AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

Activity of Cefiderocol, Ceftazidime-Avibactam, and Eravacycline against Carbapenem-Resistant *Escherichia coli* Isolates from the United States and International Sites in Relation to Clonal Background, Resistance Genes, Coresistance, and Region

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ABSTRACT Emerging carbapenem resistance in *Escherichia coli*, including sequence type 131 (ST131), the leading cause of extraintestinal *E. coli* infections globally, threatens therapeutic efficacy. Accordingly, we determined broth microdilution MICs for three distinctive newer agents, i.e., cefiderocol (CFDC), ceftazidime-avibactam (CZA), and eravacycline (ERV), plus 11 comparators, against 343 carbapenem-resistant (CR) clinical *E. coli* isolates, then compared susceptibility results with bacterial characteristics and region. The collection comprised 203 U.S. isolates (2002 to 2017) and 141 isolates from 17 countries in Europe, Latin America, and the Asia-West Pacific region (2003 to 2017). Isolates were characterized for phylogenetic group, resistance-associated sequence types (STs) and subsets thereof, and relevant beta-lactamase-encoding genes. CFDC, CZA, and ERV exhibited the highest percent susceptible (82% to 98%) after tigecycline (TGC) (99%); avibactam improved CZA's activity over that of CAZ (11% susceptible). Percent susceptible varied by phylogroup and ST for CFDC and CZA (greatest in phylogroups B2, D, and F, and in ST131, ST405, and ST648). Susceptibility also varied by resistance genotype, being higher with the *Klebsiella pneumoniae* carbapenemase (KPC) for CZA, lower with metallo-beta-lactamases for CFDC and CZA, and higher with the beta-lactamase CTX-M for ERV. Percent susceptible also varied by global region for CZA (lower in Asia-Pacific) and by U.S. region for ERV (lower in the South and Southeast). Although resistance to comparators often predicted reduced susceptibility to a primary agent (especially CFDC and CZA), even among comparator-resistant isolates the primary-agent-susceptible fraction usually exceeded 50%. These findings clarify the likely utility of CFDC, CZA, and ERV against CR *E. coli* in relation to multiple bacterial characteristics and geographical region.

KEYWORDS *E. coli*, KPC, MIC, ST131-H30, carbapenem resistant, cefiderocol, ceftazidime-avibactam, coresistance, eravacycline, metallo-beta-lactamase

Carbapenem resistance is emerging in *Escherichia coli*, including within sequence type (ST) 131 and its pandemic, multidrug-resistant (MDR) *H*30R subset (1–5). This threatens the utility of carbapenems as reliable fallback agents for infections due to organisms resistant to extended-spectrum cephalosporins and fluoroquinolones (6).

Cefiderocol (CFDC), ceftazidime-avibactam (CZA), and eravacycline (ERV) are recently developed agents with activity against carbapenem-resistant (CR) *E. coli* strains.

Citation Johnston BD, Thuras P, Porter SB, Anacker M, VonBank B, Snippes Vagnone P, Witwer M, Castanheira M, Johnson JR. 2020. Activity of cefiderocol, ceftazidime-avibactam, and eravacycline against carbapenem-resistant *Escherichia coli* isolates from the United States and international sites in relation to clonal background, resistance genes, coresistance, and region. Antimicrob Agents Chemother 64:e00797-20. https://doi.org/10.1128/AAC.00797-20.

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Received 4 May 2020
Returned for modification 10 June 2020
Accepted 16 July 2020
Accepted manuscript posted online 27 July 2020
Published 21 September 2020

CFDC is a novel siderophore cephalosporin active against CR Gram-negative bacteria, including those that produce carbapenemases of all Ambler classes or have porin channel mutations and/or efflux pump overexpression (7–9). CZA pairs ceftazidime, an extended-spectrum cephalosporin, with avibactam, a non-beta-lactam, beta-lactamase inhibitor that is active against Ambler class A, class C, and some class D beta-lactamases (10–12). ERV is a novel, fully synthetic fluorocycline antibiotic within the tetracycline class that has broad-spectrum activity against MDR Gram-negative bacteria, including those expressing all Ambler classes of beta-lactamases (13–16).

These agents have been studied minimally against ST131 and, specifically, its resistance-associated *H*30R subset, with its constituent *H*30R1 and *H*30Rx subclones. Accordingly, here, we tested CFDC, CZA, ERV, and comparator agents for activity against a large and geographically diverse collection of CR *E. coli* in relation to phylogenetic and clonal background (including relevant ST131 subclones and other STs), resistance genes, geographical region within the United States and internationally, and coresistance profiles. We sought to determine the activity of CFDC, CZA, ERV, and other agents against CR *E. coli* generally, and to what extent this varies in relation to specific bacterial characteristics.

