Plazomicin is Active against *Enterobacteriaceae* Isolates Producing Extended-Spectrum β-Lactamases, Carbapenemases, and Aminoglycoside-Modifying Enzymes from United States (US) Hospitals

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Introduction

- The increasing number of patients with prolonged hospitalization, including those in intensive care or long-term care facilities, immunodeficient patients, and others with malignant conditions, is often associated with growing rates of infections caused by multidrug-resistant (MDR) organisms
- Among MDR *Enterobacteriaceae*, commonly highlighted isolates produce extended-spectrum β-lactamases (ESBLs), carbapenem-resistant isolates (CRE), and isolates resistant to aminoglycosides that usually carry genes encoding aminoglycoside modifying enzymes (AMEs)
- Plazomicin is a next-generation aminoglycoside synthetically derived from sisomicin that is designed to have stability against most common aminoglycoside resistance mechanisms
- Plazomicin was approved by the US Food and Drug Administration (FDA) to treat complicated urinary tract infections, including acute pyelonephritis
- We evaluated the activity of plazomicin and comparators against US isolates collected in 2017 carrying genes encoding ESBLs, carbapenemases, and AMEs

Materials and Methods

- A total of 2,051 *Enterobacteriaceae* clinical isolates were collected during 2017 from 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 and 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 all comparator agents were those in the CLSI guidelines (M100, 2019), European Committee on Antimicrobial Susceptibility Testing (EUCAST) website or United States FDA website
  - Quality control (QC) was performed according to CLSI guidelines (M07, 2018), and all QC minimal inhibitory concentration (MIC) results were within acceptable ranges as published in CLSI documents
- CRE was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 µg/mL
  - *Proteus mirabilis* and indole-positive Proteeae were categorized as CRE if doripenem and/or 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 490 selected isolates
  - *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, and any *Enterobacteriaceae* isolate with plazomicin MIC values of ≥128 mg/L was screened for AMEs and 16S rRNA methyltransferase-encoding genes
  - CRE and *Enterobacteriaceae* isolates displaying an ESBL phenotype were screened for the presence of β-lactamases
- Sequences were *de novo* assembled and genes encoding resistance were searched using a curated library and applying criteria of >94% sequencing identity and 40% minimum length coverage

Results

- Among 168 isolates carrying AME-encoding genes (Figure 1a), the most common genes modifying amikacin, gentamicin, and tobramycin were *aac(6')-Ib-cr* (73 isolates), *aac(3)-IIa* (63), and *aac(3)-IId* (54)
  - Various other AME genes were also detected
- Plazomicin was active against 96.4% of isolates carrying AME genes (Figure 2)
  - Only 16.7% were susceptible to gentamicin and tobramycin, but 94.0% were susceptible to amikacin
  - Cefepime and piperacillin-tazobactam inhibited only 41.1% and 76.2% of these isolates, respectively
- ESBL-encoding genes were detected among 91 *E. coli*, 75 *K. pneumoniae*, and 3 *K. oxytoca* that were resistant to extended-spectrum cephalosporins (ceftazidime, ceftriaxone, or cefepime) and/or aztreonam and susceptible to carbapenems (Figure 1b)
  - The most common gene detected among these isolates was $bla_{CTX\text{-}M\text{-}15}$ (107/169) that was observed alone in 42 isolates or combined with other genes, most commonly $bla_{SHV\text{-}1}$ (60 isolates)
- Plazomicin was the most active agent tested against ESBL-producing isolates and inhibited 99.4% of these isolates at the US FDA breakpoint (Figure 2)
  - Amikacin, meropenem, and colistin were the most active comparators and 97.6%, 98.8%, and 98.8% of the isolates were susceptible to these agents, respectively
- Among 22 CRE isolates, 18 harbored carbapenemase genes that totaled 11 $bla_{KPC\text{-}2}$, 6 $bla_{KPC\text{-}3}$, and 1 $bla_{OXA\text{-}232}$ (Figure 1c)
  - Twelve (66.6%) of these isolates were *K. pneumoniae*, but 4 other bacterial species carried these genes: *Citrobacter freundii*, *C. koseri*, *Enterobacter cloacae*, and *E. coli*
- Plazomicin, colistin, and tigecycline inhibited 94.4%, 100.0%, and 100.0% of these isolates, respectively, and were the only agents that inhibited >75% of these isolates
  - Amikacin and gentamicin inhibited 72.2% and 50.0% of these isolates, respectively
- Only 1 *K. pneumoniae* isolate carried a 16S rRNA methyltransferase, *rmtF1*, and was resistant to plazomicin and the other aminoglycosides

Conclusions

- Plazomicin was active against 94.4% to 99.4% of this challenge set of *Enterobacteriaceae* isolates carrying AMEs, ESBLs, and carbapenemases
  - The activity of plazomicin was greater than the activity of other aminoglycosides against these isolates
- Plazomicin seems to be a valuable option to treat these troublesome isolates from US hospitals where the prevalence of 16S rRNA methyltransferases is low

Acknowledgements

This study was performed by JMI Laboratories and supported by Achaogen, which included funding for preparing this poster.

