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ORIGINAL ARTICLE

Comparative activity of plazomicin against extended-spectrum cephalosporin-resistant *Escherichia coli* clinical isolates (2012–2017) in relation to phylogenetic background, sequence type 131 subclones, $bla_{CTX\text{-}M}$ genotype, and resistance to comparator agents

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Abstract

Extended-spectrum cephalosporin-resistant *Escherichia coli* (ESCREC) are a growing threat. Leading ESCREC lineages include sequence type ST131, especially its ($bla_{CTX\text{-}M\text{-}15}$-associated) *H*30Rx subclone and ($bla_{CTX\text{-}M\text{-}27}$-associated) C1-M27 subset within the *H*30R1 subclone. The comparative activity against such strains of alternative antimicrobial agents, including the recently developed aminoglycoside plazomicin, is undefined, so was investigated here. We assessed plazomicin and 11 comparators for activity against 216 well-characterized ESCREC isolates (Minnesota, 2012–2017) and then compared broth microdilution MICs with phylogenetic and clonal background, beta-lactamase genotype ($bla_{CTX\text{-}M}$; group 1 and 9 variants), and co-resistance. Percent susceptible was > 99% for plazomicin, meropenem, imipenem, and tigecycline; 96–98% for amikacin and ertapenem; and ≤ 75% for the remaining comparators. For most comparators, MICs varied significantly in relation to multiple bacterial characteristics, in agent-specific patterns. By contrast, for plazomicin, the only bacterial characteristic significantly associated with MICs was ST131 subclone: plazomicin MICs were lowest among O16 ST131 isolates and highest among ST131-*H*30R1 C1-M27 subclone isolates. Additionally, plazomicin MICs varied significantly in relation to resistance vs. susceptibility to comparator agents only for amikacin and levofloxacin. For most study agents, antimicrobial activity against ESCREC varied extensively in relation to multiple bacterial characteristics, including clonal background, whereas for plazomicin, it varied only by ST131 subclone (C1-M27 isolates least susceptible, O16 isolates most susceptible). These findings support plazomicin as a reliable alternative for treating ESCREC infections and urge continued attention to the C1-M27 ST131 subclone.

Keywords *Escherichia coli* · Plazomicin · Antimicrobial resistance · Extended-spectrum cephalosporins · Extended-spectrum beta-lactamase · ST131

Introduction

Extended-spectrum cephalosporin-resistant *Escherichia coli* (ESCREC) are a serious and growing threat [1], resulting in increasing use of carbapenems for empirical and definitive therapy [2]. Emerging carbapenem resistance in *E. coli* creates a need to identify suitable non-carbapenem treatment options for ESCREC [3].

Plazomicin (PLZ) is a novel aminoglycoside antibiotic that was approved recently by the US Food and Drug Administration (FDA) for treating complicated urinary tract infection and pyelonephritis [4–7]. It inhibits protein synthesis by binding to the 30S ribosomal subunit. Its Gram-negative spectrum includes extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (CRE), and organisms with aminoglycoside-modifying enzymes [8–11]. Thus, PLZ may be a carbapenem-sparing alternative for ESCREC. However,

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PLZ's activity specifically against ESCREC has received limited study, especially in relation to clonal background and ESBL genotype.

Antimicrobial resistance in *E. coli* is highly clonal [12, 13]. The leading ESCREC clonal lineage currently is sequence type ST131 [14, 15], which has multiple distinctive clonal subsets, or subclones [16–18]. Of these, *H*30R, which likewise has multiple important subsets, overall is the most extensively antimicrobial resistant and epidemiologically successful [14].