RESULTS

Overall percent susceptible and MICs. Among the 343 total CR *E. coli* clinical isolates (Table 1), the percent susceptible was higher for ERV (98%), CFDC (92%), and CZA (82%) than for any nonpotentiated carbapenem (MEM, 59%; IPM, 29%; ETP, 4%) or any other comparator except TGC (99%) (Table 2). For CAZ alone, i.e., without the beta-lactamase inhibitor avibactam, the percent susceptible (11%) was 71% lower than for CZA (82%), and the MIC_{50} correspondingly was 128-fold higher (64 mg/liter versus 0.5 mg/liter, respectively).

Phylogroup. The 343 study isolates were distributed broadly by phylogroup. Individual phylogroups with $n \geq 3$ (which excludes group E with $n = 2$, 0.6%) accounted for from 8% (group C) to 31% (group B2) of isolates each (Table 3). For CFDC and CZA, percent susceptible varied significantly by phylogroup, being highest in groups B2, D, and F, and lowest in groups A, B1, and C (for CFDC, 93% to 100% versus 82% to 85%; CZA 89% to 93% versus 52% to 76%). In contrast, for ERV percent susceptible did not vary significantly by phylogroup; it ranged from 93% (group A) to 100% (groups B2 and D). Within each phylogroup, percent susceptible was much lower for CAZ alone (0 to 12%) than for CZA (52% to 93%).

Clonal group and subclone. The predominant identified STs were ST131 (group B2: 25.7% of 343), ST405 (group D: 7.3%), and ST648 (group F: 8.5%). The predominant ST131 subsets were *H*30R1 (8.2% of 343) and *H*30Rx (13.7%), which accounted for 86% of the 86 ST131 isolates (Table 4). For both CFDC and CZA, percent susceptible varied significantly by ST, being higher for isolates from the three analyzed STs than for other isolates, whereas within ST131 percent susceptible was similarly high for *H*30R1 and *H*30Rx isolates. In contrast, percent susceptible to ERV did not vary significantly by either ST or ST131 subclone (Table 4).

Resistance genotype. The 343 study isolates contained genes encoding diverse beta-lactamases, most commonly CTX-M (43%) or CMY-2 (28%), followed by metallo-beta-lactamases (MBLs) (19%), KPC (16%), and OXA-48 (13%) (Table 5). The detected MBL-encoding genes were predominantly for NDM (16% of 343), followed distantly by IMP (2%) and VIM (1%). For CFDC and CZA, percent susceptible was significantly lower (CFDC, moderately; CZA, profoundly) in the presence versus absence of a MBL-encoding gene. In contrast, for ERV percent susceptible was unrelated to beta-lactamase genotype. The comparator agents exhibited various patterns of susceptibility in relation to beta-lactamase genotype.

Geographical region. At the global level, of the three primary study drugs, only CZA showed significant regional variation in percent susceptible (51% for Asia-West Pacific versus 78% to 92% for other regions) (Table 6). Most comparators followed a similar pattern, usually significantly so. In contrast, within the United States, of the three

TABLE 1 Global region and source country of the 343 carbapenem-resistant *Escherichia coli* study isolates

Global region	Region within U.S. or country within other region[a]	No. of isolates (% of 343)
North America (U.S.)	Any of below	203 (59)
	Central U.S.	154 (45)
	Northeast U.S.	24 (7)
	South U.S.	15 (4)
	Southeast US.	5 (1.5)
	West U.S.	5 (1.5)
Asia-West Pacific	Any of below	59 (17)
	China	22 (6)
	India	17 (5)
	Taiwan	7 (2)
	Philippines	4 (1.2)
	Thailand	4 (1.2)
	Korea	3 (0.8)
	Vietnam	2 (0.6)
Europe	Any of below	64 (19)
	Turkey	37 (11)
	Italy	9 (3)
	Russia	5 (1.5)
	Spain	3 (0.8)
	UK	3 (0.8)
	Israel	2 (0.6)
	Belarus	1 (0.3)
	Belgium	1 (0.3)
	Germany	1 (0.3)
	Greece	1 (0.3)
	Poland	1 (0.3)
Latin America	Any of below	17 (5)
	Chile	5 (1.5)
	Argentina	4 (1.2)
	Brazil	4 (1.2)
	Mexico	2 (0.6)
	Ecuador	1 (0.3)
	Venezuela	1 (0.3)

[a]U.S. regions, and countries within other global regions, are listed in order of descending prevalence within the U.S. or other global region; U.S., United States.

primary study drugs, only ERV showed significant regional variation in percent susceptible (lowest for South and Southeast U.S.) (Table 7). Most comparator agents also exhibited significant within-U.S. regional variation in percent susceptible, in agent-specific patterns.

Coresistance. Among the three primary study agents, percent susceptible was significantly lower in the presence of resistance to comparator agents more commonly for CFDC (eight comparators, multiple classes) and CZA (nine comparators, multiple classes) than ERV (two comparators, TGC and MIN only) (Table 8). Nonetheless, for the primary study agents, even among isolates resistant to a comparator, the percent susceptible to the primary agent was usually >80%, and almost always >50%.

