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MAJOR ARTICLE

Distinctive Features of Ertapenem-Mono-Resistant Carbapenem-Resistant Enterobacterales in the United States: A Cohort Study

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Background. Carbapenem-resistant Enterobacterales (CRE) are highly antibiotic-resistant bacteria. Whether CRE resistant only to ertapenem among carbapenems (ertapenem "mono-resistant") represent a unique CRE subset with regards to risk factors, carbapenemase genes, and outcomes is unknown.

Methods. We analyzed surveillance data from 9 CDC Emerging Infections Program (EIP) sites. A case was the first isolation of a carbapenem-resistant *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella aerogenes*, *K. oxytoca*, *K. pneumoniae,* or *K. variicola* from a normally sterile site or urine in an EIP catchment area resident in 2016–2017. We compared risk factors, carbapenemase genes, antibiotic susceptibility, and mortality of ertapenem "mono-resistant" cases to "other" CRE cases (resistant to ≥1 carbapenem other than ertapenem) and analyzed risk factors for mortality.

Results. Of 2009 cases, 1249 (62.2%) were ertapenem-mono-resistant and 760 (37.8%) were other CRE. Ertapenem-mono-resistant CRE cases were more frequently ≥80 years old (29.1% vs 19.5%; $P < .0001$) and female (67.9% vs 59.0%; $P < .0001$). Ertapenem-mono-resistant isolates were more likely to be *Enterobacter cloacae* complex (48.4% vs 15.4%; $P < .0001$) but less likely to be isolated from a normally sterile site (7.1% vs 11.7%; $P < .01$) or to have a carbapenemase gene (2.4% vs 47.4%; $P < .0001$). Ertapenem-mono-resistance was not associated with 90-day mortality in logistic regression models. Carbapenemase-positive isolates were associated with mortality (odds ratio, 1.93; 95% CI, 1.30–2.86).

Conclusions. Ertapenem-mono-resistant CRE rarely have carbapenemase genes and have distinct clinical and microbiologic characteristics from other CRE. These findings may inform antibiotic choice and infection prevention practices, particularly when carbapenemase testing is not available.

Keywords. antibiotic resistance; carbapenemase; carbapenem-resistant Enterobacterales; ertapenem.

Infections due to carbapenem-resistant Enterobacterales (CRE) pose an urgent public health threat due to limited treatment options, high associated costs, and mortality of up to 35% among hospitalized patients [1–5]. The US Centers for Disease Control and Prevention's (CDC's) original surveillance definition of CRE included Enterobacterales not susceptible to imipenem, doripenem, or meropenem and resistant to all third-generation cephalosporins tested [6]. In 2015, the CDC published a simplified CRE definition, and, with rare exceptions, Enterobacterales resistant to any carbapenem—including ertapenem—are now considered CRE [7]. As such, under the revised definition, Enterobacterales resistant only to ertapenem (among carbapenem antibiotics) are considered CRE. Little is known about the relevance of ertapenem-"mono-resistant" CRE and whether this subset of CRE has clinically important differences compared with other CRE.

Carbapenem resistance among Enterobacterales may be mediated by carbapenemase enzymes or by membrane permeability mutations in combination with noncarbapenemase β-lactamase enzymes [8]. This distinction is important for clinicians because carbapenemase production has a greater impact on antibiotic selection [9] and may be associated with worse outcomes than resistance via other mechanisms [10]. Additionally, carbapenemase identification is important for public health response as more intensive interventions, including contact investigation and colonization screening, may be required upon identification of patients with carbapenemase-producing organisms [7, 11–13]. Despite these important differences,

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carbapenemase testing is performed variably in clinical laboratories [7, 14], and the current phenotypic CRE definition favors sensitivity for detecting carbapenemases over specificity [1, 6]. Whether ertapenem-mono-resistance in clinical CRE isolates is associated with a lack of carbapenemase production or important clinical outcomes is unknown.

Given the knowledge gaps regarding ertapenem-mono-resistant CRE, we conducted a cohort study to determine the risk factors, prevalence of carbapenemase genes, and outcomes of ertapenem-mono-resistant CRE in the catchment area of the CDC's Emerging Infections Program (EIP) Multi-Site Gram-negative Surveillance Initiative (MuGSI).

METHODS

We analyzed data collected in 2016–2017 by MuGSI, which conducts active population- and laboratory-based surveillance for CRE through the EIP [15–17]. During the study period, MuGSI conducted CRE surveillance in selected areas in 9 states (California, Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee). The total population of the MuGSI catchment area was 22 million in 2017.

Case Definition and Antibiotic Susceptibility Testing

An incident CRE case was defined as the first isolation of *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae,* or *Klebsiella variicola* resistant to at least 1 carbapenem (ie, doripenem, meropenem, and/or imipenem minimum inhibitory concentration [MIC] ≥4 μg/mL or zone diameter ≤19 mm and/or ertapenem MIC ≥2 μg/mL or zone diameter ≤18 mm) [18] collected from urine or a normally sterile body site from a resident of the EIP catchment area in a 30-day period in 2016–2017. Other Enterobacterales species (including *Serratia* spp.) were not included in this analysis.

