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Plazomicin Activity against *Enterobacterales* Isolates Producing Extended-Spectrum β-Lactamases (ESBLs), Carbapenemases, and Aminoglycoside-Modifying Enzymes (AMEs) from United States (US) Hospitals

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Introduction

- Plazomicin is a next-generation aminoglycoside synthetically derived from sisomicin.
- Unlike other aminoglycoside molecules, plazomicin is stable against most aminoglycoside modifying enzymes commonly found in Gram-negative and Gram-positive organisms.
- Plazomicin was approved by the US FDA to treat complicated urinary tract infections, including acute pyelonephritis.
- Recent studies demonstrate that plazomicin is active against *Enterobacterales* isolates producing extended-spectrum β-lactamases (ESBLs) and carbapenem-resistant isolates (CRE) which often harbor multiple resistance mechanisms and display a multidrug-resistant (MDR) phenotype.
- In this study, we evaluated the activity of plazomicin and comparators against *Enterobacterales* isolates collected in US hospitals during 2018 and 2019.
  - Isolates tested carried genes encoding ESBLs, carbapenemases, and aminoglycoside modifying enzymes (AMEs).

Materials and Methods

- A total of 3,899 *Enterobacterales* clinical isolates were collected during 2018 and 2019 from 33 US hospitals participating in the ALERT (Antimicrobial Longitudinal Evaluation and Resistance Trends) Program.
  - Isolates identified as the cause of infection were included in the study.
  - Isolates were limited to 1 per patient.
- Isolates were susceptibility tested using the reference broth microdilution method described by the Clinical and Laboratory Standards Institute (CLSI).
  - Categorical interpretations for plazomicin and comparator agents followed the CLSI and US FDA breakpoints.
  - Quality control (QC) was performed according to CLSI guidelines (M07, 2018), and all QC minimal inhibitory concentration (MIC) results were within the acceptable ranges.
- CRE was defined as any isolate exhibiting imipenem and/or meropenem MIC values at ≥2 µg/mL.
  - Proteus mirabilis and indole-positive Proteeae were categorized as CRE if meropenem MIC values were at ≥2 µg/mL due to intrinsically elevated imipenem MIC values.
- Whole genome sequencing on a MiSeq (Illumina, San Diego, California, USA) instrument targeting a 30X coverage was performed on 619 isolates selected as follows:
  - *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., and *Enterobacter* spp. isolates displaying nonsusceptible MIC values for gentamicin, amikacin, and/or tobramycin according to CLSI criteria were screened for the presence of AMEs.
  - Any *Enterobacterales* isolate with plazomicin MIC values of ≥128 mg/L was screened for AMEs and 16S rRNA methyltransferase-encoding genes.
  - CRE and isolates displaying MIC >2 mg/L for at least 2 of the following agents: cefepime, ceftazidime, ceftriaxone, and aztreonam were screened for the presence of β-lactamases.
- Sequences were de novo assembled and genes encoding resistance were searched using a curated library that applied the criteria of >94% sequencing identity and 40% minimum length coverage.

Results

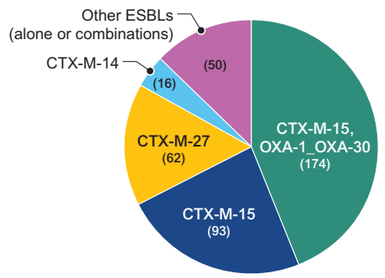
- Among 395 isolates producing ESBLs, 217 *E. coli*, 169 *K. pneumoniae*, and 9 *K. oxytoca* were resistant to extended spectrum cephalosporins (ceftazidime, ceftriaxone or cefepime) and/or aztreonam as well as susceptible to carbapenems.
  - The most common gene detected among these isolates was $bla_{CTX\text{-}M\text{-}15}$, which was observed among 273 isolates, including 93 isolates that carried this gene by itself and 174 isolates that harbored $bla_{CTX\text{-}M\text{-}15}$ plus $bla_{OXA\text{-}1}$ (Figure 1A).
  - Other prevalent genes were $bla_{CTX\text{-}M\text{-}27}$ and $bla_{CTX\text{-}M\text{-}14}$, which were noted in 62 and 16 isolates, respectively.
  - Genes encoding SHV enzymes with extended spectrum were observed among 19 isolates alone and in 9 isolates in combination with another ESBL ($bla_{CTX\text{-}M\text{-}15}$).
- Plazomicin inhibited 99.5% of the 395 isolates carrying ESBL-encoding genes at the US FDA breakpoint and was the most active aminoglycoside against these isolates (Figure 2).
  - Amikacin, gentamicin, and tobramycin inhibited 97.7%, 59.2%, and 45.8% of these isolates when CLSI breakpoints were applied.
  - The carbapenems, meropenem and imipenem, were the most active comparators. Susceptibility rates against these agents were 99.5% and 99.7%, respectively.
- Among 44 CRE isolates, 32 harbored carbapenemase genes that included 18 $bla_{KPC\text{-}2}$, 10 $bla_{KPC\text{-}3}$, 1 $bla_{NDM\text{-}5}$, 1 $bla_{VIM\text{-}1}$, 1 $bla_{KPC\text{-}2\text{-}like}$, and 1 isolate carrying $bla_{NDM\text{-}1}$ plus $bla_{OXA\text{-}232}$ (Figure 1B).
  - Carbapenemase-producing isolates were 28 *K. pneumoniae*, 2 *K. oxytoca*, and 1 each of *Serratia marcescens* and *Citrobacter freundii* species complex.
- Plazomicin and tigecycline were the only agents that displayed activity against >70% of the carbapenemase-producing *Enterobacterales*. A total of 90.3% of the isolates had intermediate results for colistin.
  - Amikacin and gentamicin inhibited only 65.6% and 53.1% of these isolates, respectively.
  - The activity of tobramycin was limited against these isolates.
- A total of 306 isolates carried AME encoding genes, including 91 *E. coli* and 117 *K. pneumoniae*.
- The most common genes modifying amikacin, gentamicin, and tobramycin were *aac(6')-Ib-cr* and *aac(3)-IIa* that were detected alone and in combination in 177 and 159 isolates, respectively (Figure 1C).
- Plazomicin was active against 97.7% of isolates carrying AME genes (Figure 2).
  - Only 14.1% and 10.8% of the AME-producing isolates were susceptible to gentamicin and tobramycin, respectively, but amikacin was active against 92.8% of these isolates.
  - The carbapenems and tigecycline were the only other agents to inhibit >90% of these isolates.
- Three *K. pneumoniae* isolates carried 16S rRNA methyltransferases, 1 *armA* (which also harbored genes encoding NDM-1 and OXA-232), and 2 *rmtB1*.
  - These isolates were resistant to all aminoglycosides, including plazomicin.

