Infection Control & Hospital Epidemiology (2021), **42**, 754–759
doi:10.1017/ice.2020.1286

Concise Communication

The epidemiology of carbapenem resistant *Enterobacter* spp: A case–case–control matched analysis

Leore Cohen Mendel MD[1], Keren Amity MD[1], David E. Katz MD, MPH[2], Tsilia Lazarovitch PhD[3], Ronit Zaidenstein MD[4,5] and Dror Marchaim MD[1,5]

[1]Unit of Infection Control, Shamir (Assaf Harofeh) Medical Center, Zerifin, Israel, [2]Division of Internal Medicine, Shaare Zedek Medical Center, the Hebrew University Hadassah Medical School, Jerusalem, Israel, [3]The Microbiology Laboratory, Shamir (Assaf Harofeh) Medical Center, Zerifin, Israel, [4]Department of Medicine A, Shamir (Assaf Harofeh) Medical Center, Zerifin, Israel and [5]Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Abstract

A case–case–control investigation (216 patients) examined the risk factors and outcomes of carbapenem-resistant *Enterobacter* (CR-En) acquisition. Recent exposure to fluoroquinolones, intensive care unit (ICU) stay, and rapidly fatal McCabe condition were independent predictors for acquisition. Acquiring CR-En was independently associated with discharge to a long-term care facility after being admitted from home.

(Received 9 May 2020; accepted 17 September 2020; electronically published 24 November 2020)

Enterobacter spp are common human pathogens, associated with a diversity of serious infectious syndromes in hospitals and intensive care units (ICUs).[1] The rise of carbapenem resistance among *Enterobacter* spp (CR-En), as with other carbapenem-resistant members of the Enterobacteriaceae family (CRE), has been defined by the World Health Organization (WHO) as one of the current biggest threats to global health.[2]

Data regarding the epidemiology of CRE have been derived primarily from cohorts consisting of *Klebsiella pneumoniae* infections.[3] The second most common CRE is *Enterobacter* (CR-En),[1] but its molecular and clinical epidemiology differs from that of *K. pneumoniae,*[1] and it has not been thoroughly analyzed while implementing advanced methodological tools and design. Specifically, data are lacking from recent years, after the changes in CRE diagnostic definition[4] and changes in the composition of circulating carbapenemase and non–carbapenemase-producing strains.[1] Extrapolating management, therapeutic, and prevention strategies from existing data might not reflect current CR-En epidemiology. Thus, we conducted a matched case–case–control investigation to explore the epidemiology of CR-En.

Methods

A retrospective matched case–case–control study was conducted among adults (≥18 years) at the Shamir (Assaf Harofeh) Medical Center, Israel, from 2007 to 2017. The study was approved by the institutional ethics committee prior to its initiation. Resistant cases (CR-En) consisted of patients with *Enterobacter* (any subspecie) that had a meropenem minimal inhibitory concentration (MIC) >1 μg/dL (VITEK 2, bioMérieux, France) and/or evidence of carbapenemase production (by phenotypic or genotypic test).[4] Cases could be either infected or asymptomatic carriers.[6] An active surveillance program for CRE detection is mandated at all Israeli hospitals, among admitted adult patients (based of established risk stratification procedure). All Cr-En patients identified at our hospital in this study period were included in this study. Susceptible cases (CS-En) consisted of patients with *Enterobacter* susceptible to carbapenems (ie, meropenem MIC ≤1 μg/dL and no carbapenemase production).[4] The uninfected control group consisted of patients without any Enterobacteriales culture and no clinical signs or symptoms of infection. Patients were included in the analysis only once. A CS-En case patient and an uninfected control patient were matched to a CR-En case patient (1:1:1 ratio) according to the following characteristics, in order of importance: (1) infection versus colonization status,[6] (2) age (in decades), (3) time at risk (ie, the number of days from admission to culture date, and for uninfected controls, the whole length of stay was captured as the time at risk), (4) hospitalization department, and (5) the calendar year.

Data were retrieved from all available records. Posthospitalization mortality data were obtained from a national registry governed by the Israeli Ministry of the Interior. Logistic and Cox regression models were constructed, including parameters with significant ($P \leq .05$) association per bivariable analysis, to assess predictors (ie, matched analysis) and outcomes (ie, nonmatched analysis, with the carbapenem-resistance determinant enforced into each model) of CR-En carriers. All models were assessed for collinearity and were controlled for confounding.