Case ascertainment was performed by obtaining line lists of isolates that met the case definition phenotype from participating clinical laboratories through queries of the laboratory information systems or automated testing instruments. We obtained MICs and zone diameters for all isolate–antibiotic combinations tested by all methods used at the clinical laboratory. If antibiotic susceptibility testing was performed by both an automated and manual testing method (Etest [bioMérieux, Durham, NC, USA] or disc diffusion), we considered the manual testing method the gold standard. 2017 Clinical Laboratory and Standards Institute clinical breakpoints were applied to determine antibiotic susceptibility or resistance [18]. We defined ertapenem-"mono-resistant" CRE as an isolate resistant to ertapenem but not resistant to any other carbapenem tested and "other" CRE as an isolate resistant to ≥1 carbapenem other than ertapenem. A convenience sample of isolates was tested at the CDC for specific carbapenemase genes (bla_{KPC}, bla_{NDM}, and $bla_{OXA\text{-}48\text{-}like}$) via real-time polymerase chain reaction (PCR) using laboratory-developed assays [19, 20].

We included only the first incident case per patient. In cases where a patient had both a urine and sterile site CRE isolate collected within 30 days of each other, we considered only the sterile site isolate. We excluded isolates tested against ertapenem but no other carbapenems, isolates without a reported MIC (or zone diameter) for any carbapenem, and cases with unknown death status.

Clinical Data Collection

For all incident CRE cases, EIP staff completed a case report form, which included information on patient demographics, comorbidities, county of residence, type of setting (eg, health care facility vs outpatient) at the time of culture collection, organism, antibiotic MICs, and specimen source through medical record review. We calculated and then dichotomized the Charlson Comorbidity Index score as >2 or ≤2 [21]. Epidemiological classification (ie, community-associated, health care–associated community onset, hospital onset, and long-term care facility onset) is defined in Supplementary Table 1. EIP staff conducted queries of state vital records to determine mortality within 90 days of incident culture collection.

Statistical Analyses

We compared differences in proportion of categorical variables between ertapenem-mono-resistant and other CRE cases with the χ^2 or Fisher exact test as appropriate, and then stratified by specimen collection site to assess differences between ertapenem-mono-resistant and other CRE cases with isolates collected from either a sterile site or urine. We used univariable logistic regression to determine risk factors for 90-day mortality and multivariable logistic regression to determine if ertapenem-mono-resistance was independently associated with 90-day mortality; covariates were selected based on clinical relevance and biologic plausibility and were not included if they were highly collinear (variance inflation factor >5). As a sensitivity analysis, we created models with and without carbapenemase status as a covariate given that carbapenemase status was only assessed in 52% of total isolates. Survival distributions were compared with the log-rank test. Analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and P values <.05 were considered statistically significant.

Patient Consent

This secondary analysis of MuGSI surveillance data was approved by the Emory Institutional Review Board, which additionally approved a waiver of informed consent. The CDC did not conduct the data analysis and was determined to be nonengaged in this research study after review by the Human Subjects Advisor in the National Center for Emerging and Zoonotic Infectious Diseases at the CDC. The CDC provided

the data to the coordinating EIP site (Georgia) for analysis under a data use agreement and with permission from the other participating sites.

RESULTS

Carbapenem-Resistant Enterobacterales Cases

Of 2449 incident CRE cases identified in the 9 catchment areas from 2016 to 2017, 440 (18.0%) were excluded, leaving a total of 2009 cases (Figure 1). Georgia and Maryland contributed nearly half of all cases (Supplementary Table 2). The most common methods for carbapenem susceptibility determination were automated testing instruments including Vitek (bioMérieux), MicroScan (Beckman Coulter, Brea, CA, USA), and BD Phoenix (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) (see Supplementary Table 3 for details by carbapenem). Most isolates were tested against ertapenem and meropenem only (27.1%), or ertapenem, meropenem, and imipenem only (39.1%) (Supplementary Table 4).

Risk Factors for Ertapenem-Mono-Resistant CRE

Of 2009 CRE cases, 1249 (62.2%) were ertapenem-mono-resistant CRE, and 760 (37.8%) were other CRE (Table 1). Ertapenem-mono-resistant CRE cases were more likely to be age ≥80 years (29.1% vs 19.5%; $P < .0001$), female (67.9% vs 59.0%; $P < .0001$), and White (62.6% vs 45.1%; $P < .0001$). Ertapenem-mono-resistant cases were more likely to be health care–associated community onset (38.4% vs 32.6%; $P < .01$) and less likely to be long-term care facility onset (20.7% vs 25.0%; $P = .02$) [22]. The proportions of cases with Charlson Comorbidity Index >2 and individual comorbidities were similar in both groups.

