of healthcare needs. Screening for CPOs, pre-emptive identification, and isolation measures among patients with a history of (prolonged) hospitalization, ICU or HDU stay, ENM diseases, or being immunocompromised would be a cost-effective way to identify, manage, and reduce the spread of CPOs.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2020.1351

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