All *H*30R members are densely fluoroquinolone resistant, due to four canonical amino acid replacement mutations in *gyrA* and *parC* [19]. *H*30R1 has two main sublineages, *H*30R1 and *H*30Rx. *H*30Rx was recognized first [20], due to its association with the (globally dominant) extended-spectrum beta-lactamase (ESBL)-encoding gene $bla_{CTX-M-15}$. However, *H*30R1, the historically "less resistant" sister clade to *H*30Rx, now has an emerging subclone, C1-M27, that is closely associated with $bla_{CTX-M-27}$ and $bla_{CTX-M-14}$ [21]. Unlike $bla_{CTX-M-15}$ (from bla_{CTX-M} group 1), these two *bla* variants are from bla_{CTX-M} group 9. Additionally, some non-*H*30R ST131 strains—especially within the O16-*fimH41* subclone (or clade A)—have horizontally acquired ESBL-encoding genes [16–18, 22].

Here, we sought to clarify the activity of PLZ against recent ESCREC isolates in comparison with conventional agents, including carbapenems, and in relation to other bacterial characteristics. For that, we determined broth microdilution MICs to PLZ among 216 unique-by-episode ESCREC isolates from the Minneapolis Veterans Affairs Health Care System (MVAHCS) and then compared the MICs statistically with bacterial characteristics, including phylogenetic group, clonal background, bla_{CTX-M} genotype, and susceptibility to 11 relevant comparators.

Methods

Study setting The MVAHCS is a teaching hospital that provides a full range of patient care services. The MVAHCS clinical microbiology laboratory processes specimens from the Minneapolis campus and 14 outlying community clinics across MN and western WI. Patients are mostly older men, many with multiple chronic medical conditions.

Isolates From May 2012 through December 2017, with approval from the Institutional Review Board (i.e., Ethics Committee), the research laboratory prospectively collected consecutive *E. coli* clinical isolates from the MVAHCS clinical microbiology laboratory. In the research laboratory, isolates were stored at −70 C in LB broth supplemented with 20% glycerol.

During the approximately 5.5-year study period, 6324 total *E. coli* isolates were collected. The clinical laboratory found 267 (4.2%) of these to be resistant or intermediate to ceftazidime and/or ceftriaxone, according to a VITEK-2 instrument (bioMérieux, Durham, NC) and then-current MIC breakpoints, so here were classified as ESCREC. Exclusion of repeat isolates from the same patient within 30 days after an initial isolate left 216 putative unique-by-episode ESCREC isolates as the study population.

By specimen type, the 216 ESCREC study isolates were from (no. of isolates, % of 216) urine (173, 80%); blood (21, 10%); wound (10, 5%); sputum (4, 1.9%); bone (3, 1.4%); fluid (2, 0.9%); and tissue, swab, and other (each: 1, 0.5%). They were derived from 138 unique source patients, with ages ranging from 24 to > 90 years (median, 68 years); 113 (82%) were male.

Susceptibility testing

Isolates underwent standardized broth microdilution MIC determinations with PLZ and, as reported elsewhere [23], 11 comparators, including ertapenem (ETP), imipenem (IPM), and meropenem (MEM), plus eight non-carbapenem agents, i.e., amikacin (AMK), ceftazidime (CAZ), colistin (CLS), gentamicin (GEN), levofloxacin (LVX), minocycline (MIN), tigecycline (TGC), and piperacillin/tazobactam (TZP). Test methods and reference strains were per the Clinical Laboratory Standards Institute (CLSI) [24]. The tazobactam concentration was fixed at 4 mg/L. Interpretive criteria were per CLSI (all agents except TGC and PLZ) or the FDA (TGC and PLZ). Note: the European Committee on Antimicrobial Susceptibility Testing (EUCAST) specifies different MIC breakpoints (mg/L) than does CLSI for GEN (EUCAST, ≥ 4 resistant, vs. CLSI, 8 intermediate) and AMK (EUCAST, ≥ 16 resistant, vs. CLSI, 32 intermediate). Here, isolates with intermediate MIC values were considered resistant.

Molecular typing As reported elsewhere [23], established PCR-based assays were used to identify *E. coli* phylogroups A, B1, B2, C, D, E, and F [25]; selected STs associated with multidrug resistance, recent emergence, and/or extraintestinal infections generally [15, 26, 27]; ST131 subsets O16 (clade A), *H*30R, C1-M27, and *H*30Rx [27–29]; and bla_{CTX-M}. Isolates with bla_{CTX-M} (according to universal bla_{CTX-M} primers [30]) were further characterized with group 1- and group 9-specific multiplex PCR analysis [30].