Ertapenem-mono-resistant isolates were more likely to be *Enterobacter cloacae* complex (48.4% vs 15.4%; $P < .0001$) and less likely to be *Klebsiella pneumoniae* (14.5% vs 46.1%; $P < .0001$) than other CRE (Table 1). Overall, 1831 (91.1%) of all CRE isolates were isolated from urine and 178 (8.9%) from a normally sterile site. Ertapenem-mono-resistant isolates were less likely to be isolated from a normally sterile site (7.1% vs 11.7%; $P < .01$), including blood (4.2% vs 8.6%; $P < .0001$).

Sterile site infections comparing ertapenem-mono-resistant CRE with other CRE (n = 89 in each group) had similar risk factors for acquisition, including epidemiological class (most commonly hospital onset, 55.1%) (Supplementary Table 5). Among isolates from a urine source (n = 1831), cases with ertapenem-mono-resistant isolates were more likely than cases with other CRE to be ≥80 years old and female and less likely to be long-term care facility onset (all $P < .01$). Of isolates with a urine source, 41.9% were associated with a symptom or sign of a urinary tract infection (UTI; including dysuria, urinary frequency/urgency, fever, suprapubic tenderness, and/or costovertebral angle tenderness), and the proportion of cases with ≥1 UTI symptom or sign did not differ between groups.

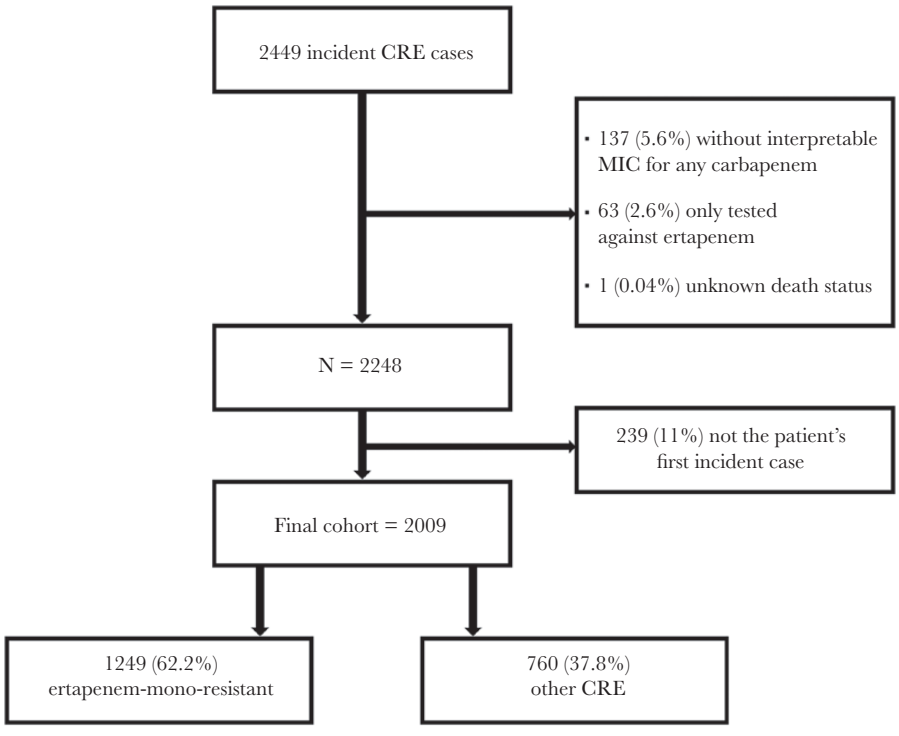

Figure 1. Flow diagram of CRE cases included in analysis, 2016–2017. Ertapenem-mono-resistant CRE are only resistant to ertapenem (among carbapenems). Other CRE are resistant to ≥1 carbapenem other than ertapenem. Abbreviations: CRE, carbapenem-resistant Enterobacterales; MIC, minimum inhibitory concentration.

Table 1. Characteristics of CRE Cases Included, Comparing Those Resistant Only to Ertapenem (Ertapenem-"Mono-Resistant") With Other CRE (ie, Resistant to ≥1 Carbapenem Other Than Ertapenem)