Author for correspondence: Dror Marchaim, MD, E-mail: drormarchaim@gmail.com

PREVIOUS PRESENTATION: Some of the information pertaining to patients with CR-En which was included in this publication, was also retrieved for a study previously published as Lazarovitch T, Amity K, Coyle JR, et al. The complex epidemiology of carbapenem-resistant enterobacter infections: a multicenter descriptive analysis. *Infect Control Hosp Epidemiol* 2015;36:1283–1291.

Cite this article: Cohen Mendel L, *et al.* (2021). The epidemiology of carbapenem resistant *Enterobacter* spp: A case–case–control matched analysis. *Infection Control & Hospital Epidemiology*, 42: 754–759, https://doi.org/10.1017/ice.2020.1286

Table 1. Comparison of Characteristics and Outcomes of Case Patients with a Resistant Strain, Case Patients with a Susceptible Strain, and Uninfected Control Patients[a]

Parameter	CR-En, No. (valid %[b])	CS-En, No. (valid %[b])	Controls, No. (valid %[a])	CR-En vs Controls, OR (95% CI)	*P* Value	CS-En vs controls, OR (95% CI)	*P* Value	CR-En vs CS-En, OR (95% CI)	*P* Value
Demographics									
Age, median y (IQR)	73.5 (61.3–82)	73.0 (61.0–82)	72.5 (61.8–82)		.90		1.0		.90
Elderly, aged ≥ 65 y	48 (66.7)	44 (61.1)	49 (68.1)	0.9 (0.5–1.9)	.90	0.7 (0.4–1.5)	.40	1.3 (0.6–2.5)	.50
Sex, female	34 (47.2)	41 (56.9)	36 (50)	0.9 (0.5–1.7)	.70	1.3 (0.7–2.6)	.40	0.7 (0.4–1.3)	.20
Background conditions and comorbidities on admission									
Functional status, partially or fully dependent	51 (70.8)	40 (55.6)	31 (43.7)	**3.1 (1.6–6.2)**	**.001**	1.6 (0.8–3.1)	.20	1.9 (0.9–3.9)	.06
Impaired cognition	27 (37.5)	17 (23.6)	12 (16.9)	**2.9 (1.3–6.4)**	**.006**	1.5 (0.7–3.5)	.30	1.9 (0.9–4.0)	.07
Ischemic heart disease	19 (26.4)	18 (25.0)	16 (22.2)	1.3 (0.6–2.7)	.60	1.2 (0.5–2.5)	.70	1.1 (0.5–2.3)	.80
Congestive heart failure	28 (38.9)	27 (37.5)	28 (38.9)	1.00 (0.5–2.0)	>.99	0.9 (0.5–1.8)	.90	1.1 (0.5–2.1)	.90
Peripheral vascular disease	17 (23.6)	12 (16.7)	10 (13.9)	1.9 (0.8–4.5)	.10	1.2 (0.5–3.1)	.60	1.5 (0.7–3.5)	.30
Diabetes mellitus	34 (47.2)	26 (36.1)	25 (34.7)	1.7 (0.9–3.3)	.10	1.1 (0.5–2.1)	.90	1.6 (0.8–3.1)	.20
Chronic renal disease	17 (23.6)	12 (16.7)	21 (29.6)	0.7 (0.3–1.6)	.40	0.5 (0.2–1.1)	.70	1.5 (0.7–3.5)	.30
Chronic lung disease	22 (30.6)	26 (36.1)	24 (33.8)	0.9 (0.4–1.7)	.70	1.1 (0.6–2.2)	.80	0.8 (0.4–1.6)	.50
Peptic ulcer disease	6 (8.3)	3 (4.2)	6 (8.3)	1.00 (0.3–3.3)	>.99	0.5 (0.1–2.0)	.50	2.1 (0.5–8.7)	.50
Hemiplegia	13 (18.1)	7 (9.7)	4 (5.6)	**3.7 (1.2–12.1)**	**.04**	1.8 (0.5–6.5)	.50	2.0 (0.8–5.5)	.15
Dementia	20 (27.8)	11 (15.3)	12 (16.7)	1.9 (0.9–4.3)	.10	0.9 (0.4–2.2)	.80	2.1 (0.9–4.9)	.07
Malignancy (previous or active)	17 (23.6)	18 (25.0)	12 (16.7)	1.5 (0.7–3.5)	.30	1.7 (0.7–3.8)	.20	0.9 (0.4–2.0)	.85
Chronic skin ulcers	18 (25.0)	12 (16.7)	9 (12.5)	2.3 (1.0–5.6)	.06	1.4 (0.6–3.6)	.50	1.7 (0.7–3.8)	.20
Charlson weighted comorbidity index,[7] mean ± SD	3.9 ±2.6	2.9 ± 2.4	2.9 ± 2.4		**.024**		.945		**.019**
Charlson combined condition score,[7] mean ± SD[1]	6.5 ± 3.0	5.6 ± 3.0	5.6 ± 3.2		.073		.979		.058
Charlson 10-y survival probability,[7] median (IQR)	2 (0–21)	21 (0–53)	2 (0–77)		**.05**		.899		.067
Immunosuppression[b]	10 (13.9)	12 (16.7)	8 (11.1)	1.3 (0.5–3.5)	.60	1.6 (0.6–4.2)	.30	0.8 (0.3–2.0)	.60
McCabe score,[8] mean ± SD	1.9±0.67	2.25±0.65	2.4±0.67		**<.001**		**.129**		**.001**
Exposure to healthcare settings and to antibiotics, prior culture (cases with *Enterobacter*) or admission (uninfected controls)									
LTCF residence in previous 3 mo	18 (25.7)	12 (16.7)	9 (12.5)	**2.4 (1.0–5.8)**	**.045**	1.4 (0.5–3.6)	.50	1.7 (0.8–3.9)	.187
Hospitalized in previous 3 mo	44 (62)	31 (43.1)	26 (36.1)	**2.9 (1.5–5.7)**	**.002**	1.3 (0.7–2.6)	.40	**2.2 (1.1–4.2)**	**.02**
Time from last hospitalization, median d (range)	11 (2,27)	57 (9,274)	42 (11,241)		**<.001**		.80		**.001**
ICU stay in current hospitalization	38 (52.8)	28 (40.0)	16 (22.9)	**3.8 (1.8–7.8)**	**<.001**	**2.3 (1.1–4.8)**	**0.02**	1.6 (0.8–3.1)	.20
Hemodialysis	10 (14.1)	2 (2.8)	2 (2.8)	**5.7 (1.2–27.2)**	**.02**	1.00 (0.1–7.3)	>.99	**5.7 (1.2–27.2)**	**.02**
Regular visits to outpatient clinic	7 (10.1)	16 (22.2)	10 (13.9)	0.7 (0.3–2.0)	.50	1.8 (0.7–4.2)	.20	0.4 (0.2–1.0)	.052