References

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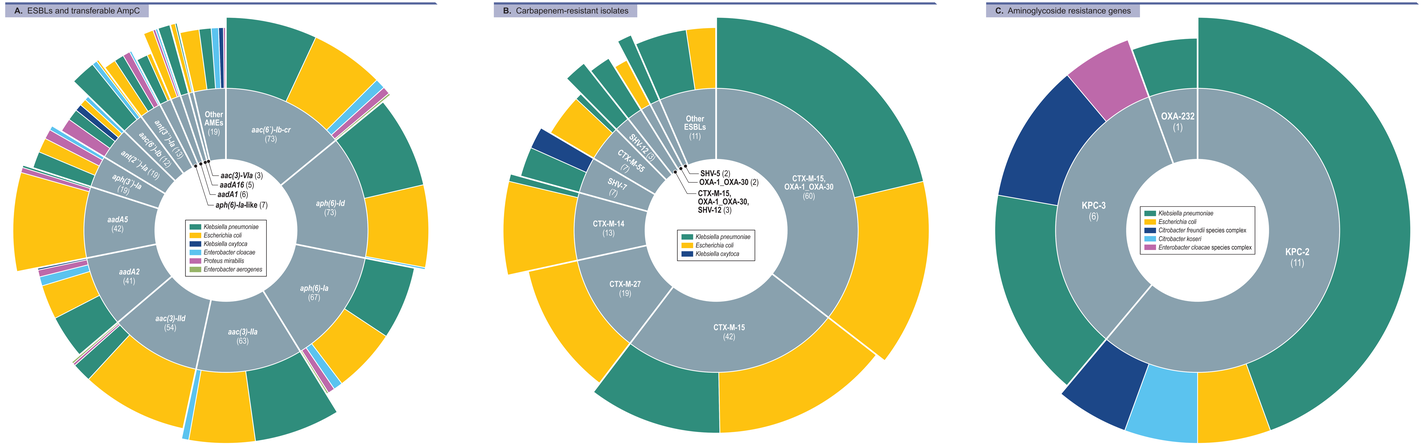
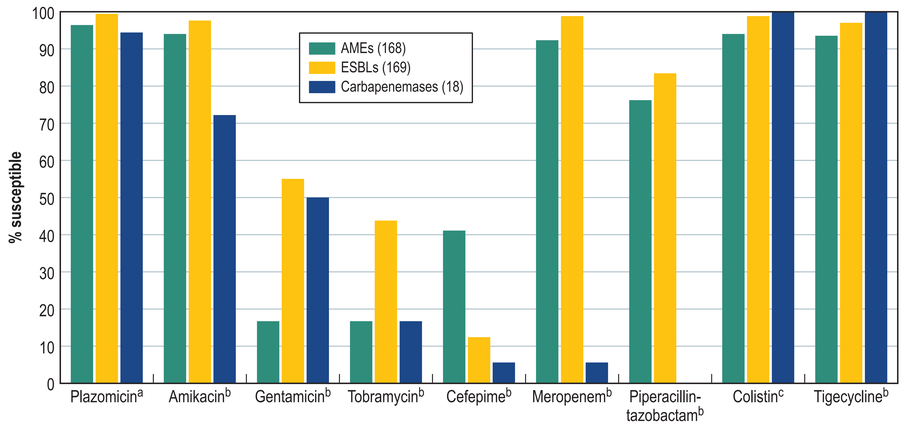
Figure 1 Distribution of β-lactamases and aminoglycoside resistance mechanisms among isolates submitted to whole genome sequencing



Other AMEs include positive results for aac(6')-Ib; aph(3')-Ia-like, aph(4)-Ia, aac(3)-IV (2 each) and aad41-like, aac(3)-IIa-like, aac(6')-33, aac(6')-Ib-cr-like, aadA22, aad46, aph(6)-Id-like, aac(6')-Ib', aac(6')-Ib-cr5, aac(6')-Ib-cr7 and aph416 (1 each)

Other ESBLs include 1 each of CTX-M-1, CTX-M-14 plus CTX-M-15, CTX-M-15 plus SHV-27, CTX-M-24, CTX-M-27 plus SHV-27, CTX-M-3, CTX-M-55 plus SHV-12, SHV-12 plus SHV-27, SHV-2, SHV-2A, SHV-38

Figure 2 Activity of plazomicin and comparator agents



[a] % susceptible based on FDA criteria
[b] % susceptible based on CLSI criteria
[c] % susceptible based on EUCAST criteria