ORIGINAL ARTICLE

The Complex Epidemiology of Carbapenem-Resistant *Enterobacter* Infections: A Multicenter Descriptive Analysis

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BACKGROUND. The pandemic of carbapenem-resistant Enterobacteriaceae (CRE) was primarily due to clonal spread of bla_{KPC} producing *Klebsiella pneumoniae*. Thus, thoroughly studied CRE cohorts have consisted mostly of *K. pneumoniae*.

OBJECTIVE. To conduct an extensive epidemiologic analysis of carbapenem-resistant *Enterobacter* spp. (CREn) from 2 endemic and geographically distinct centers.

METHODS. CREn were investigated at an Israeli center (Assaf Harofeh Medical Center, January 2007 to July 2012) and at a US center (Detroit Medical Center, September 2008 to September 2009). bla_{KPC} genes were queried by polymerase chain reaction. Repetitive extragenic palindromic polymerase chain reaction and pulsed-field gel electrophoresis were used to determine genetic relatedness.

RESULTS. In this analysis, 68 unique patients with CREn were enrolled. Sixteen isolates (24%) were from wounds, and 33 (48%) represented colonization only. All isolates exhibited a positive Modified Hodge Test, but only 93% (27 of 29) contained bla_{KPC}. Forty-three isolates (63%) were from elderly adults, and 5 (7.4%) were from neonates. Twenty-seven patients died in hospital (40.3% of infected patients). *Enterobacter* strains consisted of 4 separate clones from Assaf Harofeh Medical Center and of 4 distinct clones from Detroit Medical Center.

CONCLUSIONS. In this study conducted at 2 distinct CRE endemic regions, there were unique epidemiologic features to CREn: (i) polyclonality, (ii) neonates accounting for more than 7% of cohort, and (iii) high rate of colonization (almost one-half of all cases represented colonization). Since false-positive Modified Hodge Tests in *Enterobacter* spp. are common, close monitoring of carbapenem resistance mechanisms (particularly carbapenemase production) among *Enterobacter* spp. is important.

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Enterobacter spp. are the sixth most common cause of healthcare-associated infections,[1–4] and the emergence of resistance to carbapenems among this species represents a clear epidemiologic threat.[2,4–6] The initial spread of carbapenem-resistant Enterobacteriaceae (CRE) was mediated primarily by bla_{KPC} producing *Klebsiella pneumoniae* strains (ie, >90% of CRE isolations[5,7]). Therefore, the CRE cohorts that have been extensively analyzed consisted predominantly of bla_{KPC} producing *K. pneumoniae* isolates.[8–10] Despite the established differences between carbapenem-resistant *Enterobacter* spp. (CREn) and *K. pneumoniae*,[3,4,8,11] the epidemiology of CREn has not been thoroughly investigated, particularly in recent years.[3,4,12] Moreover, the phenotypic method for carbapenemase detection, used routinely by many laboratories—that is, the Modified Hodge Test (MHT), is less reliable (has a low specificity) in *Enterobacter*.[13] Therefore, without additional molecular investigations, the interpretation of the scarce scientific epidemiologic data that do exist pertaining to these pathogens is theoretically subject to classification bias.[3,4,12]

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The aim of this study was to conduct an epidemiologic investigation of CREn from 2 endemic and geographically distinct medical centers. Both clinical and molecular epidemiology analyses were conducted, in order to provide novel information pertaining to one of the lesser studied among the ESKAPE pathogens (ie, enterococci, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterobacter* species).

METHODS

Study Settings

This was a multicenter multinational retrospective case series analysis conducted at 2 institutions during 2 different periods. The first study cohort was from the Detroit Medical Center (DMC) healthcare system (8 hospitals, ~2,200 inpatient beds, in Michigan); CRE had emerged and spread since 2008.[8,9,14–17] Patients at DMC were enrolled from September 2008 to September 2009. The second study group was from Assaf Harofeh Medical Center (AHMC; 813-bed tertiary facility, in Southern-Central Israel); CRE has been endemic since 2007, and patients were enrolled from January 2007 to July 2012.[7,18] Data at both DMC and AHMC were extracted from all available records. Other molecular investigations were executed at a research laboratory, located at the Veterans Affairs Medical Center, Cleveland, Ohio. The study was approved before its initiation by the institutional ethics committees at DMC, Wayne State University, AHMC, and the Cleveland Veterans Affairs Medical Center.