Characteristic	All Isolates (n = 2009), No. (%)	Ertapenem-Mono-Resistant CRE (n = 1249), No. (%)	Other CRE (n = 760), No. (%)	*P* Value[a]
Age, y				
<1–18	47 (2.3)	38 (3.0)	9 (1.2)	<.01
19–49	349 (17.4)	183 (14.7)	166 (21.8)	<.0001
50–64	406 (20.2)	226 (18.1)	180 (23.7)	<.01
65–79	695 (34.6)	438 (35.1)	257 (33.8)	.57
≥80	512 (25.5)	364 (29.1)	148 (19.5)	<.0001
Female sex	1296 (64.5)	848 (67.9)	448 (59.0)	<.0001
Race				
White	1125 (56.0)	782 (62.6)	343 (45.1)	<.0001
Black	519 (25.8)	243 (19.5)	276 (36.3)	<.0001
Asian	62 (3.1)	32 (2.6)	30 (4.0)	.08
American Indian/Alaskan	14 (0.7)	9 (0.7)	5 (0.7)	.87
Hawaiian/Pacific Islander	1 (0.1)	0 (0.0)	1 (0.1)	.38
Unknown	288 (14.3)	183 (14.7)	105 (13.8)	.60
Hispanic ethnicity	163 (8.1)	116 (9.3)	47 (6.2)	.01
Epidemiological class[b]				
CA	540 (26.9)	339 (27.1)	201 (26.5)	.12
HACO	728 (36.2)	480 (38.4)	248 (32.6)	<.01
HO	293 (14.6)	172 (13.8)	121 (15.9)	.19
LTCFO	448 (22.3)	258 (20.7)	190 (25.0)	.02
CCI >2 (n = 1933)	664 (34.4)	412 (34.1)	252 (34.9)	.72
Comorbidities				
Diabetes	687 (34.2)	427 (34.2)	260 (34.2)	.99
Chronic pulmonary disease	426 (21.2)	252 (20.2)	174 (22.9)	.15
Obesity	366 (18.2)	238 (19.1)	128 (16.8)	.21
Cerebrovascular accident	311 (15.5)	190 (15.2)	121 (15.9)	.18
Malignancy	309 (15.4)	206 (16.5)	103 (13.5)	.08
Heart failure	296 (14.7)	191 (15.3)	105 (13.8)	.37
Dementia	289 (14.4)	178 (14.3)	111 (14.6)	.83
Chronic kidney disease	252 (12.5)	148 (11.9)	104 (13.7)	.23
Cirrhosis	66 (3.3)	39 (3.1)	27 (3.6)	.60
Organism				
Enterobacter cloacae	722 (35.9)	605 (48.4)	117 (15.4)	<.0001
Escherichia coli	583 (29.0)	392 (31.4)	191 (25.1)	<.01
Klebsiella pneumoniae	531 (26.4)	181 (14.5)	350 (46.1)	<.001
Klebsiella aerogenes	130 (6.5)	51 (4.3)	76 (10.0)	<.0001
Klebsiella oxytoca	43 (2.1)	17 (1.4)	26 (3.4)	<.01
Source				
Urine	1831 (91.1)	1160 (92.9)	671 (88.3)	<.01
Sterile	178 (8.9)	89 (7.1)	89 (11.7)	<.01
Blood	117 (5.8)	52 (4.2)	65 (8.6)	<.0001
Peritoneal fluid	27 (1.3)	18 (1.4)	9 (1.2)	.63
Other	34 (1.7)	19 (1.5)	15 (2.0)	0.45
90-d mortality	272 (13.5)	158 (12.7)	114 (15.0)	.14

Abbreviations: CA, community-associated; CCI, Charlson Comorbidity Index; CRE, carbapenem-resistant Enterobacterales; HACO, health care–associated community onset; HO, hospital-onset; LTCFO, long-term care facility onset.

[a]Determined by χ^2 test or Fisher's exact test.

[b]Defined in Supplementary Table 1.

Carbapenemase Genes and Antibiotic Susceptibility

A convenience sample of 1046 CRE isolates (52.1% of total) was tested for carbapenemase genes at the CDC by PCR. Of these, 668 (63.9%) were ertapenem-mono-resistant and 378 (36.1%) were other CRE as defined by the clinical laboratory. Of all CRE isolates tested, 195 (18.6%) were positive for any carbapenemase. Ertapenem-mono-resistant isolates were less likely to have any carbapenemase than other CRE (2.4% vs 47.4%; $P < .0001$). bla_{KPC} was the most commonly detected carbapenemase gene (92.3% of carbapenemase genes detected),

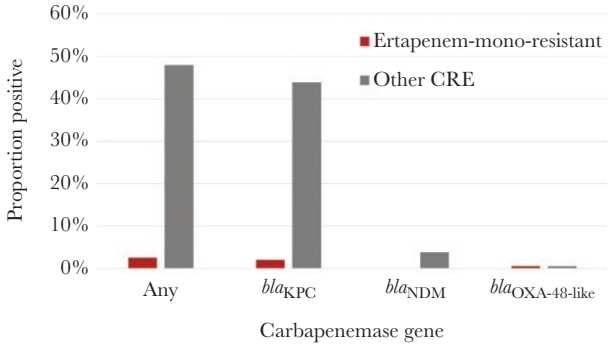

Figure 2. Proportion of ertapenem-mono-resistant CRE vs other CRE isolates with specific carbapenemase genes. Ertapenem-mono-resistant CRE are only resistant to ertapenem (among carbapenems). Other CRE are resistant to ≥1 carbapenem other than ertapenem. Testing for carbapenemase genes was performed by real-time polymerase chain reaction at the CDC. Abbreviations: CDC, Centers for Disease Control and Prevention; CRE, carbapenem-resistant Enterobacterales.

and ertapenem-mono-resistant isolates were significantly less likely to have bla_{KPC} than other CRE (2.0% vs 44.2%; $P < .0001$) (Figure 2). No ertapenem-mono-resistant isolates had bla_{NDM}, compared with 4.3% of other CRE; $bla_{OXA-48-like}$ was detected in 0.4% of ertapenem-mono-resistant isolates and 0.7% of other isolates. These differences persisted when analyzing isolates by sterile vs urine source (Supplementary Table 6).