Fluoroquinolone-resistant ST131-*H*30 isolates were classified operationally as *H*30R; *H*30R isolates that tested negative for *H*30Rx were classified as *H*30R1 [27, 28]. All *H*30R1 isolates were tested for a C1-M27 subclone-specific prophage marker [29] and based on the result were classified operationally as (*H*30R1) C1-M27 or (non-C1-M27) *H*30R1.

Statistical methods Statistical analysis was limited to variables present in ≥ 2 isolates (≥ 1.0 % of 216). Comparisons involving dichotomous variables were tested using chi-squared tests, including an “N-1” chi-squared test for two-group comparisons [31]. Comparisons involving MIC distributions were tested using the Mann-Whitney or Kruskal-Wallis test (two-tailed), due to the nonparametric distribution of the data. Off-scale high or low MICs were analyzed statistically as representing the dilution step above or below (as appropriate) the tested dilution range. For PLZ, MICs were analyzed in relation to susceptibility vs. resistance to each comparator agent that was represented by sufficient resistant (or susceptible) isolates to qualify for statistical analysis.

Summary statistics used for MIC values included the MIC_{min} (lowest detected MIC), MIC_{50}, MIC_{90}, and MIC_{max} (highest detected MIC). Additionally, for PLZ, GEN, and AMK, cumulative percent MIC distributions were tabulated. Throughout, the criterion for statistical significance was $P < 0.05$, without adjustment for multiple comparisons, given the study’s exploratory nature. For MIC comparisons that yielded a statistically significant difference despite similar or identical MIC summary statistics, mean MIC ranks (note: not mean MICs) were used to clarify the direction of the difference.

Results

Overall susceptibility Of the 12 study agents, four (PLZ, IMP, MEM, and TGC) exhibited > 99% susceptibility (Table 1). These were followed, in descending order, by AMK (98%), ETP (96%), MIN (75%), GEN (64%), CAZ (36%), and LVX (12%). No isolate—by definition (per CLSI)—was susceptible to CL (Table 1). PLZ exhibited the lowest MIC_{50}/MIC_{90} ratio (i.e., 4) of all study agents excepting LVX (MIC_{50} and MIC_{90} both > 8 mg/L; ratio uninterpretable).

Phylogroups PLZ MICs did not vary significantly across phylogroups, by contrast with MICs for all but three comparators (IPM, GEN, AMK) Suppl. Table (1). The PLZ MIC_{50} was 1 mg/L for all phylogroups except phylogroup C (0.5 mg/L), and the PLZ MIC_{90} was consistently 2 mg/L. The cumulative percent MIC distribution for PLZ, GEN, and AMK likewise showed minor variation across phylogroup Suppl. Table (2).

STs PLZ MICs also did not vary significantly across the four most prevalent STs and all other STs combined, by contrast with MICs all but four of the comparators (IPM, GEN, AMK, TGC) (Table 2). Within each ST category, the PLZ MIC_{50} was consistently 1 mg/L and the PLZ MIC_{90} consistently 2 mg/L. The cumulative percent MIC distribution for PLZ, GEN, and AMK showed minor variation across STs (Supplemental Table 3).

ST131 subclone By contrast with phylogroup and ST, PLZ MICs did vary significantly by ST131 subclone status, albeit subtly, as reflected in mean MIC ranks (Table 2 footnote) and the cumulative percent MIC distribution (Supplemental Table 4), not the MIC_{50} or MIC_{90} (Table 2). Specifically, according to mean MIC ranks, PLZ MICs were lowest among the O16 (clade A) ST131 isolates; highest among the (*H*30R1) C1-M27 ST131 isolates; and intermediate among the non-

Table 1 Overall percent susceptible and MIC_{min}, MIC_{50}, MIC_{90}, and MIC_{max} for plazomicin and 11 comparators among 216 extended-spectrum cephalosporin-resistant *Escherichia coli* clinical isolates