Case Finding and Definition

The study enrolled all patients who had a positive culture for CREn. CREn was defined as any *Enterobacter* spp. that were either (1) nonsusceptible to any group 2 carbapenem on the basis of Clinical and Laboratory Standards Institute criteria set in 2009[13]; or (2) determined to be a carbapenemase-producer per phenotypic (MHT) or genotypic (bla_{KPC} polymerase chain reaction [PCR]) tests.[13]

Differentiation between colonization and infection was determined on the basis of established criteria.[19,20] For patients who had more than 1 CREn isolated during the study period, only the first episode was analyzed.

Microbiology and Molecular Analyses

Bacteria were identified to the species level, and susceptibilities were determined to predefined antimicrobials by means of automated systems at DMC (MicroScan; Siemens) and at AHMC (Vitek 2; bioMérieux), and in accordance with Clinical and Laboratory Standards Institute criteria.[13] Minimum inhibitory concentrations (MICs) to colistin and tigecycline were determined by using Etests strips (bioMérieux). In AHMC only, beginning in 2010, the colistin MICs were determined via specified panel of the Vitek 2 automated system. Breakpoints to define nonsusceptibility to colistin and to tigecycline were set to at least 4 μg/dL for both agents.[13,21] All *Enterobacter* spp. that were resistant to 1 or more third-generation cephalosporin and had an MIC greater than 1 mg/L to ertapenem were screened for carbapenemase production with the MHT.[13] A positive phenotypic extended-spectrum β-lactamase test was defined on the basis of the automated systems at each center, validated with a disc diffusion test.[13]

CREn isolates were tested for the presence of bla_{KPC} by PCR.[22] The DMC isolates were tested at the Cleveland Veterans Affairs Medical Center and the isolates from AHMC were tested locally. Previously characterized KPC-producing strains were used as controls.[22–25]

Repetitive extragenic palindromic PCR was used to determine genetic relatedness among CREn from DMC. Analyses were conducted at the Cleveland Veterans Affairs Medical Center using an automated system (DiversiLab; bioMérieux).[9] A dendrogram was generated using the DiversiLab software. Isolates with band patterns similarity of at least 95% were considered genetically related.[23] CREn from AHMC were genotyped by pulsed-field gel electrophoresis at the Central Laboratories of the Israeli Ministry of Health (Jerusalem, Israel). The *Xba*I restriction enzyme was used, and the electrophoresis was performed in the CHEF DR III system (Bio-Rad) using an established protocol (www.pulsenetinternational.org/protocols). Isolates with band patterns similarity of at least 95% were considered genetically related.[26]

Data Extraction

For persons meeting inclusion criteria, the following parameters were extracted: (1) demographic characteristics; (2) comorbidities and background conditions[27]; (3) healthcare exposures; (4) microbiology results (eg, culture source, MICs); (5) severity of acute illness at the time of isolation—for example, McCabe score,[28] level of Systemic Inflammatory Response Syndrome,[19] and the type of the infectious clinical syndrome[20] (determined by infectious diseases experts at the 2 centers); (6) factors related to antimicrobial therapy such as recent (3 months) exposure history, empirical therapy (from 2 days before to 3 days following the culture date), consolidative regimens (from 3 to 14 days following the culture date), and time to initiation of appropriate therapy (defined as the time frame from obtaining the CREn culture to administration of the first dose of an antimicrobial agent that possessed in vitro activity against the CREn); and (7) outcomes including mortality parameters (extracted from the Israeli Ministry of Interior for AHMC patients, and the Social Security Death Index for DMC patients), length of hospital stay (LOS) from CREn isolation to discharge among those who survived the hospitalization, functional status deterioration,[29] discharge to long-term care facility after being admitted from home, and direct costs (for AHMC patients only).