(*Continued*)

Table 1. (*Continued*)

Parameter		CR-En, No. (valid %[b])	CS-En, No. (valid %[b])	Controls, No. (valid %[a])	CR-En vs Controls, OR (95% CI)	*P* Value	CS-En vs controls, OR (95% CI)	*P* Value	CR-En vs CS-En, OR (95% CI)	*P* Value
Invasive procedure[c] in previous 3 mo		54 (77.1)	45 (62.5)	17 (23.6)	**10.9 (5.0–23.8)**	**<.001**	**5.4 (2.6–11.1)**	**<.001**	2.0 (1.0–4.2)	.06
Permanent devices (at least 48 h prior to the event)		45(63.4)	30 (41.7)	11 (15.3)	**9.6 (4.3–21.4)**	**<.001**	**4.0 (1.8–8.8)**	**<.001**	**2.4 (1.2–4.7)**	**.009**
Received antibiotics in previous 3 mo		62 (89.9)	40 (55.6)	18 (25.0)	**26.6 (10.3–66.4)**	**<.001**	**3.7 (1.8–7.6)**	**<.001**	**7.1 (2.9–17.6)**	**<.001**
Time from last antibiotics, median d (IQR)		1 (1,1)	1 (1,4.75)	1 (1,9)		.187		.525		.404
No. of antibiotics classes given, in previous 3 mo, median (IQR)		3 (2,4)	1 (0,3)	0 (0,0)		**<.001**		**<.001**		**<.001**
No. of antibiotics courses given, in previous 3 mo, median (IQR)		3 (2,4)	1 (0,3)	0 (0,0)		**<.001**		**<.001**		**<.001**
Penicillin in previous 3 mo		45 (66.2)	25 (35.2)	6 (8.3)	**21.5 (8.1–57.1)**	**<.001**	**6.0 (2.3–15.7)**	**<.001**	**3.6 (1.8–7.2)**	**<.001**
Cephalosporin in previous 3 mo		54 (80.6)	34 (47.2)	8 (11.1)	**33.3 (12.8–83.3)**	**<.001**	**7.1 (3.0–17.0)**	**<.001**	**4.7 (2.2–9.9)**	**<.001**
Carbapenem in previous 3 mo		25 (36.8)	11 (15.3)	0 (0)		**<.001**		**<.001**	**3.2 (1.4–7.2)**	**.04**
Fluoroquinolone in previous 3 mo		22 (32.4)	10 (13.9)	7 (9.7)	**4.4 (1.8–11.2)**	**.001**	1.5 (0.5–4.2)	.40	**3.0 (1.3–6.8)**	**.009**
Glycopeptide in previous 3 mo		28 (41.8)	14 (19.4)	3 (4.2)	**16.4 (4.7–58.8)**	**<.001**	**5.6 (1.5–20.3)**	**.008**	**3.0 (1.4–6.4)**	**.04**
Macrolide in previous 3 mo		10 (14.9)	10 (13.9)	2 (2.8)	**6.1 (1.3– 26.4)**	**.01**	**5.6 (1.2–26.8)**	**.03**	1.1 (0.4–2.8)	.90
Metronidazole in previous 3 mo		27 (39.7)	13 (18.1)	2 (2.8)	**23.3 (5.2–100)**	**<.001**	**7.7 (1.7–35.7)**	**.005**	**3.0 (1.4–6.5)**	**.005**
Microbiology										
Past MDRO[d] in previous 3 mo		37 (52.1)	26 (38.2)	3 (4.5)	**23.2 (6.7–80.1)**	**<.001**	**13.2 (3.8–45.5)**	**<.001**	1.8 (0.9–3.5)	.10