Ertapenem-mono-resistant isolates additionally were more likely to be susceptible to several antibiotics including cefepime, piperacillin-tazobactam, levofloxacin, and gentamicin (Figure 3).

Mortality

Overall 90-day mortality was 13.5%, and overall mortality was similar between ertapenem-mono-resistant and other CRE (12.7% vs 15.0%; $P = .14$). When stratifying by specimen source, there was also no difference in mortality between ertapenem-mono-resistant and other CRE cases; however, mortality for cases with a sterile source isolate (31.5% ertapenem-mono-resistant and 31.5% other) was higher than for cases with urine isolates (11.2% ertapenem-mono-resistant and 12.8% other). Survival distribution was similar between ertapenem-mono-resistant and other CRE (Figure 4A), but different when stratifying these groups further by specimen source (log-rank $P < .0001$) (Figure 4B). Among isolates tested for carbapenemases, cases with carbapenemase-positive isolates had significantly higher 90-day mortality than those without (log-rank $P < .01$) (Figure 4C). When stratifying by both specimen source and carbapenemase status, carbapenemase-positive isolates from a normally sterile site were associated with highest mortality, and carbapenemase-negative isolates from urine were associated with lowest mortality (log-rank $P < .0001$) (Figure 4D). Sterile site origin was more strongly associated with mortality than was carbapenemase status (Figure 4D).

In univariable analysis, ertapenem-mono-resistance was not associated with a difference in 90-day mortality (odds ratio [OR], 0.82; 95% CI, 0.63–1.06) (Table 2). Having a carbapenemase-positive isolate (OR, 1.93; 95% CI, 1.30–2.86) or isolate from a sterile source (OR, 3.43; 95% CI, 2.43–4.86) was associated with mortality, as were *Enterobacter cloacae* complex (OR, 2.09; 95% CI, 1.46–2.99), *Klebsiella pneumoniae* (OR, 2.34; 95% CI, 1.61–3.39), and *Klebsiella oxytoca* isolates (OR, 2.95; 95% CI, 1.34–6.51, all compared with *E. coli*). The strongest univariable predictor of mortality was epidemiological class, specifically hospital-onset (OR, 23.12; 95% CI, 11.79–45.34) or long-term care facility–onset infections (OR, 14.07;

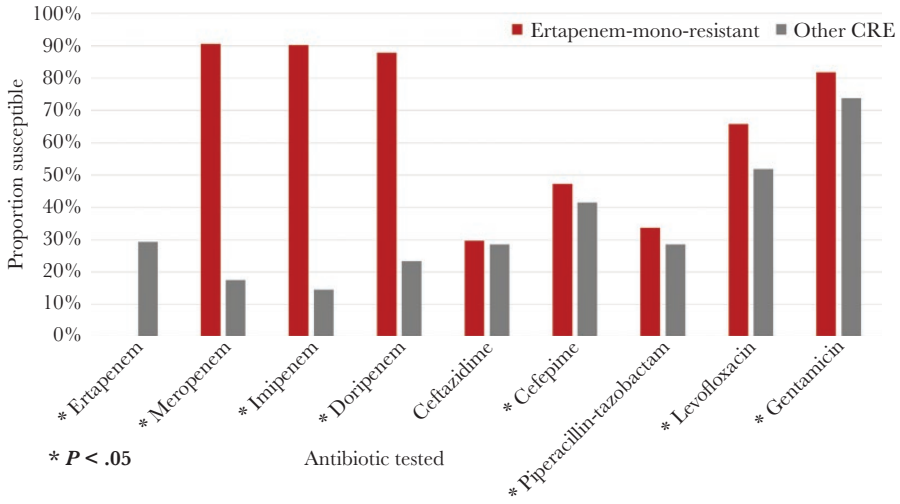

Figure 3. Proportion of ertapenem-mono-resistant CRE vs other CRE isolates susceptible to selected antibiotics. Ertapenem-mono-resistant CRE are only resistant to ertapenem (among carbapenems). Other CRE are resistant to ≥1 carbapenem other than ertapenem. Classification of an isolate as susceptible, intermediate, or resistant was determined for minimum inhibitory concentrations of selected antibiotics according to CLSI criteria based on testing performed at clinical laboratories [18]. If an isolate was not tested against a certain antibiotic, it was not included in this figure. *$P < .05$. Abbreviation: CRE, carbapenem-resistant Enterobacterales.