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Statistical Analysis

All analyses were performed by SPSS, version 21.0 (IBM). Bivariate analyses were performed using the Fisher exact or the χ^2 test for categorical variables and the independent samples *t* test or the Mann-Whitney test for continuous variables. Multivariable models for outcomes were constructed using logistic regression, including only infected patients (vs "colonized only"). A stepwise selection procedure was used to select variables for inclusion in the final models. The final selected model was tested for confounding. If a covariate affected the ß-coefficient of a variable in the model by more than 10%, then the confounding variable was maintained in the model. All *P* values were 2-sided. A Kaplan-Meier survival analysis was performed as well.

RESULTS

Cohort Descriptive Analysis: Demographic Characteristics and Comorbid Conditions

During the study period, there were 68 patients with CREn who met inclusion criteria: 54 from AHMC and 14 from DMC. The overall mean (SD) age of the entire cohort (including pediatric patients) was 63.1 (26) years and 43 patients (63%) were older than 65 years (Table 1). Adult patients (>18 years) were chronically ill, as reflected by the high mean (SD) Charlson weighted index score of 4.4 (2.5).[27]

There were 5 neonates (<3 months of age) and 1 child (1 year of age) with CREn diagnosed at AHMC. All pediatric CREn isolations were among patients with prolonged LOS (median, 58 days [interquartile range, 40–85 days]). All acquisitions were nosocomial (ie, >72 hours after hospital admission[20]). None of the neonatal cultures were determined to be vertically transmitted. The median (interquartile range) time at risk—that is, days from admission (or birth) to culture, was 11 (3–27) days.

Previous Healthcare Exposures

In general, adult patients from both centers had extensive exposures to healthcare procedures and/or environments (Table 1). Nonetheless, patients from DMC had increased frequency of recent healthcare encounters and exposures, as reflected by higher proportion of patients with recent intensive care unit (ICU) stay (36% at DMC vs none at AHMC, $P < .001$), regular (ie, at least weekly) outpatient clinic visits (36% vs 6%, $P = .008$), invasive procedures (of any sort) in the previous 6 months (71% vs 26%, $P = .004$), and presence of a chronic or a permanent invasive device prior to CREn isolation (71% vs 20%, odds ratio, 9.5, $P = .001$).

Microbiology

Forty-nine isolates (91%) from AHMC were *E. cloacae*, 1 (1.9%) was *E. aerogenes*, and 4 (7.4%) were other *Enterobacter* species, compared with 9 (64.3%), 4 (28.6%), and 1 (7.1%) from DMC, respectively (Table 2). The portion of *E. aerogenes* was significantly higher at DMC than at AHMC (odds ratio, 21, $P = .006$).

There were more isolations of CREn from rectal surveillance cultures at AHMC (26 [48%]), compared with DMC (none). Twenty-three cases (42.6%) from AHMC represented "true" clinical infection, compared with 10 patients (76.9%) from DMC (odds ratio, 4.3, $P = .06$). These differences are due in part to screening practices at the study hospitals: at AHMC rectal surveillance was routinely conducted for CREn, whereas at DMC, rectal surveillance was not conducted routinely.

The MHT and the extended-spectrum β-lactamase test results were positive in most cases (ie, 98% for both tests). The presence of bla_{KPC} was confirmed by PCR among all 4 isolates tested from DMC and among 23 (92%) of 25 isolates tested at AHMC.

In general, CREn isolates from AHMC exhibited broader resistance compared with isolates from DMC. Significant variations between institutions in terms of MIC values were noted for colistin, tobramycin, ciprofloxacin, all carbapenems, and trimethoprim/sulfamethoxazole. Significant variations with regards to the proportions of nonsusceptible isolates were noted for amikacin (83% of the isolates from AHMC were nonsusceptible vs 0 at DMC, $P < .001$), ciprofloxacin (90% from AHMC vs 11% from DMC, $P < .001$), and trimethoprim/sulfamethoxazole (84% from AHMC vs 0 from DMC, $P < .001$).

