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Plazomicin Activity against Enterobacteriaceae Isolates Carrying Genes Encoding Extended-Spectrum β-Lactamases, Carbapenemases, and/or Aminoglycoside-Modifying Enzymes

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Introduction

- Aminoglycosides are important for the treatment of serious gram-negative infections and are often used in combination with cell wall biosynthesis inhibition agents, such as β-lactams
- Resistance to aminoglycosides occurs mainly by the acquisition of aminoglycoside-modifying enzymes (AMEs)
  - AMEs modify aminoglycoside molecules causing poor binding of these to the ribosome target
  - AME-encoding genes are carried by mobile genetic structures often harbouring β-lactamases and/or other resistance determinants that can be selected and disseminated concomitantly
- Plazomicin is a semi-synthetic aminoglycoside derived from sisomicin containing structural modifications that make this molecule stable in the presence of the clear majority of AMEs
  - Plazomicin is a next-generation aminoglycoside recently approved by the US Food and Drug Administration (FDA) for complicated urinary tract infections, including acute pyelonephritis against certain Enterobacteriaceae species
  - Plazomicin exhibits activity against carbapenem-resistant Enterobacteriaceae (CRE) and isolates carrying extended-spectrum β-lactamase (ESBL) genes that do not carry 16S rRNA methyltransferases
- In this study we evaluated the activity of plazomicin and comparator agents against Enterobacteriaceae isolates collected in 18 European countries during 2017 that encoded ESBLs, carbapenemases, and/or AME genes

Materials and Methods

- A total of 1,966 Enterobacteriaceae clinical isolates were collected during 2017 from 37 European 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 all comparator agents were those in the EUCAST 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 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 a plazomicin MIC value of ≥128 μg/mL 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 (CLSI criteria)
- 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

- ESBLs were detected among 300 isolates that were not resistant to carbapenems
  - The most common ESBL gene was $bla_{CTX\text{-}M\text{-}15}$ (n=239) detected alone or in combination with other enzymes (Figure 1)
  - Other ESBLs included $bla_{CTX\text{-}M\text{-}14}$, $bla_{CTX\text{-}M\text{-}27}$ (13 and 17 isolates), 8 other $bla_{CTX\text{-}M}$ variants, and $bla_{SHV\text{-}12}$, $bla_{SHV\text{-}2}$, $bla_{GES\text{-}1}$ (5, 1, and 1 isolates)
  - Additionally, transferrable AmpCs were detected among 13 isolates alone, and $bla_{CMY\text{-}2}$, $bla_{CMY\text{-}4}$, and $bla_{DHA\text{-}1}$ were detected among 7, 2, and 4 isolates, respectively
- Plazomicin inhibited 98.7% of the 300 isolates carrying ESBL genes at ≤2 μg/mL (Figure 2)
  - Amikacin, gentamicin, and tobramycin inhibited 85.3%, 48.3%, and 25.7% of these isolates, respectively
  - Meropenem inhibited all isolates harbouring ESBL genes, and colistin and tigecycline inhibited 97.3% and 92.0% of the isolates, respectively (EUCAST/US FDA breakpoints)
- Carbapenemase genes were observed among 77 isolates and included 34 $bla_{KPC\text{-}3}$, 13 $bla_{KPC\text{-}3}$, 17 $bla_{OXA\text{-}48}$, 10 $bla_{NDM\text{-}1}$ (alone or with $bla_{OXA\text{-}48}$-like), and 2 $bla_{VIM\text{-}1}$
- Plazomicin inhibited 88.3% of the 77 carbapenemase-producing isolates at the US FDA breakpoint (susceptible at ≤2 μg/mL; Figure 2) and was the most active agent tested
  - Colistin and tigecycline inhibited 80.3% and 84.4% of the isolates, respectively
  - Amikacin and gentamicin inhibited 51.9% and 51.7% of the carbapenemase-producers using CLSI breakpoints
  - Tobramycin inhibited only 15.6% of the isolates
  - A total of 12 isolates carried 16S rRNA methyltransferase genes and were resistant to all aminoglycosides tested
- AMEs were observed among 348 isolates tested and the most common genes were *aac(6')-Ib-cr* (n=217) and *aac(3)-IIa* (n=175; Figure 2)
  - Plazomicin inhibited 94.8% of the AME-carrying isolates at ≤2 μg/mL
  - Amikacin, gentamicin, and tobramycin inhibited 71.6%, 26.7%, and 0.9%, respectively, of these isolates
- A total of 202 isolates carrying ESBL-encoding genes and 53 harbouring carbapenemase also carried AMEs
  - Plazomicin inhibited 98.0% and 88.7% of the Enterobacteriaceae carrying ESBL or carbapenemase genes, respectively (Figure 2)
  - Amikacin, gentamicin, and tobramycin inhibited 78.7%, 24.3%, and 0.0% of the ESBL-harbouring isolates, respectively, and 35.8%, 47.2%, and 0.0% of the carbapenemase-producers, respectively
  - Plazomicin was more active than tigecycline and colistin against isolates carrying genes encoding AMEs plus an ESBL or a carbapenemase enzyme