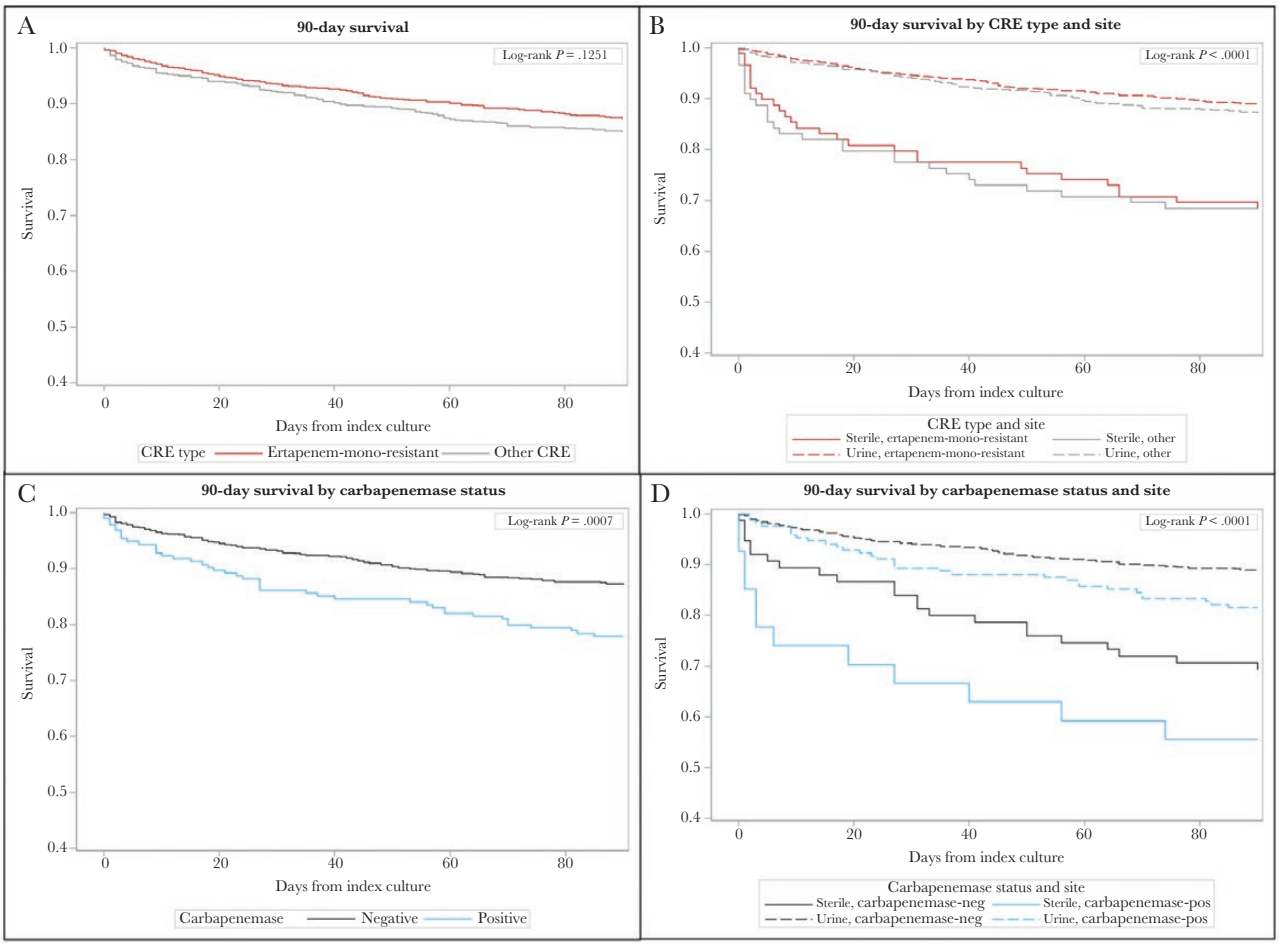

Figure 4. Survival analysis comparing patients with CRE that are ertapenem-mono-resistant to other CRE (ie, resistant to ≥1 carbapenem other than ertapenem), either total (A) or stratified by isolate site (ie, sterile site vs urine) (B); and comparing patients with CRE that have carbapenemase genes, either total (C) or stratified by isolate site (D). Presence of carbapenemase gene and sterile isolate site was associated with differences in survival, but ertapenem-mono-resistant CRE were not associated with a mortality difference compared with other CRE. Abbreviation: CRE, carbapenem-resistant Enterobacterales.

95% CI, 7.23–27.38) compared with community-associated infections. In multivariable logistic regression models with and without adjusting for carbapenemase status, ertapenem-mono-resistant isolates were not associated with decreased mortality (Table 3).

DISCUSSION

In this large, geographically diverse US cohort of >2000 CRE cases, most isolates were ertapenem-mono-resistant. These cases had distinct clinical characteristics, and the isolates rarely (2.4%) had carbapenemase genes. Ertapenem-mono-resistant CRE were not associated with 90-day mortality in either univariable or multivariable analyses; carbapenemase-positive isolates and isolate site were both significantly associated with mortality.