CREn Genetic Relatedness

Overall, 23 strains from AHMC were available for genotyping by using pulsed-field gel electrophoresis (Figure 1A). There were 4 pulsotypes diagnosed.[26] The results of the repetitive extragenic palindromic PCR conducted on 12 strains from DMC are depicted in Figure 1B. Only *E. cloacae* and *E. aerogenes* isolates from DMC were investigated. There were 4 distinct clones among the isolates tested: 2 clones of *E. cloacae* and 2 clones of *E. aerogenes* (Figure 1B).

Severity of Acute Illness at the Time of CREn Isolation

At the time of CREn isolation, 28 (46%) of the adults had a rapidly fatal condition (Table 3).[28] The proportion of patients with severe sepsis, septic shock, or multi-organ failure[19] was significantly higher among AHMC than DMC patients (52% vs 18%, $P = .05$).

Antimicrobial Therapy

Compared with patients from AHMC, patients from DMC had more often received antibiotics in the previous 3 months (43% vs 93%, odds ratio, 17.0; $P = .001$) (Table 3). The mean number of antimicrobial classes that patients from DMC had received in the preceding 3 months was 2.8, compared with 0.6

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TABLE 1. Characteristics of Patients With Carbapenem-Resistant *Enterobacter* Species

Variable	Assaf Harofeh Medical Center (N = 54)		Detroit Medical Center (N = 14)	
Demographic characteristics				
Age, mean ± SD, y	64.25 ± 26.1		58.86 ± 29	
Female sex	24	44.4	9	64.3
Elderly (>65 y)	35	64.8	8	57.1
Neonate (<3 mo)	5	9.3	0	0
Comorbidities and background conditions				
Charlson weighted index of comorbidity[27]	4.31 ± 2.62		4.64 ± 1.57	
Fatal McCabe score[28]	13	24.1	2	14.3
Dependent functional status	34	63.0	10	76.9
Dementia	14	25.9	4	28.6
Neurologic disorder	20	37.0	7	50.0
Congestive heart failure	21	38.9	4	28.6
Diabetes	26	48.1	8	57.1
Chronic renal disease	11	20.4	6	42.9
Malignancy	13	24.1	2	14.3
Immunosuppressive state	6	11.1	1	7.1
Exposure to healthcare settings and environments				
Resident of LTCF or other hospital before index hospitalization	6	11.1	4	28.6
Stay at LTCF in the past year	9	16.7	5	35.7
Hospitalized in past 3 mo	26	48.1	7	50.0
Invasive procedure in past 6 mo	14	25.9	10	71.4
Permanent foreign devices	11	20.4	10	71.4
ICU stay in current hospitalization	31	57.4	7	53.8

NOTE. Data are no. (%) of patients unless otherwise specified. The percents provided are the valid percents—that is, excluding the missing cases from the denominator. ICU, intensive care unit; LTCF, long-term care facility.

TABLE 2. Microbiologic Characteristics of Carbapenem-Resistant *Enterobacter* Species Strains

	Assaf Harofeh Medical Center (N = 54)		Detroit Medical Center (N = 14)	
Variable	Number	Percent	Number	Percent
Bacterial subspecies				
E. cloacae	49	90.7	9	64.3
E. aerogenes	1	1.9	4	28.6
Other *Enterobacter* spp.	4	7.4	1	7.1
Culture source				
Blood	5	9.3	2	14.3
Sputum/other respiratory	0	0	5	35.7
Urine	8	14.8	5	35.7
Wound	14	25.9	2	14.3
Tip of catheter	1	1.9	…	…
Rectal surveillance	26	48.1	…	…
Modified Hodge Test positive	39	97.5	…	…
bla_{KPC} positive	23	92	4	100
Ciprofloxacin nonsusceptible	47	90.4	1	11.1
Tobramycin nonsusceptible	35	81.4	0	0
Tigecycline nonsusceptible	9	20.5	0	0
Colistin nonsusceptible	1	2.6	0	0

NOTE. The percents provided are the valid percents—that is, excluding the missing cases from the denominator.

among AHMC patients ($P = .02$). Time from receipt of last prior antibiotic was significantly shorter at DMC (3.9 days), compared with AHMC (14.2 days, $P < .001$ between groups). None of the patients from DMC, and only 4 (7%) of the patients from AHMC, were exposed to carbapenems in the 3 months preceding the isolation of CREn.