Bacteria Isolated	*Enterobacter cloacae*	57 (79.2)	57 (79.2)	…	…		…		1.0 (0.8–1.2)	>.99
	E. aerogenes	13 (18.1)	12 (16.7)	…	…		…		1.1 (0.5–2.2)	>.99
	Other *Enterobacter*	2 (2.8)	3 (4.2)	…	…		…		0.7 (0.1–3.9)	>.99
Severity of acute illness indices (among *Enterobacter* cases only)										
Severe sepsis/septic shock/multiple-organ failure		10 (52.9)	5 (26.3)	…	…		…		3.1 (0.8–12.1)	.10
Mechanical ventilation (48 h before to a week after isolation)		11 (23.4)	8 (13.8)	…	…		…		1.9 (0.7–5.2)	.20
Acute renal failure (48 h before to a week after isolation)		14 (19.7)	17 (23.6)	…	…		…		0.8 (0.4–1.8)	.60
Clinical syndrome	Colonization alone	55 (76.4)	54 (75)	…	…		…		1 (0.8–1.2)	.80
	Central-line–associated infection	2 (2.8)	2 (2.8)	…	…		…		1 (0.1–6.9)	>.99
	Pneumonia	2 (2.8)	2 (2.8)	…	…		…		1 (0.1–6.9)	>.99
	Urinary tract infection	3 (4.3)	6 (8.3)	…	…		…		0.5 (0.1–1.9)	.50
	Skin or soft-tissue infection	5 (6.9)	4 (5.6)	…	…		…		1.3 (0.3–4.5)	>.99
	Intra-abdominal infection	2 (2.8)	2 (2.8)	…	…		…		1 (0.1–6.9)	>.99
	Bacteremia without determined focus	3 (4.3)	2 (2.8)	…	…		…		1.5 (0.3–8.7)	>.99

https://doi.org/10.1017/ice.2020.1286 Published online by Cambridge University Press

Outcomes										
Total LOS, median d (IQR)		28 (12–59)	15 (6–40)	12 (6–27)		**<.001**		0.223		**0.006**
Died in current hospitalization		26 (36.1)	17 (23.6)	6 (8.3)	**6.2 (2.4–16.3)**	**<.001**	**3.4 (1.3–9.2)**	**.01**	1.8 (0.9–3.8)	.10
30-d mortality		25 (35.2)	16 (22.2)	3 (4.2)	**12.5 (3.6–43.8)**	**<.001**	**6.6 (1.8–23.8)**	**.002**	1.9 (0.9–4.0)	.09
90-d mortality		36 (50.7)	21 (29.2)	14 (19.4)	**4.3 (2.0–9.0)**	**<.001**	1.7 (0.8–3.7)	.20	**2.5 (1.3–5.0)**	**.009**
Among survivors of the hospitalization only (n=167)	LOS after culture, excluding the dead, median (IQR)	9 (3,24)	5 (2,10)							**.039**
	Functional deterioration	27 (57.4)	24 (43.6)	22 (33.3)	**2.7 (1.2–5.8)**	**.01**	1.5 (0.7–3.2)	.20	1.7 (0.8–3.8)	.20
	Discharged to LTCF	27 (58.7)	17 (30.9)	18 (27.7)	**3.7 (1.7–8.3)**	**.001**	1.2 (0.5–2.6)	.70	**3.2 (1.4–7.2)**	**.05**
	Additional hospitalizations (6 mo after event)	20 (47.6)	22 (41.5)	28 (44.4)	1.1 (0.5–2.5)	.70	0.9 (0.4–1.9)	.80	1.3 (0.6–2.9)	.60