Agent[a, b]	Susceptible, no (% of 216)[c]	MIC_{min}	MIC_{50}	MIC_{90}	MIC_{max}
PLZ	215 (99.5)	0.025	1	2	4
MEM	215 (99.5)	≤ 0.03	≤ 0.03	≤ 0.03	> 4
IPM	215 (99.5)	0.0.06	0.25	0.5	> 4
ETP	208 (96)	≤ 0.016	0.03	0.25	> 2
GEN	138 (64)	0.25	1	>16	> 16
TZP	208 (96)	≤ 1	2	8	> 128
AMK	211 (98)	≤ 0.5	4	16	64
LVX	26 (12)	0.12	> 8	> 8	> 8
TGC	216 (100)	0.25	0.5	1	2
CAZ	77 (36)	≤ 0.125	0.12	> 16	> 16
CL	n.a.	≤ 0.06	0.12	0.25	2
MIN	163 (75)	≤ 0.5	4	16	> 16

[a] *AMK* amikacin, *CAZ* ceftazidime, *CL* colistin, *ETP* ertapenem, *GEN* gentamicin, *IPM* imipenem, *LVX* levofloxacin, *MEM* meropenem, *MIN* minocycline, *PLZ* plazomicin, *TZP* piperacillin-tazobactam, *TGC* tigecycline, MIC_{min} lowest detected MIC, MIC_{max} highest detected MIC

[b] *n.a.* not applicable (no susceptible category for CL; all isolates resistant)

[c] Based on breakpoints as specified by CLSI (all but PLZ and TGC) or FDA (PLZ and TGC)

Table 2 Distribution of MIC_{50} and MIC_{90} by sequence type and ST131 subclone for plazomicin and 11 comparators among 216 extended-spectrum cephalosporin-resistant *Escherichia coli* clinical isolates

Agent[a]	MIC_{50} and MIC_{90} by sequence type (ST)					P[b]	MIC_{50} and MIC_{90} by ST131 subclone status					P[d]
							non-ST131[d] (*n* = 80)	ST131 subclone				
	ST131 (*n* = 136)	ST405 (*n* = 7)	ST648 (*n* = 7)	ST1193 (*n* = 7)	Other STs (*n* = 59)			O16[d] (*n* = 8)	(non-C1-M27) *H*30R1[d] (*n* = 44)	(*H*30R1) C1-M27[d] (*n* = 14)	*H*30Rx[d] (*n* = 70)	
PLZ	1, 2	1, 2	1, 2	1, 2	1, 2		1, 2[e]	1, 2[e]	1, 2[e]	1, 2[e]	1, 2[e]	0.04[e]
MEM	≤ 0.03, ≤ 0.03	≤ 0.03, 0.06	≤ 0.03, ≤ 0.03	≤ 0.03, ≤ 0.03	≤ 0.03, ≤ 0.03	< 0.001	≤ 0.03, ≤ 0.03	≤ 0.03, ≤ 0.03	≤ 0.03, ≤ 0.03	≤ 0.03, ≤ 0.03	≤ 0.03, ≤ 0.03	
IPM	0.25, 0.5	0.25, 0.5	0.25, 0.5	0.12, 0.25	0.25, 0.5		0.25, 0.5	0.25, 0.5	0.25, 0.5	0.25, 0.5	0.25, 0.25	0.049
ETP	0.03, 0.125	1, 2	0.06, 0.25	≤ 0.016, 0.03	0.05, 0.25	< 0.001	≤ 0.016, 0.5	0.03, 0.06	0.03, 0.25	≤ 0.016, 0.03	0.03, 0.125	0.01
GEN	1, > 16	1, > 16	1, > 16	1, > 16	0.5, > 16		1, > 16	1, > 16	> 16, > 16	0.5, 2	1, > 16	0.001
TZP	2, 8	8, 64	4, 16	1, 2	4, 32	0.03	2, 16	1, 2	2, 32	1, 4	2, 8	0.008
AMK	4, 16	4, 32	8, 16	4, 8	4, 16		4, 16	4, 4	4, 8	4, 8	4, 16	
LVX	> 8, > 8[f]	> 8, > 8[f]	> 8, > 8[f]	> 8, > 8[f]	> 8, > 8[f]	< 0.001[f]	> 8, > 8	2, > 8	> 8, > 8	> 8, > 8	> 8, > 8	< 0.001
TGC	0.5, 1	0.5, 1	0.5, 1	0.5, 1	0.5, 1		0.5, 1	0.5, 1	0.5, 1	0.5, 1	0.5, 1	
CAZ	16, >16	>16, >16	16, >16	1, >16	16, >16	0.03	16, > 16	2, > 16	4, > 16	4, 16	16, > 16	< 0.001
CL	0.25, 0.25[g]	0.12, 0.25[g]	0.12, 0.25[g]	0.12, 0.25[g]	0.12, 0.25[g]	0.002[g]	0.12, 0.25	0.25, 0.25	0.25, 0.25	0.25, 0.5	0.25, 0.25	0.001
MIN	4, 4	8, 16	8, >16	2, 4	4, 16	0.004	4, 16	4, 8	4, 8	4, 16	2, 8	0.02