Principle coordinates analysis. Principle coordinates analysis (PCoA) plots were based on subsets of the extensive metadata as follows: (i) the first PCoA series involved geography, specimen type, phylogenetic/clonal background, and β-lactamase genotype; and (ii) the second PCoA series involved coresistance to 10 conventional comparator agents. Isolates found to be resistant versus susceptible to the particular primary agent (CFDC, CZA, or ERV) consistently were separated spatially to a statistically significant extent (Fig. S1). The significant differences between populations involved the first coordinate (X1) in all instances excepting the first-series PCoA for ERV, where it involved instead the second coordinate (X2). Within a given PCoA series, the overall

TABLE 2 Overall percent susceptible and MIC_{min}, MIC_{50}, MIC_{90}, and MIC_{max} for cefiderocol, ceftazidime-avibactam, eravacycline, and comparators among 343 carbapenem-resistant *Escherichia coli* clinical isolates

Agent[a]	No. susceptible (% of 343)	MIC_{min}	MIC_{50}	MIC_{90}	MIC_{max}
CFDC	315 (92)	≤0.004	0.5	2	>64
CZA	281 (82)	≤0.125	0.5	>256	>256
ERV	335 (98)	≤0.03	0.125	0.5	2
MEM	203 (59)	≤0.03	1.0	>4	>4
IPM	100 (29)	0.125	4	>4	>4
ETP	15 (4)	≤0.016	>2	>2	>2
GEN	189 (55)	0.25	2	>16	>16
TZP	72 (21)	≤1.0	>128	>128	>128
AMK	269 (78)	≤0.5	4	>64	≤
LVX	62 (18)	≤0.06	>8	>8	> 8
TGC	340 (99)	≤0.25	0.5	1.0	8
CAZ	36 (11)	≤0.125	32	>256	>256
CL	n.a.[b]	≤0.06	0.125	0.25	8
MIN	231 (67)	≤0.5	4	16	>16

[a]Abbreviations: AMK, amikacin; CFDC, cefiderocol; CAZ, ceftazidime; CZA, ceftazidime-avibactam; CL, colistin; ERV, eravacycline; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; TZP, piperacillin-tazobactam; TGC, tigecycline; MIC_{min}, lowest detected MIC; MIC_{max}, highest detected MIC.
[b]n.a., not applicable; all isolates were resistant.

spatial distribution of primary-agent-resistant isolates in the (X1)-by-(X2) plots was generally similar across the three primary agents.

DISCUSSION

In this study, we assessed 343 domestic and international-source CR *E. coli* clinical isolates for susceptibility to CFDC, CZA, ERV, and 11 comparator agents, then compared these results with phylogenetic and clonal background, beta-lactamase genotype, geographical origin, and coresistance. The results support five main conclusions. First, CFDC, CZA, and ERV exhibited a higher percent susceptible (82% to 98%) than any comparator except TGC (99%), with avibactam clearly improving CZA's activity over that of CAZ alone (i.e., 82% versus 11% susceptible). Second, percent susceptible varied by phylogroup and ST for CFDC and CZA but not ERV. Third, percent susceptible varied by resistance genotype for all three primary study agents (MBLs, lower for CFDC and CZA; KPC, higher for CZA; CTX-M, higher for ERV). Fourth, percent susceptible varied by global region for CZA (Asia-Pacific lower), and by U.S. region for ERV (South and

TABLE 3 Percent susceptible to cefiderocol, ceftazidime-avibactam, eravacycline, and comparators by phylogroup among 343 carbapenem-resistant *Escherichia coli* clinical isolates

Agent[b,c]	No. total susceptible (% of 343)	Phylogroup[a] and no. susceptible (%)						P^d
		A (n = 54)	B1 (n = 46)	B2 (n = 105)	C (n = 28)	D (n = 66)	F (n = 42)	
CFDC	315 (92)	45 (83)	39 (85)	101 (96)	23 (82)	66 (100)	39 (93)	0.002
CZA	281 (82)	41 (76)	24 (52)	98 (93)	19 (68)	59 (89)	38 (91)	<0.001
ERV	335 (98)	50 (93)	45 (98)	105 (100)	27 (96)	64 (97)	42 (100)	
MEM	203 (59)	24 (44)	18 (39)	68 (65)	12 (43)	43 (65)	36 (86)	<0.001
IPM	100 (29)	9 (17)	5 (11)	43 (41)	2 (7)	27 (41)	14 (33)	<0.001
ETP	15 (4)	2 (4)	3 (7)	6 (6)	3 (11)	0 (0)	1 (2)	
GEN	189 (55)	29 (54)	19 (41)	69 (66)	10 (36)	38 (57)	39 (93)	0.046
TZP	72 (21)	4 (7)	6 (13)	32 (31)	4 (14)	19 (29)	0 (0)	0.007
AMK	269 (78)	44 (82)	28 (61)	82 (78)	24 (86)	57 (86)	32 (76)	
LVX	62 (18)	5 (9)	10 (22)	18 (17)	2 (7)	20 (30)	7 (17)	0.047
TGC	340 (99)	52 (96)	46 (100)	105 (100)	28 (100)	65 (99)	42 (100)	
CAZ	36 (11)	5 (9)	6 (13)	11 (11)	0 (0)	9 (14)	5 (12)	
MIN	231 (67)	29 (54)	25 (54)	89 (85)	15 (54)	43 (65)	28 (67)	<0.001