The first striking finding is that a large proportion of CRE cases (62%) were ertapenem-mono-resistant. Few studies have assessed the contribution of ertapenem-mono-resistance to CRE, and there are few data on ertapenem-mono-resistance from the United States. A single-center study in Thailand from 2011 to 2016 found that 30% of CRE cases were not susceptible to ertapenem only, and these cases were associated with lower rates of critical illness and previous carbapenem exposure [23]. Given widespread differences in CRE epidemiology, data from Thailand are unlikely to be relevant to US settings, and the data presented here expand these findings to the United States. The significant number of isolates that now qualify as CRE after the addition of ertapenem resistance to the CRE definition in 2015 [7, 24] increases the resources required for carbapenemase detection and infection control.

These data have important clinical relevance. The 2021 Infectious Diseases Society of America (IDSA) treatment guidance on antimicrobial-resistant gram-negative infections recommends using meropenem for ertapenem-mono-resistant CRE when carbapenemase testing is not available [9]. Studies from the United Kingdom and South Korea demonstrated that ertapenem resistance usually arises from a combination of altered membrane porins and noncarbapenemase ß-lactamase enzymes, including AmpC and extended-spectrum ß-lactamases

Table 2. Risk Factors for 90-Day Mortality Among n = 2009 Patients With CRE

Characteristic	Unadjusted Odds Ratio (95% CI)
Age, y	
<1–18	Ref
19–49	1.01 (0.22–4.56)
50–64	3.75 (0.89–15.88)
65–79	4.00 (0.96–16.76)
≥80	4.93 (1.17–20.68)
Female sex	0.68 (0.52–0.88)
Race	
White	Ref
Black	1.34 (1.00–1.79)
Asian	1.43 (0.73–2.82)
American Indian/Alaskan	0.51 (0.07–3.94)
Hispanic ethnicity	0.38 (0.20–0.74)
Epidemiological class[a]	
CA	Ref
HACO	6.45 (3.31–12.58)
HO	23.12 (11.79–45.34)
LTCFO	14.07 (7.23–27.38)
CCI >2	3.37 (2.58–4.40)
Comorbidities	
Diabetes	1.31 (1.01–1.71)
Chronic pulmonary disease	1.71 (1.29–2.28)
Obesity	0.87 (0.62–1.23)
Cerebrovascular accident	1.81 (1.33–2.47)
Malignancy	2.45 (1.81–3.30)
Heart failure	2.37 (1.75–3.22)
Dementia	1.82 (1.32–2.50)
Chronic kidney disease	3.27 (2.40–4.46)
Cirrhosis	1.93 (1.07–3.48)
Ertapenem-mono-resistance[b]	0.82 (0.63–1.06)
Carbapenemase-positive[c]	1.93 (1.30–2.86)
Sterile source	3.43 (2.43–4.86)
Organism	
Escherichia coli	Ref
Klebsiella aerogenes	0.83 (0.40–1.74)
Enterobacter cloacae	2.09 (1.46–2.99)
Klebsiella pneumoniae	2.34 (1.61–3.39)
Klebsiella oxytoca	2.95 (1.34–6.51)

Abbreviations: CA, community-associated; CCI, Charlson Comorbidity Index; CDC, Centers for Disease Control and Prevention; CRE, carbapenem-resistant Enterobacterales; HACO, health care–associated community onset; HO, health care onset; LTCFO, long-term care facility onset.

[a]Defined in Supplementary Table 1.

[b]Ertapenem-mono-resistant CRE are isolates resistant only to ertapenem (among carbapenems), compared with other CRE (ie, resistant to ≥1 carbapenem other than ertapenem).

[c]Detected via real-time polymerase chain reaction testing for bla_{KPC}, bla_{NDM}, and $bla_{OXA\text{-}48\text{-}like}$ performed on a subset (52%) of isolates at the CDC.

Table 3. Odds of 90-Day Mortality of Patients With CRE Resistant Only to Ertapenem Compared With Patients With Other CRE (ie, Resistant to ≥1 Carbapenem Other Than Ertapenem)

Model	Odds Ratio (95% CI)
Unadjusted	0.82 (0.63–1.06)
Limited model[a]	
Including carbapenemase status	0.82 (0.62–1.10)
Not including carbapenemase status	1.06 (0.65–1.72)
Full model[b]	
Including carbapenemase status	0.85 (0.60–1.19)
Not including carbapenemase status	0.96 (0.57–1.63)

Abbreviation: CRE, carbapenem-resistant Enterobacterales.

[a]Adjusted for age, sex, race, and Charlson Comorbidity Index.

[b]Adjusted for age, sex, race, Charlson Comorbidity Index, epidemiological class, site of isolation (sterile vs urine), and organism.