The median (interquartile range) time to appropriate antimicrobial therapy among the entire cohort of patients was

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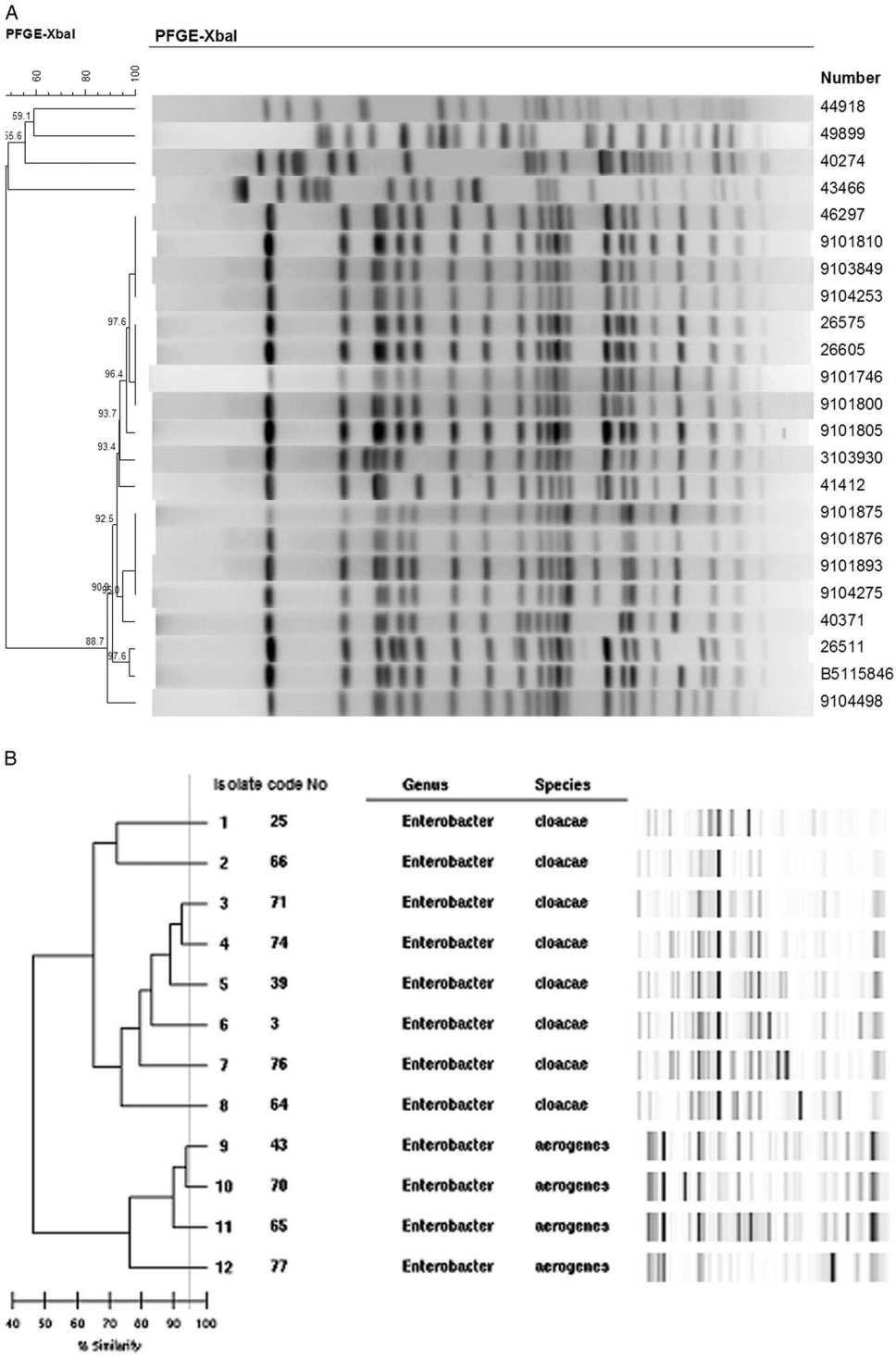