[a]Phylogroups shown are only those with $n > 3$ (phylogroup E: $n = 2$ [0.6%]).
[b]Abbreviations: AMK, amikacin; CFDC, cefiderocol; CAZ, ceftazidime; CZA, ceftazidime-avibactam; ERV, eravacycline; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; TZP, piperacillin-tazobactam; TGC, tigecycline.
[c]CL, colistin: not shown; all isolates resistant.
[d]P values, as determined by chi-square test for six-group comparisons across phylogroup, are shown where $P < 0.05$.

TABLE 4 Percent susceptible[a] for cefiderocol, ceftazidime-avibactam, eravacycline, and comparators by clonal group among 343 carbapenem-resistant *Escherichia coli* clinical isolates

		Sequence type (ST) and no. of isolates (%)					ST131 subclone and no. of isolates (%)			
Agent[b,c]	Total no. (% of 343)	ST131 ($n = 88$)	ST405 ($n = 25$)	ST648 ($n = 29$)	Other STs ($n = 201$)	P[e]	Non-*H*30[d] ($n = 268$)	*H*30R1[d] ($n = 28$)	*H*30Rx[d] ($n = 47$)	P[f]
CFDC	315 (92)	86 (98)	25 (100)	28 (97)	176 (88)	0.007	241 (90)	28 (100)	46 (98)	0.048
CZA	281 (82)	85 (97)	22 (88)	26 (90)	148 (74)	<0.001	207 (77)	27 (96)	47 (100)	<0.001
ERV	335 (98)	88 (100)	24 (96)	29 (100)	194 (97)		260 (97)	28 (100)	47 (100)	
MEM	203 (59)	58 (66)	13 (52)	25 (86)	107 (53)	0.003	149 (56)	18 (64)	36 (77)	0.02
IPM	100 (29)	39 (44)	15 (60)	11 (38)	35 (17)	<0.001	63 (24)	8 (29)	29 (62)	<0.001
ETP	15 (4)	3 (3)	0 (0)	0 (0)	12 (6)		13 (5)	0 (0)	2 (4)	
GEN	159 (55)	54 (61)	12 (48)	14 (48)	109 (54)		142 (53)	14 (50)	33 (70)	
TZP	72 (21)	26 (30)	7 (28)	5 (17)	34 (17)		46 (18)	4 (14)	22 (47)	<0.001
AMK	269 (78)	68 (77)	21 (84)	20 (69)	160 (80)		212 (79)	25 (89)	32 (68)	
LVX	62 (18)	5 (6)	1 (4)	5 (17)	51 (25)	<0.001	62 (23)	0 (0)	0 (0)	<0.001
TGC	340 (99)	88 (100)	24 (96)	29 (100)	199 (99)		265 (99)	28 (100)	47 (100)	
CAZ	36 (11)	8 (9)	2 (8)	2 (7)	24 (12)		29 (11)	5 (18)	2 (4)	
MIN	231 (67)	75 (85)	10 (40)	20 (69)	126 (63)	<0.001	168 (63)	24 (86)	39 (83)	0.002

[a]Values for each agent are expressed as no. of isolates (column %).
[b]Abbreviations: AMK, amikacin; CFDC, cefiderocol; CZA, ceftazidime-avibactam; CAZ, ceftazidime; ERV, eravacycline; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; TZP, piperacillin-tazobactam.
[c]CL, colistin: not shown; all isolates resistant.
[d]non-*H*30, not a member of the ST131-*H*30R1 or *H*30Rx subclone (includes mainly non-ST131 strains); *H*30R1, fluoroquinolone resistance-associated subclone within ST131 (excludes *H*30Rx); *H*30Rx, ESBL-associated.
[e]*P* values, as determined by chi-square test, for four-group comparisons across ST-defined categories, are shown where $P < 0.05$.
[f]*P* values, as determined by chi-square test for three-group comparisons across ST131 subclones, are shown where $P < 0.05$.

Southeast lower). Fifth, especially for CFDC and CZA, although resistance to a comparator agent was often associated with a lower percent susceptible to the primary agent, even among coresistant isolates susceptibility to the primary agent usually remained substantial. These findings provide novel perspectives on the likely utility of CFDC, CZA, and ERV against CR *E. coli* in relation to multiple bacterial characteristics and geographical region.