Conclusions

- Plazomicin was more active than other aminoglycosides, tigecycline, colistin, and non-carbapenem β-lactams against isolates from European hospitals carrying ESBL genes in the presence or absence of AMEs
- This new aminoglycoside was more active than all agents against carbapenemase producers that include isolates carrying KPC, OXA-48, and NDM genes with or without AMEs
- Plazomicin displayed activity against contemporary troublesome isolates from European hospitals
  - This agent is an important addition to the armamentarium against multidrug-resistant infections that have high mortality rates and are a matter of concern worldwide

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

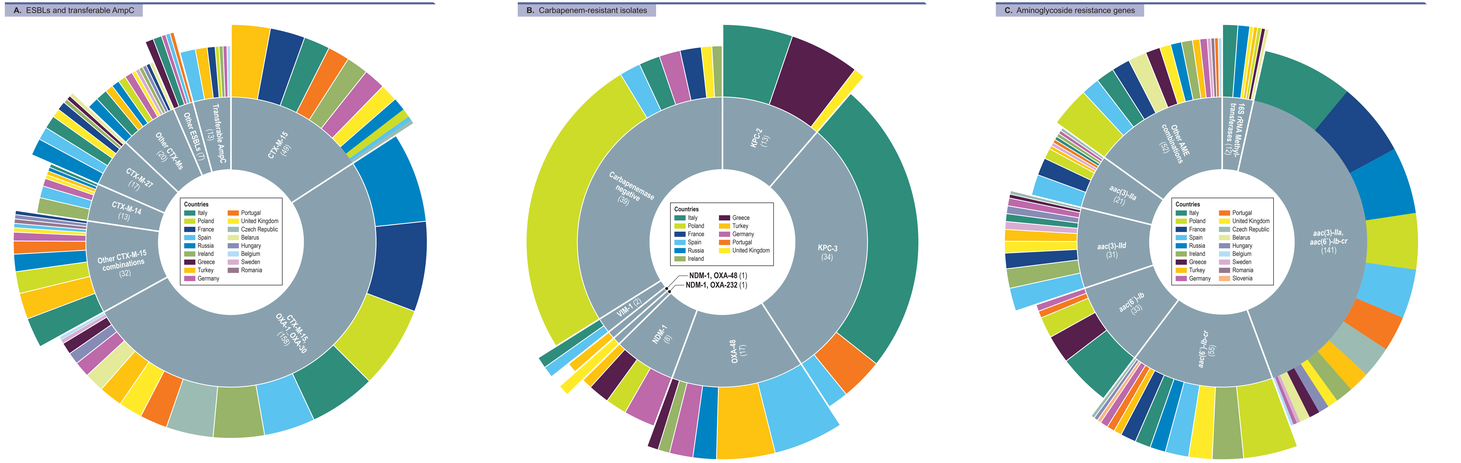
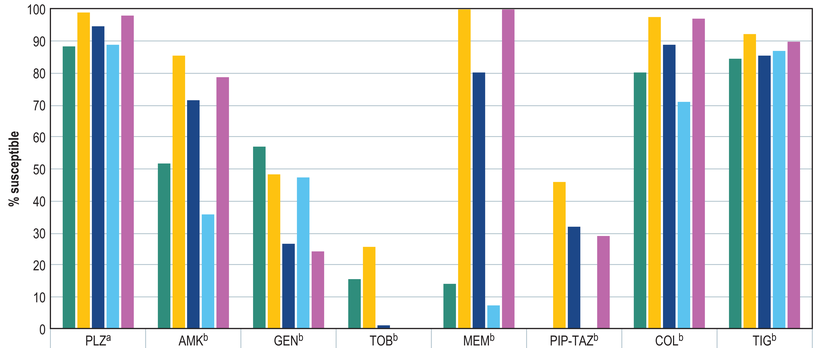


Figure 2 Activity of plazomicin and comparator agents against isolates



	PLZ[a]	AMK[b]	GEN[b]	TOB[b]	MEM[b]	PIP-TAZ[b]	COL[b]	TIG[b]
Carbapenemases (77)	88.3	51.9	57.1	15.6	14.3	0.0	80.3	84.4
ESBL (non-CRE) (300)	98.7	85.3	48.3	25.7	100.0	45.7	97.3	92.0
AMEs (348)	94.8	71.6	26.7	0.9	79.9	31.9	89.0	85.6
Carbapenemase + AMEs (53)	88.7	35.8	47.2	0.0	7.5	0.0	71.2	86.8
ESBL (non-CRE) + AMEs (202)	98.0	78.7	24.3	0.0	100.0	29.2	97.0	89.6

PLZ, plazomicin; AMK, amikacin; GEN gentamicin; TOB, tobramycin; MEM, meropenem; PIP-TAZ, piperacillin-tazobactam; COL, colistin; TIG, tigecycline
[a] % susceptible based on FDA criteria
[b] % susceptible based on EUCAST criteria

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