[a] *AMK* amikacin, *CAZ* ceftazidime, *CL* colistin, *ETP* ertapenem, *GEN* gentamicin, *IPM* imipenem, *LVX* levofloxacin, *MEM* meropenem, *MIN* minocycline, *PLZ* plazomicin, *TZP* piperacillin-tazobactam

[b] *P* values, as determined by Kruskal Wallis test for five-group comparisons involving overall MIC distributions across ST-defined categories, are shown where $P < 0.05$

[c] non-ST131, not a member of ST131; O16, O16 ST131 subclone; *H*30R1, subclone within the (fluoroquinolone-resistance associated) ST131 *H*30R subclone; C1-M27, subclone within *H*30R1 that is associated with $bla_{CTX-M-27}$ and $bla_{CTX-M-14}$; *H*30Rx, sister subclone to *H*30R1 within the ST131 *H*30R subclone that is associated with $bla_{CTX-M-15}$

[d] *P* values, as determined by Kruskal-Wallis test for five-group comparisons involving overall MIC distributions across non-ST131 isolates and ST131 subclones, are shown where $P < 0.05$

[e] For PLZ MICs by ST131 subclone, mean ranks were 100 (non-ST131), 76 (O16 ST131), 111 ([non-C1-M27] *H*30R1), 143 ([*H*30R1] C1-M27), and 114 (*H*30Rx)

[f] For LVX MICs, mean ranks were 122 (ST131), 115 (ST405), 115 (ST648), 129 (ST1193), and 73 (other STs)

[g] For CL MICs, mean ranks were 120 (ST131), 104 (ST405), 81 (ST648), 98 (ST1193), and 87 (other STs)

ST131 isolates, the non-C1-M27 *H*30R1 isolates, and the *H*30Rx isolates. Likewise, MICs for all but three comparators (MEM, AMK, TGC) also varied significantly by ST131 subclone status, in agent-specific patterns.

CTX-M genotype PLZ MICs did not vary significantly by CTX-M status or CTX-M group (Supplemental Table 5). By contrast, MICs did so vary for eight of the 11 comparators (i.e., all but MEM, GEN, and TGC). For these eight agents, MICs were usually higher among CTX-M-positive isolates, and/or CTX-M group 1-positive isolates. The cumulative percent MIC distribution for PLZ, GEN, and AMK illustrated with greater granularity this distinction between GEN (higher MICs among CTX-M and group 1-positive isolates) vs. PLZ and AMK (minimal variation in relation to resistance genotype) (Supplemental Table 6).

Resistance to comparators PLZ MICs varied significantly with comparator-agent-resistance only for AMK or LVX, in both instances being higher among comparator-resistant isolates (Supplemental Table 7). With AMK, the fact that PLZ MICs were higher among resistant isolates was reflected in the twofold higher MIC_{50} (2 mg/L, vs. 1 mg/L). By contrast, with LVX, the direction of the difference was evident only from mean MIC ranks (88, LVX-susceptible isolates; vs. 111, LVX-resistant isolates: Supplemental Table 7 footnote).