Conclusions

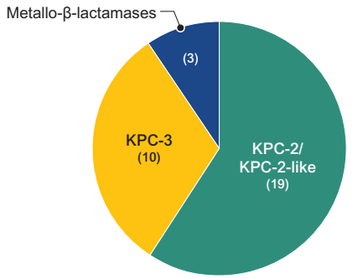
- Plazomicin displayed activity against *Enterobacterales* isolates from US hospitals carrying ESBLs, carbapenemases, and AMEs.
  - This aminoglycoside exhibited greater activity than other agents from the same class against these challenging isolates.
- Continuous surveillance in US hospitals demonstrates a low occurrence (<0.1%) of isolates that carry genes encoding 16S rRNA methyltransferase that confer resistance to all aminoglycosides.
- Plazomicin seems to be a valuable alternative for the treatment isolates carrying genes encoding ESBLs, AMEs, and carbapenemases, the genes that usually are multidrug resistant and have limited therapeutic options.

Figure 1 Occurrence of ESBLs, carbapenemases, and AMEs in US hospitals during 2018–2019

A. ESBLs (395 isolates)



B. Carbapenemases (32 isolates)



C. AMEs (306 isolates)

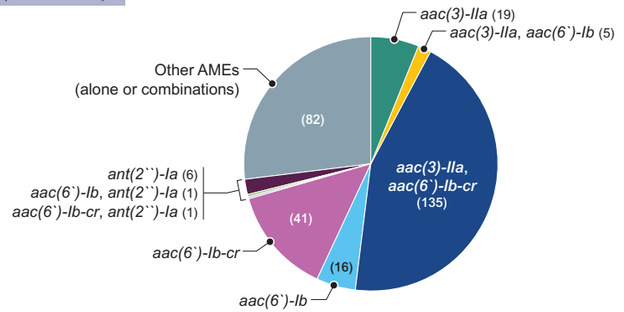
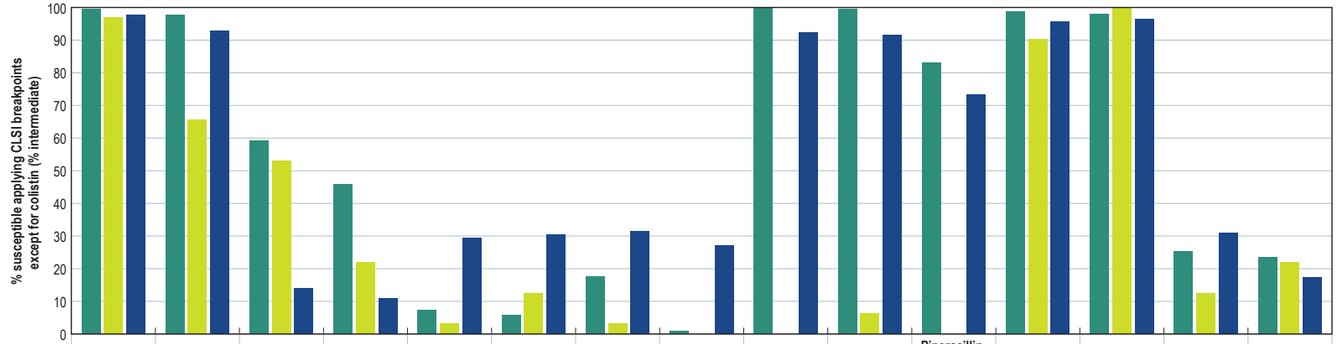


Figure 2 Activity of plazomicin and comparator agents against *Enterobacterales* producing ESBLs, carbapenemases and AMEs



	Plazomicin	Amikacin	Gentamicin	Tobramycin	Aztreonam	Cefepime	Ceftazidime	Ceftriaxone	Imipenem	Meropenem	Piperacillin-tazobactam	Colistin	Tigecycline	Levofloxacin	Trimethoprim-sulfamethoxazole
ESBL (395 isolates)	99.5	97.7	59.2	45.8	7.3	5.8	17.7	0.8	99.7	99.5	83.0	98.7	98.0	25.4	23.5
Carbapenemase (32 isolates)	96.9	65.6	53.1	21.9	3.1	12.5	3.1	0.0	0.0	6.2	0.0	90.3	100.0	12.5	21.9
AME (306 isolates)	97.7	92.8	14.1	10.8	29.4	30.4	31.4	27.1	92.2	91.5	73.4	95.7	96.4	31.0	17.3

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The abstract for this study has been amended.

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