FIGURE 1. *A*, Genotypic characterization per pulsed-field gel electrophoresis from patients with carbapenem-resistant *Enterobacter* species, Assaf Harofeh Medical Center, Israel, 2007–2012. *B*, Genotypic characterization per repetitive extragenic palindromic polymerase chain reaction from patients with carbapenem-resistant *Enterobacter* species, Detroit Medical Center, Michigan, September 2008–September 2009.

50 (25–115) hours, and it did not significantly differ between institutions ($P = .2$). Overall, only 39% from AHMC and only 50% from DMC received appropriate consolidative regimens. Main appropriate consolidative regimens consisted of colistin (1 patient [8%] from DMC and 10 [19%] from AHMC), tigecycline (1 patient [8%] from DMC and none from

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TABLE 3. Acute Illness Indices and Antimicrobial Therapy Parameters Among Patients With Carbapenem-Resistant *Enterobacter* Species

Variable	Assaf Harofeh Medical Center (N = 54)		Detroit Medical Center (N = 14)	
Severity of Illness indices (at time of *Enterobacter* isolation)				
Rapidly fatal disease condition among adult patients[28]	24	49	4	33
True infection (not "just" colonization with no infection)[19]	23	42.6	10	76.9
Severe sepsis or septic shock or multi-organ failure[19]	28	51.9	2	18.2
Had to be acutely transferred to an ICU	2	9.5	0	0
Developed acute renal failure	9	16.7	3	21.4
Clinical syndrome				
Colonization only	29	53.7	4	28.6
Urinary tract infection	7	13.0	4	28.6
Skin and/or soft-tissue infection	10	18.5	2	14.3
Pneumonia	0	0	2	14.3
Central line–associated infection	2	3.7	2	14.3
Intra-abdominal	4	7.4	0	0
Antimicrobial therapy				
Antibiotics in preceding 3 mo	23	42.6	13	92.9
Hours to appropriate therapy, median (IQR)	41.6 (20–72)		117.33 (52–128.3)	
Penicillins in preceding 3 mo	7	13.0	9	64.3
Cephalosporins in preceding 3 mo	15	27.8	12	85.7
Carbapenems in preceding 3 mo	4	7.4	0	0
Number of antibiotic classes administered in preceding 3 mo, median (IQR)	1 (0–2)		3 (2–4)	
Penicillin empirical	22	41.5	2	15.4
Cephalosporins empirical	10	18.9	8	61.5
Carbapenem empirical	13	24.5	1	7.7

NOTE. Data are no. (%) of patients unless otherwise indicated. The percents provided are the valid percents—that is, excluding the missing cases from the denominator. ICU, intensive care unit; IQR, interquartile range.

AHMC), and aminoglycosides (5 patients [39%] from DMC and 10 [19%] from AHMC), sometimes given in combination with a carbapenem (1 patient [8%] from DMC and 2 [4%] from AHMC) (Table 3).

OUTCOMES

Descriptive Analysis

Clinical outcomes of patients infected with CREn (not including "colonized only" individuals) were similar between the 2 institutions (Table 4). The median (range) total LOS for the entire cohort was 14 (0–239) days, and the LOS from culture to discharge, after excluding patients who died, was 1 (0–151) days. The median cost from culture date to discharge (after excluding the dead) from AHMC was more than US $18,000 per affected patient.

The in-hospital mortality rate for the entire cohort was approximately 40%. Carriage was also associated with other devastating outcomes—for example, 39% of patients experienced a decrease in functional status, 27% were discharged to a long-term care facility after being admitted from home, and 48% were readmitted to the hospital in the following 6 months (Table 4). The rate of microbiologic failure was nearly 18%.

The median (interquartile range) survival time for CREn carriers was 65 (14–75) days and was similar between institutions (Figure 2).