The high percentage of isolates susceptible to CFDC, CZA, and ERV supports the presumptive use of any of these agents against CR *E. coli* isolates, pending (or possibly even without) confirmatory *in vitro* susceptibility testing. Decisions regarding which to use likely will be influenced by such factors as region, cost, availability of drug and

TABLE 5 Percent susceptible[a] to cefiderocol, ceftazidime-avibactam, eravacycline and comparator agents in relation to individual resistance genes[b] among 343 carbapenem-resistant *Escherichia coli* isolates

	No. of isolates (%)					
Agent[c,d]	Total no. ($n = 343$)	KPC ($n = 55$)[f]	MBL[c,e] ($n = 64$)[f]	OXA-48 ($n = 46$)[f]	CTX-M ($n = 147$)[f]	CMY-2 ($n = 97$)[f]
CFDC	315 (92)	53 (96)	45 (70)***	4 (96)	134 (91)	87 (90)
CZA	281 (82)	54 (98)**	5 (8)***	42 (91)	115 (78)	76 (78)
ERV	335 (98)	54 (98)	61 (95)	46 (100)	147 (100)*	93 (96)
MEM	203 (59)	24 (44)*	2 (3)***	35 (76)*	84 (57)	61 (63)
IPM	100 (29)	0 (0)***	0 (0)***	1 (2)***	60 (41)***	25 (26)
ETP	15 (4)	0 (0)	5 (8)	2 (4)	4 (3)	7 (7)
GEN	189 (55)	27 (49)	12 (19)***	24 (52)	65 (44)***	58 (60)
TZP	72 (21)	3 (6)**	8 (13)	1 (2)**	39 (27)*	18 (19)
AMK	269 (78)	44 (80)	30 (47)***	40 (87)	105 (71)**	81 (84)
LVX	62 (18)	16 (29)*	3 (5)**	12 (26)	2 (1.4)***	23 (24)
TGC	340 (99)	55 (100)	63 (98)	46 (100)	147 (100)	96 (99)
CAZ	36 (11)	2 (4)	1 (1.6)*	18 (39)***	4 (3)***	0 (0)***
MIN	231 (67)	42 (76)	35 (54)*	30 (65)	85 (58)**	59 (61)

[a]Data are expressed as no. of isolates (column %).
[b]Percent susceptible of isolates with resistance gene irrespective of the presence/absence of other resistance genes.
[c]Abbreviations: AMK, amikacin; CFDC, cefiderocol; CAZ, ceftazidime; CZA, ceftazidime-avibactam; ERV, eravacycline; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; TZP, piperacillin-tazobactam; TGC, tigecycline; MBL, metallo-beta-lactamase.
[d]CL, colistin: not shown; all isolates resistant.
[e]MBL category includes multiple MBL-encoding resistance genes (NDM [$n = 53$]; IMP [$n = 8$]; VIM [$n = 3$]).
[f]*P* value symbols, as determined by chi-square test, for indicated group versus all others: *, $P < 0.05$; **, $P < 0.01$; ***, $P \leq 0.001$.

TABLE 6 Percent susceptible for cefiderocol, ceftazidime-avibactam, eravacycline, and comparator agents by region among 343 carbapenem-resistant *Escherichia coli* clinical isolates

	No. of isolates (%)[a]					
Agent[b,c]	Total (n = 343)	North America (n = 203)	Asia-West Pacific (n = 59)	Europe (n = 64)	Latin America (n = 17)	P[d]
CFDC	315 (92)	189 (93)	53 (90)	57 (89)	16 (94)	
CZA	281 (82)	186 (92)	30 (51)	50 (78)	15 (88)	<0.001
ERV	335 98)	197 (97)	58 (98)	64 (100)	16 (94)	
MEM	203 (60)	153 (75)	7 (12)	35 (55)	8 (47)	<0.001
IPM	100 (29)	90 (44)	4 (7)	3 (5)	3 (18)	<0.001
ETP	15 (4)	7 (3)	2 (4)	5 (8)	1 (6)	
GEN	189 (56)	131 (65)	18 (31)	32 (50)	8 (47)	<0.001
TZP	72 (21)	56 (28)	10 (17)	3 (5)	3 (18)	0.001
AMK	269 (78)	166 (82)	40 (68)	50 (78)	13 (77)	<0.001
LVX	62 (18)	40 (20)	1 (1.7)	18 (28)	3 (18)	0.001
TGC	340 (99)	200 (99)	59 (100)	64 (100)	17 (100)	
CAZ	36 (1)	19 (9)	0 (0)	16 (25)	1 (6)	<0.001
MIN	231 (67)	141 (70)	35 (59)	45 (70)	10 (59)	

[a]Values for each agent are expressed as no. of isolates (column %).
[b]Abbreviations: AMK, amikacin; CFDC, cefiderocol; CAZ, ceftazidime; CZA, ceftazidime-avibactam; ERV, eravacycline; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; TZP, piperacillin-tazobactam; TGC, tigecycline.
[c]CL, colistin: not shown; all isolates resistant.
[d]P values, as determined by chi-square test, for overall four-group comparisons are shown where $P < 0.05$.

susceptibility testing, type of infection, local cumulative susceptibility data, and patient factors, including travel history, concurrent medications, and drug allergies.