Note. Significant associations are highlighted in bold. OR, odds ratio; IQR, interquartile range; SD, standard deviation; LTCF, long-term care facility; ICU, intensive care unit; LOS, length of stay; MDRO, multidrug-resistant organism; TNF, tumor necrosis factor; HIV, human immunodeficiency virus.

[a]Each group contained 72 patients.

[b]Valid %: count divided by the total number of valid (ie, nonmissing) observations.

[b]Immunosuppression includes any of the following: (1) neutropenia at culture date (<500 neutrophils/mm^3), (2) glucocorticoid exposure in the past month, (3) chemotherapy in the previous 3 months, (4) radiotherapy, (5) after transplantation of any kind, (6) anti-TNF therapy in previous 3 months, or (7) HIV infection.

[c]Invasive procedures: any procedure causing potential exposure to bacteria in a normally axenic environment including, but not limited to, PEG insertion, thoracic puncture and pleurocentesis, abdominal paracentesis, minor and major surgical procedures, percutaneous procedures, endoscopies, and permanent central-line insertion.

[d]MDRO includes methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.

Results

Also, 72 CR-En case patients were matched to 72 CS-En case patients and to 72 uninfected control patients (total, 216). The study population consisted mainly of elderly patients (65%), with complex and diverse background illnesses, high rate of baseline functional disabilities (57%), and high Charlson comorbidity indexes[7] (Table 1). Most patients (76%) were asymptomatic carriers (Table 1).

Predictors for CR-En acquisition

Many of the bivariate predictors associated with CR-En were also associated with CS-En (Table 1). In a multivariable model, the independent predictors of CR-En, which were not associated with CS-En, remained: (1) recent exposure (3 months) to fluoroquinolones (adjusted odds ratio [aOR], 2.94; 95% confidence interval [CI], 1.1–8.1), (2) ICU stay in the current hospitalization prior to isolation (aOR, 3.56; 95% CI, 1.6–8.1), and (3) a rapidly fatal McCabe condition[8] (aOR, 2.1; 95% CI, 1.2–3.8).

Clinical outcomes of CR-En carriers

Overall, 49 (23%) died in the hospital, 44 (21%) died within 30 days, and 71 (33%) died within 90 days. Of the 167 patients who survived the index hospitalization, the median duration of stay after the date of event was 5 days (IQR, 3–16 days); 73 (43.5%) experienced functional deterioration (compared to their baseline condition);[9] and 62 (37.7%) were discharged to a long-term care facility (LTCF) after being admitted to the index hospitalization from home.

In bivariable analyses (Table 1), both in-hospital and 30-day mortality rates were higher for patients with CR-En and with CS-En. In multivariable outcome models, CR-En acquisition remained independently associated with discharge to LTCF among patients who were admitted from home and survived the index hospitalization (aOR, 3.27; 95% CI, 1.2–8.7).