Discussion

In this study of the activity PLZ and 11 comparators against 216 ESCREC clinical isolates from veterans in relation to bacterial characteristics, PLZ distinguished itself from most or all comparators in multiple respects. These included (i) a very high overall percent susceptible (99.5%); (ii) very similar MIC_{50} and MIC_{90} values (only a four-fold difference); (iii) minimal MIC variation in relation to phylogroup, ST, or beta-lactamase genotype; and (iv) subtle but statistically significant MIC variation in relation to ST131 subclone status (lowest among O16 isolates, highest among C1-M27 *H*30R1 isolates). PLZ MICs were also independent of resistance to comparator agents, except for AMK (possibly due to shared resistance mechanisms [32]) and LVX (possibly due to clonally or genetically linked resistance mechanisms [33]). These findings demonstrate the distinctiveness of PLZ and its preserved activity against even multidrug-resistant ESCREC isolates, and recommend it as a potential non-beta-lactam, carbapenem-sparing alternative for treating ESCREC infections.

The high percent susceptible for most agents obliged comparisons based on MICs rather than percent susceptible. In these analyses, multiple comparator agents—but rarely PLZ—exhibited MIC shifts in relation to each category of variable studied. The observed MIC differences within the susceptible range conceivably could be clinically significant, depending on the site and severity of infection [34–37], if drug levels at the site were limited by local or systemic factors, or with immune compromise.

The only phylogenetic entity to exhibit comparatively higher PLZ MICs was the recently recognized and emerging C1-M27 subset within ST131-*H*30R1, which is associated with $bla_{CTX\text{-}M\text{-}27}$ and $bla_{CTX\text{-}M\text{-}14}$ [21, 29, 38]. The basis for the higher PLZ MICs of C1-M27 isolates is unclear. Conceivably, the same plasmids that carry $bla_{CTX\text{-}M\text{-}27}$ may carry genes that encode resistance mechanisms (e.g., ribosomal methyl-transferases or efflux pumps) that raise PLZ MICs, without conferring full resistance.

Study limitations include the single-institution source of the isolates (MVAHCS); the distinctiveness of the veteran population, which may constrain generalizability; the minimal data regarding the source patients and their clinical presentations; the lack of information regarding PLZ resistance mechanisms; and the uncertain therapeutic implications of the MIC data. Study strengths include the relatively large and recent sample, the extensive molecular and phenotypic characterization of the isolates, and the analysis of MICs in relation to multiple bacterial characteristics, including resistance to comparators.

In conclusion, we found that PLZ exhibited activity against recent ESCREC clinical isolates comparable to that of carbapenems and that most bacterial characteristics were unassociated with shifts in the PLZ MIC, by contrast with the extensive associations of these variables with MICs for most comparators. These findings support PLZ as a potential alternative to carbapenems for treating ESCREC infections, largely irrespective of phylogenetic/clonal background or ESBL genotype, and support further attention to PLZ susceptibility within the emerging C1-M27 ST131 subclone.

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Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contribution 1. Brian Johnston: Data collection and validation, laboratory procedures, data analysis, construction of tables, and manuscript writing and editing

2. Paul Thuras: Statistical analysis

3. Stephen B. Porter: Isolate collection, data collection, and manuscript editing

4. Connie Clabots: Isolate collection, data collection, and manuscript editing
5. James R. Johnson: Concept, funding, project oversight, and manuscript drafting and editing

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Declarations

Ethics approval (include appropriate approvals or waivers): The study was approved by the MVAMC Institutional Review Board.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest James R. Johnson has had grants and/or consultancies with Allergan/Actavis, Cipla/Achaogen, Janssen/Crucell, Melinta/The Medicines Company, Merck, Shionogi, Syntiron, and Tetraphase. The other authors report no financial conflicts of interest.

Disclaimer The opinions expressed here are strictly those of the authors and do not necessarily represent those of the Department of Veteran Affairs or the authors' institutions.

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