Bivariable and Multivariable Analyses of Outcome Parameters

Twelve separate bivariable and multivariable analyses were executed, for all outcomes as listed in Table 4, in order to isolate specific predictors or features associated with each outcome. There were 3 outcomes for which multivariable analyses are presented. Older age and ICU stay were independent predictors for being discharged to a long-term care facility following CREn isolation. Only female sex was an independent predictor for functional status deterioration following the CREn isolation. Acute illness indices parameters and cognitive impairment at baseline were independently associated with in-hospital mortality.

DISCUSSION

This study is one of the largest CREn cohorts ever reported and several notable findings were described. CREn was isolated from 6 pediatric patients at AHMC, all bla_{KPC}-producing strains: 5 neonates and 1 child (a 1-year-old who was chronically ill with severe congenital defects and prolonged LOS). In 2010, there was a reported cluster of cases of CREn in the neonatal ICU (NICU) of one of the DMC facilities as well.[30] Invasive *Enterobacter* spp. infections are relatively common in NICUs and are usually associated with device-related infections.[4,31–33] Per surveillance criteria,[20] all acquisitions were nosocomial, with no vertical transmissions. Two of the

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TABLE 4. Clinical Outcomes of Patients With Carbapenem-Resistant *Enterobacter* Species

Variable	Assaf Harofeh Medical Center (n = 23)		Detroit Medical Center (n = 10)		Total (n = 33)	
Total LOS, median (IQR), d	14 (5.5–24.5)		12 (7–26)		14 (5.75–26)	
LOS after culture, excluding the dead, median (IQR), d	1 (0–1)		1 (.25–1)		1 (0–1)	
LOS in ICU from culture to discharge or death, median (IQR), d	22 (4.5–47)		9.5 (5.5–23.5)		12 (4–44)	
Death during hospitalization	10	43	3	30	13	39
30-day mortality	11	48	…	…	11	33
90-day mortality	12	52	3	30	15	45
Deterioration of patient's functional status after culture	8	35	5	50	13	39
Discharge to LTCF after being admitted from home	6	26	3	30	9	27
Additional hospitalization 6 mo after index hospitalization	10	43	6	60	16	48
Invasive procedure 3 mo after index hospitalization	6	26	5	50	11	33
Bacteriologic failure	5	22	1	10	6	18
Hospitalization cost, median (IQR), US $	18,235 (11,916–31,743)		…		18,235 (11,916–31,743)	

NOTE. Data are no. (%) of patients unless otherwise specified. The percents provided are the valid percents—that is, excluding the missing cases from the denominator. ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; LTCF, long-term care facility.

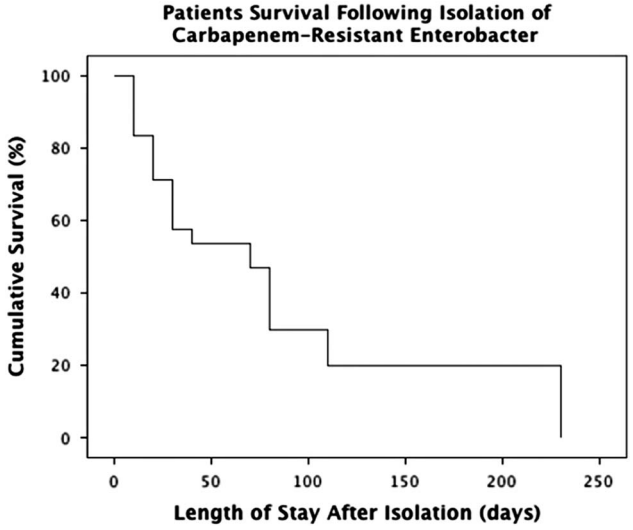


FIGURE 2. Kaplan-Meir survival analysis following the isolation of carbapenem-resistant *Enterobacter* during the hospital stay.

affected neonates were twins. One twin harbored the pathogen in his fourth day of life, and his sister became infected with CREn in her 29th day of life. This suggests that patient-to-patient transmission is a mode of CREn acquisition in NICUs.[4,33] Although in *Enterobacter*, the chromosomally encoded resistance mechanism may lead to "emergence of resistance" to a wide range of antibiotics, including carbapenems,[34] at least in NICUs, horizontal transmission seems to be a mode for acquisition as well.