The observed phylogenetic and clonal group effects on percent susceptible to the primary and comparator agents within this all-CR *E. coli* collection diverge from those expected based on previous studies of "all comer" *E. coli*, or isolates selected based on other resistance phenotypes (17). Here, for the primary study agents, the by-phylogroup differences, although statistically significant, were modest, and the by-ST differences showed the (traditionally "resistance-associated") predominant STs and the *H*30Rx subclone (18) to have paradoxically higher percent susceptible values than the population as a whole. This illustrates the context-specific nature of associations of resistance profiles with specific phylogroups and STs, and supports continued exploration of this topic as new agents become available and the corresponding resistance phenotypes emerge.

The observed associations with resistance genotypes are largely as might be expected for the MBLs (potent activity against all beta-lactams, even CFDC, but unaf-

TABLE 7 Percent susceptible[a] for cefiderocol, ceftazidime-avibactam, eravacycline, and comparator agents by U.S. region among 343 carbapenem-resistant *Escherichia coli* clinical isolates

	No. of isolates (%)						
Agent[b,c]	Total U.S. (% of 203)	Central (n = 154)	Northeast (n = 24)	South (n = 15)	Southeast (n = 5)	West (n = 5)	P[d]
CFDC	189 (93)	144 (94)	24 (100)	12 (80)	5 (100)	4 (80)	
CZA	186 (92)	141 (92)	24 (100)	12 (80)	5 (100)	4 (80)	
ERV	197 (97)	152 (99)	23 (96)	13 (87)	4 (80)	5 (100)	0.01
MEM	153 (75)	122 (79)	15 (62)	7 (47)	5 (100)	4 (80)	0.02
IPM	90 (44)	69 (45)	24 (100)	13 (87)	4 (80)	3 (60)	<0.001
ETP	7 (3)	6 (4)	1 (4)	0 (0)	0 (0)	0 (0)	
GEN	131 (65)	108 (70)	9 (38)	9 (60)	2 (40)	3 (60)	0.02
TZP	56 (28)	50 (33)	1 (4)	2 (13)	3 (60)	0 (0)	0.006
AMK	166 (82)	129 (84)	18 (75)	10 (67)	4 (80)	5 (100)	
LVX	40 (20)	34 (22)	4 (17)	1 (7)	1 (20)	0 (0)	
TGC	200 (99)	153 (99)	24 (100)	14 (93)	4 (80)	5 (100)	0.003
CAZ	19 (9)	142 (92)	23 (96)	14 (93)	1 (20)	4 (80)	<0.001
MIN	141 (70)	105 (68)	18 (75)	10 (67)	4 (80)	4 (80)	

[a]Values for each agent are expressed as no. of isolates (column %).
[b]Abbreviations: AMK, amikacin; CFDC, cefiderocol; CAZ, ceftazidime; CZA, ceftazidime-avibactam; ERV, eravacycline; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; TZP, piperacillin-tazobactam; TGC, tigecycline.
[c]CL, colistin: not shown; all isolates resistant.
[d]P values, as determined by chi-square test, for overall five-group comparisons are shown where $P < 0.05$.

TABLE 8 Percent susceptible to cefiderocol, ceftazidime-avibactam, and eravacycline in relation to susceptibility or resistance to comparator agents among 343 carbapenem-resistant *Escherichia coli* study isolates

Comparator agent[a,b]	No. susceptible to agent (% of 343)	CFDC susceptible[a]			CZA susceptible[a]			ERV susceptible[a] (%)		
		Susceptible to comparator (%)	Resistant to comparator (%)	P[c]	Susceptible comparator (%)	Resistant to comparator (%)	P[c]	Susceptible to comparator (%)	Resistant to comparator (%)	P[c]
CFDC	315 (92)	n.a.	n.a.	n.a.	272/315 (86)	9/28 (32)	<0.001	309/315 (98)	26/28 (93)	
CZA	281 (82)	272/281 (97)	43/62 (69)	<0.001	n.a.	n.a.	n.a.	276/281 (98)	59/62 (95)	
ERV	335 (98)	309/335 (92)	6/8 (75)		276/335 (82)	5/8 (63)		n.a.	n.a.	n.a.
MEM	203 (59)	199/203 (98)	116/140 (83)	<0.001	201/203 (99)	80/140 (57)	<0.001	198/203 (98)	137/140 (98)	
IPM	100 (29)	98/100 (98)	217/243 (89)	0.008	100/100 (100)	181/243 (75)	<0.001	100/100 (100)	235/243 (97)	
ETP	15 (4)	14/15 (93)	301/328 (92)		11/15 (73)	270/328 (82)		14/15 (93)	321/328 (98)	
GEN	189 (55)	179/189 (95)	136/154 (88)	0.03	176/189 (93)	105/154 (68)	<0.001	186/189 (98)	149/154 (97)	
TZP	72 (21)	71/72 (97)	244/271 (90)	0.02	66/72 (92)	215/271 (79)	0.02	72/72 (100)	263/271 (97)	
AMK	269 (78)	255/269 (95)	60/74 (81)	<0.001	239/269 (89)	42/74 (57)	<0.001	263/269 (98)	72/74 (97)	
LVX	62 (18)	61/62 (98)	254/281 (90)	0.04	59/62 (95)	222/281 (79)	0.003	62/62 (100)	273/281 (97)	
TGC	340 (99)	313/340 (92)	2/3 (67)		279/340 (82)	2/3 (67)		335/340 (98)	0/3 (0)	<0.001
CAZ	36 (11)	36/36 (100)	279/307 (91)		36/36 (100)	245/307 (80)	0.003	35/36 (97)	300/307 (98)	
MIN	231 (67)	218/231 (94)	97/112 (87)	0.02	197/231 (85)	84/112 (75)	0.02	231/231 (100)	104/112 (93)	<0.001