Discussion

Resistance to carbapenems among *Enterobacter* offending strains poses a substantial epidemiological burden.[1] A case–case–control analysis was executed at a tertiary-care center for 11 consecutive years (2007–2017), involving 216 patients (72 patients in each group). The matched case–case–control design is the gold standard methodology to explore independent predictors for acquiring multidrug-resistant organisms (MDROs) in hospitals.[5] This method better reflects the source population from which resistant isolates arose, while controlling for factors related to the "infection," therefore isolating the true independent predictors for the "emergence" of the resistance determinant.[5] Apart from a recent ICU stay and rapidly fatal McCabe[8] condition, which might represent the confounding effects of severe background conditions and/or acute illness indices, we identified an independent modifiable predictor for CR-En acquisition, ie, recent exposure to fluoroquinolones. The epidemiological association of fluoroquinolone exposure with emergence of resistance to β-lactam agents among Enterobacterales, including to carbapenems, was reported in the past. It is still uncertain whether the exposure to fluoroquinolones results a direct cellular causative effect (ie, evolving energetically beneficial gyrase and topoisomerase IV mutations conferring resistance both to fluoroquinolones but concomitantly permitting the acquisition of an extra resistance gene load without evoking appreciable fitness cost) or is simply the high fitness cost associated with resistance to fluoroquinolones, which contributes to the selection of certain "successful" clones.[10] This finding is important: in *Enterobacter* infections, fluoroquinolones could be the mainstay of therapy whenever long treatment courses are planned (eg, osteomyelitis, prosthetic joint infections), and β-lactams are avoided due to the inducible chromosomal production of broad-spectrum β-lactamases (eg, bla_{AmpC}).[1] This factor stresses the significance of this finding and should prompt a directed stewardship intervention to reduce the in-house use of fluoroquinolones.[10]

Most patients in this study (76%) were asymptomatic carriers. This is a study strength because it better reflects the true predictors of the acquisition event in the initial phases, prior the development of the infection event. This approach dilutes the potential confounding effects of the infection's acute illness indices. Still, recent ICU stay and rapidly fatal McCabe condition were both independent predictors for acquiring CR-En but not CS-En. However, due to the predominance of asymptomatic carriers in this cohort, we could not thoroughly analyze other issues pertaining to CR-En epidemiology due to the low sample size of infected individuals: the comparative efficacy of various antimicrobials, the impact of delay in initiation of appropriate antimicrobial therapy, and the independent association with mortality parameters (despite significant associations per bivariable analyses). Nevertheless, acquiring CR-En remained an independent predictor for discharge to an LTCF, among patients who survived the index hospitalization and were initially admitted from home.

Our study involved a single center, and theoretically, clonality issues and outbreaks within the hospital could have introduced bias into the results. In addition, theoretically, patients in the control group could still be CS-En carriers (but not CR-En carriers). There were also differences between the active surveillance process for CR-En carriers and the use of only clinical cultures for detection of CS-En carriers. Moreover, genotyping information and mechanism of carbapenem resistance were not available for all CR-En patients. The study is also a retrospective chart-review–based investigation, with all its inherent limitations. However, the matched case–case–control design, the large sample size, and the finding of exposure to fluoroquinolones, could lead to practical interventions in terms of antimicrobial stewardship. It is important to conduct controlled analyses to curb the continued emergence and spread of one of the most epidemiologically threatening, yet understudied, human pathogens.

Acknowledgments.

Financial support. No financial support was provided relevant to this article.

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

References

1. Lazarovitch T, Amity K, Coyle JR, *et al.* The complex epidemiology of carbapenem-resistant enterobacter infections: a multicenter descriptive analysis. *Infect Control Hosp Epidemiol* 2015;36:1283–1291.
2. WHO publishes list of bacteria for which new antibiotics are urgently needed. World Health Organization website. http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/. Published April 14, 2017. Accessed October 1, 2020.
3. Marchaim D, Chopra T, Perez F, *et al.* Outcomes and genetic relatedness of carbapenem-resistant Enterobacteriaceae at Detroit medical center. *Infect Control Hosp Epidemiol* 2011;32:861–71.
4. Leclercq R, Cantón R, Brown DFJ, *et al.* EUCAST expert rules in antimicrobial susceptibility testing. *Clin Microbiol Infect* 2013;19:141–60.

https://doi.org/10.1017/ice.2020.1286 Published online by Cambridge University Press

5. Kaye KS, Harris AD, Samore M, Carmeli Y. The case–case–control study design: addressing the limitations of risk factor studies for antimicrobial resistance. *Infect Control Hosp Epidemiol* 2005;26:346–351.
6. Types of healthcare-associated infections. Centers for Disease Control and Prevention website. https://www.cdc.gov/hai/infectiontypes.html. Updated March 2014. Accessed October 29, 2020.
7. Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
8. Bion JF, Edlin SA, Ramsay G, *et al.* Validation of a prognostic score in critically ill patients undergoing transport. *Br Med J (Clin Res Ed)* 1985;291:432–434.
9. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA* 1963;185:914–919.
10. Fuzi M, Rodriguez Baño J, Toth, A. Global evolution of pathogenic bacteria with extensive use of fluoroquinolone agents. *Front Microbiol* 2020;11:271.

https://doi.org/10.1017/ice.2020.1286 Published online by Cambridge University Press