As previously published in other cohorts of CRE, CREn adult carriers had extensive exposures to healthcare procedures and/or environments (Table 1).[8,10] Interestingly the exposures of patients from DMC were significantly more frequent compared with carriers from AHMC. Although 54 patients from AHMC had CREn recovered less than 72 hours into their hospitalization, 53 (98%) of 54 patients were "healthcare-associated" cases per established definitions, suggesting the importance of nonhospital healthcare reservoirs of CREn.[35] This finding supports targeted screening of patients who have prior healthcare exposure for CREn at the time of hospital admission.[7,15,36]

The molecular descriptive characteristics of this cohort merit attention (Table 2). DMC isolates were all obtained from patients during the time when a dominant transposon (*Tn*4401) containing bla_{KPC} had disseminated among Enterobacteriaceae in this region (2008–2009)[8,9,14–17] in similar fashion as in other parts of the world.[37,38] Some of the strains analyzed from AHMC were bla_{KPC}-negative and were resistant to carbapenems owing to other mechanisms.[39] There were 2 CREn from AHMC, both obtained from patients in 2012 (last study year), that were non-bla_{KPC}-producers and not genetically related (Figure 1a). Phenotypic tests like the MHT, which is performed by many laboratories as the only screening method to detect CRE, have low specificity in *Enterobacter* spp.[13,34] As this analysis demonstrates, genotypic tests such as the PCR bla_{KPC} might not detect all CREn. Therefore, close attention and active surveillance programs should be instituted, at institutional,[40] regional,[41] and national[7] levels, in order to monitor the evolution of circulating CREn strains. An additional worrisome trend was that strains from AHMC (from later years) were significantly more resistant to other classes of antibiotics (eg, aminoglycosides, fluoroquinolones, trimethoprim/sulfamethoxazole), compared with strains from DMC (earlier years).

CREn infection was associated with devastating outcomes (Table 4), as has been demonstrated with other CRE cohorts from all over the world.[11,42] This was not a matched case-control investigation. Therefore, the independent association of CREn infection with the various outcomes could not have been measured.

Since nearly 50% of the AHMC cases were diagnosed through rectal surveillance cultures, the importance of

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screening high-risk populations for CRE upon admission, coupled with implementation of infection control processes and measures, is stressed.[7,36,40]

Antimicrobial use is a predictor for many multidrug-resistant organisms including CRE[8] and, not surprisingly, previous antimicrobial use was common among patients in this study. Any policy to prevent and control CREn infections should include antimicrobial stewardship at its core.

Our study's strengths are its large sample size, the detailed clinical and molecular data that were extracted, and the potential generalizability of the results since it included 2 institutions located at the opposite sides of the world (both are CRE endemic). In addition, our study included both inpatients and outpatients, both pediatric and adult patients, and both asymptomatic carriers and truly infected patients. The study, however, has several limitations. In order to isolate independent epidemiologic predictors for CREn, a matched case-case-case-control study design would be appropriate.[8,11,43] An additional limitation is that isolates were genotyped and MIC testing was conducted at both centers using different methods, which limits the ability to explore genetic relatedness between the US and the Israeli strains. Our case definition in this specific study might have limited us in diagnosing CREn that harbored other carbapenemases (eg, metallo-β-lactamases, oxacillinases), though these types of carbapenemases have never been reported from these facilities.

This study depicts a comprehensive analysis of one of the largest CREn cohorts studied to date. Patients with CREn tended to be at the extremes of age. Many patients were elderly and had poor baseline health. Of particular interest was the inclusion of several NICU patients in the study. The devastating outcomes among infected patients of this cohort demonstrate the clinical significance of CREn. Laboratories routinely conducting MHT or PCR bla_{KPC} as the only screening method for CRE detection might not be identifying all CREn. Developing novel methodologic strategies to improve diagnostics would aid in shortening the time to initiating appropriate therapy for infected patients and in improving the management and outcomes of patients with CREn infections.

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