[a]Abbreviations: AMK, amikacin; CFDC, cefiderocol; CAZ, ceftazidime; CZA, ceftazidime-avibactam; CL, colistin; ERV, eravacycline; ETP, ertapenem; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; n.a., not applicable (comparison with self); TZP, piperacillin-tazobactam; TGC, tigecycline.

[b]CL, colistin: not shown; all isolates resistant.

[c]*P* values, as determined by chi-square test, are shown were $P < 0.05$.

fected by avibactam) and KPC (well inhibited by avibactam) (9, 12, 19). In contrast, the association of CTX-M with heightened susceptibility to ERV is less readily explained. Whether strains for which CTX-M contributes to carbapenem resistance (doubtless in concert with other mechanisms) are less likely to have resistance mechanisms that reduce susceptibility to ERV would be an appropriate topic for future study.

The observed geographical variation in percent susceptible to the primary study agents likely reflects differences in the geographical distribution of the corresponding resistance mechanisms and lineages (20), an analysis of which is ongoing and will be presented separately. This finding illustrates the importance of considering geographical context when assessing patterns of susceptibility and resistance to newer and established agents, since results from one locale may or may not generalize well to other locales, and this cannot be determined without empirical assessment.

The observed patterns of susceptibility to the primary study agents in relation to coresistance to comparator agents support the concept that different resistance phenotypes, and the corresponding resistance mechanisms, are often linked (6, 21). As such, isolates resistant to a given agent are, on average, more likely to be resistant to other agents, even if these are chemically unrelated to the given agent, than are isolates that are susceptible to the given agent. Here, ERV stood out as being largely unaffected by resistance to other agents, apart from the tetracycline derivatives MIN and TGC. This suggests that although ERV is affected by some tetracycline resistance mechanisms (16, 22), these do not track closely with resistance to other drug classes.

Study limitations include the convenience sampling approach used (i.e., participating SENTRY centers and Minnesota Department of Health [MDH] only; no African isolates), the absence of associated epidemiological and clinical data, and the paucity of isolates from some countries and regions of the United States. Study strengths include the otherwise broad geographic coverage, attention to phylogenetic background, resistance genes, coresistance, and geography, and extensive statistical analyses of susceptibility data in relation to these variables.

In conclusion, we found that CFDC, ERV, and CZA were substantially active against a global collection of *E. coli* clinical isolates. Activity varied in relation to geographical region and multiple bacterial characteristics, and, paradoxically, was especially high against members of the *H*30R1 and *H*30Rx ST131 subclones. Our results suggest that all three agents should be useful for treating CR *E. coli* infections globally, largely independent of coresistance, although this likely will vary in relation to the local prevalence of specific *E. coli* lineages and carbapenem resistance mechanisms.

MATERIALS AND METHODS

Study isolates. The 343 CR *E. coli* study isolates included 203 U.S. isolates (classified here as representing North America) (23) and 140 isolates derived from 17 different countries in 3 other global regions (Asia-West Pacific, Europe, and Latin America) (Table 1).

The U.S. CR isolates were derived from an initial set of 312 presumptive CR clinical *E. coli* isolates from across the United States, as obtained from the Minnesota Department of Health (MDH) ($n = 250$; isolation years, 2009 to 2017 [median, 2015]) and JMI Laboratories ($n = 62$; isolation years, 2002 to 2017 [median, 2013]) (23). They represented all CR *E. coli* isolates available from these two reference laboratories as of study onset. Isolates were categorized into the following subregions of the United States for geographical comparison: central, northeast, south, southeast, and west.

The MDH isolates (initial $n = 250$: isolation years, 2009 to 2017 [median, 2015]) had been collected as part of statewide public health surveillance in Minnesota for CR *Enterobacteriaceae*, which included voluntary (pre-2016) or mandatory (as of 2016) reporting by all clinical laboratories in the state and submission of the corresponding isolates. The isolates had been classified as CR by the submitting laboratories according to then-current definitions, which varied by year and relied on the results of phenotypic +/− molecular tests done in the submitting clinical laboratories, which varied by laboratory. Of the 250 MDH isolates, 141 were confirmed here as CR (i.e., nonsusceptible to ≥1 carbapenem) according to standardized broth microdilution testing (as described below), so were included in the study.