(eg, SHV, TEM, and CTX-M) [25–29], and could therefore be overcome with nonertapenem carbapenems. Our analysis argues that ertapenem-mono-resistance among CRE is driven by noncarbapenemase mechanisms, and therefore supports the IDSA expert opinion guidance. However, without carbapenemase testing, there may be some risk of treatment failure in patients with carbapenemase-producing CRE treated with a carbapenem. Despite our data showing a low proportion of carbapenemase production among ertapenem-mono-resistant CRE, these enzymes were still detected. This argues for increased resources for carbapenemase detection in clinical laboratories to better ensure that all patients are treated with appropriate antibiotics [7]. However, the capacity for carbapenemase testing in clinical microbiology laboratories is not universal [7, 14]. Therefore, in health care facilities where capacity for rapid carbapenemase detection is limited, our data suggest that prioritizing carbapenemase testing for CRE that are not ertapenem-mono-resistant would be the most efficient use of resources.

Carbapenemase production impacts antibiotic choice [9, 30] and the intensity of public health response [7, 14], but whether it additionally impacts important outcomes including mortality is unclear. In 2017, the first US study to address this question found that patients with carbapenemase-positive CRE bacteremia had higher unadjusted mortality than those with carbapenemase-negative CRE bacteremia (32% vs 13%). This difference persisted when adjusting for important clinical factors including severity of illness and antibiotic administration [10]. In a 2020 multicenter US study of >400 patients with CRE infection using standardized definitions, mortality did not differ between patients with carbapenemase-positive and -negative isolates [1]. In our analysis, patients with carbapenemase-positive isolates had twice the odds of 90-day mortality as those with carbapenemase-negative isolates. Interestingly, we found higher mortality despite including a large number of urine isolates, which may reflect colonization and not true infection. The higher mortality among patients with carbapenemase-positive isolates in our current study likely reflects both the difficult-to-treat nature of these isolates and significant comorbidities among patients who acquire carbapenemase-positive CRE. Although ertapenem-mono-resistant isolates were associated with less frequent carbapenemase detection, ertapenem-mono-resistant isolates were not associated with decreased mortality; this may reflect insufficient power to detect a statistically significant difference in mortality between ertapenem-mono-resistant and other CRE cases.

Our study has several limitations. First, this study was conducted in 9 separate metropolitan regions, which may not be representative of the rest of the country; CRE prevalence and carbapenemase production vary widely by region [1] Second, we relied on MIC determination by local clinical laboratories, and not standardized central laboratories as in other studies [1], to determine antibiotic susceptibility. Certain automated testing instruments used in clinical laboratories, including Vitek, may misclassify a subset of isolates as ertapenem resistant [31, 32]. In a large prospective study on CRE prevalence, a high proportion (22%) of isolates that were determined to be CRE by local clinical laboratories were not confirmed to be CRE by standardized testing at reference laboratories [1]. Further clinical validation of automated testing instruments is required to determine why certain isolates thought to be CRE after initial testing (especially ertapenem-mono-resistant CRE isolates) are not ultimately confirmed to be CRE. Third, not all isolates were tested for susceptibility to all carbapenem antibiotics, so some isolates classified as ertapenem-mono-resistant may have been "other" CRE (eg, if imipenem MIC was not determined but the isolate was actually imipenem resistant). Fourth, only a convenience sample of isolates, which may not be representative of all CRE cases, was available for carbapenemase testing. Although this sample may not be reflective of all CRE isolates, the large number of isolates tested (n = 1046, 52% of all isolates) increases confidence in our results. Fifth, we only tested for a subset of known carbapenemase genes, and therefore may have missed carbapenem-producing isolates. Further research, including whole-genome sequencing, is needed to test CRE isolates for all carbapenemases and to detect new and emerging mechanisms of resistance. Sixth, mechanisms of resistance in CRE are constantly evolving, so the proportion of carbapenemase genes presented here (from 2016 to 2017) may not reflect current prevalence. Seventh, a large proportion of isolates in this study (91%) were from the urine, and a majority of these (58%) were not associated with a symptom or sign of urinary tract infection. These isolates do not reflect clinical infection, and therefore characteristics of patients harboring these isolates may be expected to be different from patients with true CRE infection. While not a specific focus of this manuscript, the large number of isolates associated with asymptomatic bacteriuria highlights the need for improved diagnostic stewardship. Despite these limitations, the EIP's systematic, population-based approach to CRE surveillance and data collection, as well as sampling from multiple large metropolitan areas in the United States, is an important strength.

In this large, geographically diverse cohort study of >2000 patients with CRE, a substantial proportion (>60%) of CRE isolates were ertapenem-mono-resistant. This CRE subset has unique risk factors for acquisition, including increasing age and female sex, and is significantly less likely to have carbapenemase genes than other CRE isolates. Whether ertapenem-mono-resistant isolates should be conflated with other CRE (ie, CRE resistant to ≥1 other carbapenem) or whether CRE should be classified based on resistance mechanism (ie, carbapenemase vs other) remains an area of active debate [33]. We found that ertapenem-mono-resistant isolates had a similar overall mortality to other CRE. Nevertheless, differentiating CRE based on ertapenem-mono-resistance may help front-line clinicians better care for patients with CRE infection, particularly when carbapenemase testing is not readily available.

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