In contrast, the JMI Laboratories isolates (U.S., $n = 62$: isolation years, 2002 to 2017 [median, 2013]; international, $n = 140$: isolation years 2003–2017 [median, 2012]) represented all *E. coli* isolates held by the epidemiologically representative SENTRY Antimicrobial Surveillance Program (which has contributing centers distributed across the United States and globally) (24) that exhibited resistance to at least one

carbapenem (doripenem, imipenem, meropenem) according to the standardized broth microdilution testing performed by JMI Laboratories for all SENTRY isolates. All were confirmed here as CR.

Susceptibility testing. In the research laboratory, isolates underwent standardized broth microdilution MIC determinations with cefiderocol (CFDC), ceftazidime-avibactam (CZA), and eravacycline (ERV); three carbapenems, i.e., ertapenem (ETP), imipenem (IPM), and meropenem (MEM); and eight noncarbapenem comparators, i.e., amikacin (AMK), ceftazidime (CAZ), colistin (CL), gentamicin (GEN), levofloxacin (LVX), minocycline (MIN), tigecycline (TGC), and piperacillin-tazobactam (TZP). Test methods and reference strains were per the Clinical and Laboratory Standards Institute (CLSI) (25), except that CFDC testing was done using iron-depleted broth in prefabricated plates (Shionogi & Co. Ltd.). Interpretive criteria were per CLSI (all agents except cefiderocol and tigecycline) or the U.S. Food and Drug Administration (cefiderocol and tigecycline). For cefiderocol, the FDA criteria as of November 2019 were used (i.e., S $\leq$2 mg/liter, I or R $\geq$4 mg/liter; based on a dosage regimen of 2 g every 8 h administered over 3 h). The concentrations of avibactam and tazobactam were fixed at 4 mg/liter, respectively. Intermediate MIC values were considered resistant. This testing confirmed all 343 study isolates ($n = 203$, North American; $n = 140$, international) as being nonsusceptible (here considered resistant) to $\geq$1 carbapenem. Results were reported both as percent susceptible and as MIC_{min} (i.e., lowest detected MIC), MIC_{50}, MIC_{90}, and MIC_{max} (i.e., highest detected MIC). Results for the comparator agents against the U.S. isolates were presented elsewhere (23).

Molecular typing. Established PCR-based assays were used to identify *E. coli* phylogroups A, B1, B2, C, D, E, and F (26); selected STs associated with multidrug resistance, recent emergence, and/or extraintestinal infections generally (27–29); the *H*30 and *H*30Rx clonal subset within ST131 (29, 30); and resistance genes encoding KPC, NDM, VIM, IMP, OXA, CTX-M, and CMY-2 (31–33). The genes encoding NDM, VIM, and IMP were classified as metallo-beta-lactamase (MBL) genes. Fluoroquinolone-resistant ST131-*H*30 isolates were classified as *H*30R, and *H*30R isolates that tested negative for *H*30Rx were classified as *H*30R1 (29, 30).

Statistical methods. Conventional statistical analysis was limited to variables present in $\geq$4 isolates ($\geq$1.1% of 343). Comparisons involving dichotomous variables were tested using chi-square tests (including an "N-1" chi-square test) (34). Principle coordinates analysis (PCoA), a type of hierarchical clustering, was used to collapse the extensive metadata for comparison with resistance status to CFDC, CZA, and ERV (i.e., the primary agents). One series of PCoAs (one per primary agent) was done based on isolate geographical origin, source (specimen type), phylogenetic group, ST, ST131 subclone, and β-lactamase genotype. Another series of PCoAs was done based on coresistance phenotype for 10 comparator agents (MEM, IPM, ETP, GEN, TZP, AMK, LVX, TGC, CAZ, and MIN). PCoA results were displayed graphically using two-dimensional plots based on the first two principle coordinates (X1, X2), which capture the greatest share of variance in the data set. For each PCoA, isolates resistant versus susceptible to the particular primary agent were compared statistically for their values on the X1 versus X2 coordinates by using a two-tailed *t* test. The significance criterion throughout was $P < 0.05$. Due to the study's exploratory nature, no adjustment was made for multiple comparisons. PCoA analyses were conducted in R (R Core Team, Vienna, Austria, 2020; https://www.R-project.org/). All other analyses were conducted with SPSS v.19 (IBM Corp., Armonk, NY, 2010).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.

ACKNOWLEDGMENTS

This work was supported in part by research grants from Allergan, Shionogi & Co. Ltd., and Tetraphase Pharmaceuticals, and by the Office of Research Development, Department of Veterans Affairs, grant number 2I01CX000920-04 (J.R.J.). The funders had no control over the content of the report or the decision to publish.

The opinions expressed are those of the authors and not necessarily those of the authors' institutions or the Department of Veterans Affairs.

James R. Johnson has had research grants and/or consultancies involving Achaogen, Allergan, Crucell/Janssen, Melinta, Merck, Shionogi, Syntiron, and Tetraphase. The other authors report no financial conflicts of interest.

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