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Population-based inference of aminoglycoside resistance mechanisms in Escherichia coli

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Abstract: BACKGROUND Interpretative reading of antimicrobial susceptibility test (AST) results allows inferring biochemical resistance mechanisms from resistance phenotypes. For aminoglycosides, however, correlations between resistance pathways inferred on the basis of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints and expert rules versus genotypes are generally poor. This study aimed at developing and validating a decision tree based on resistance phenotypes determined by disc diffusion and based on epidemiological cut-offs (ECOFFs) to infer the corresponding resistance mechanisms in Escherichia coli. METHODS Phenotypic antibiotic susceptibility of thirty wild-type and 458 aminoglycoside-resistant E. coli clinical isolates was determined by disc diffusion and the genomes were sequenced. Based on well-defined cut-offs, we developed a phenotype-based algorithm (Aminoglycoside Resistance Mechanism Inference Algorithm - ARMIA) to infer the biochemical mechanisms responsible for the corresponding aminoglycoside resistance phenotypes. The mechanisms inferred from susceptibility to kanamycin, tobramycin and gentamicin were analysed using ARMIA- or EUCAST-based AST interpretation and validated by whole genome sequencing (WGS) of the host bacteria. FINDINGS ARMIA-based inference of resistance mechanisms and WGS data were congruent in 441/458 isolates ($96 \cdot 3\%$). In contrast, there was a poor correlation between resistance mechanisms inferred using EUCAST CBPs/expert rules and WGS data (418/488, $85 \cdot 6\%$). Based on the assumption that resistance mechanisms can result in therapeutic failure, EUCAST produced 63 ($12 \cdot 9\%$) very major errors (vME), compared to only 2 ($0 \cdot 4\%$) vME with ARMIA. When used for detection and identification of resistance mechanisms, ARMIA resolved >95% vMEs generated by EUCAST-based AST interpretation. INTERPRETATION This study demonstrates that ECOFF-based analysis of AST data of only four aminoglycosides provides accurate information on the resistance mechanisms in E. coli. Since aminoglycoside resistance mechanisms, despite having in certain cases a minimal effect on the minimal inhibitory concentration, may compromise the bactericidal activity of aminoglycosides, prompt detection of resistance mechanisms is crucial for therapy. Using ARMIA as an interpretative rule set for editing AST results allows for better predictions of in vivo activity of this drug class.

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Commentary

Aminoglycoside resistance mechanism inference algorithm: Implication for underlying resistance mechanisms to aminoglycosides

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The discovery of antibiotics in 1928 and their subsequent large-scale production are considered to be one of the most important achievements in the history of medicine [1]. One of the most important discoveries after that of β-lactams was streptomycin, the first aminoglycoside discovered. The history of aminoglycosides was then marked by the successive introduction of a series of compounds (kanamycin, gentamicin, and tobramycin) for the treatment of infections due to Gram-negative bacilli [2].

The recent expansion of extensively drug-resistant (XDR) pathogens and particularly that of carbapenem-producing *Enterobacteriaceae* (CRE) has brought into light aminoglycosides, which may retain activity even in XDR isolates [3]. Specific indications for aminoglycoside therapy include amikacin and gentamicin administered intravenously for infections caused by MDR Gram-negative organisms [4].

Interpretative reading of antimicrobial susceptibility test results allows to analyze the susceptibility pattern and to predict the underlying resistance mechanisms [5]. Contrary to β-lactams antibiotics, correlations between resistance to aminoglycosides inferred based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints and expert rules are generally poor [6]. Therefore, the need for improvement of detection of aminoglycosides resistance mechanisms in routine is of great importance.

Recently in *EBioMedicine*, Mancini and colleagues presented an Aminoglycoside Resistance Mechanism Inference Algorithm (ARMIA) for the inference of resistance mechanisms from inhibition zone diameters [7]. This algorithm uses ECOFFs for gentamicin, tobramycin and kanamycin as well as a working separator cut-off for amikacin. They compared the performance of ARMIA and EUCAST CBPs/expert rules with that of whole-genome sequencing (WGS) in predicting aminoglycoside resistance. The results of this study showed that ARMIA-based inference of resistance mechanisms and WGS data were congruent in 96·3%. In contrast, there was a poor correlation between resistance mechanisms inferred using EUCAST CBPs/expert rules and WGS data (85·6%) [7].

When assessing the accuracy of various susceptibility testing methods as compared to standard reference methods, the terms very major errors (vME) have been used to describe false susceptible [8]. Thus, in the comparison made by Mancini and colleagues, they reported that EUCAST produced 63 (12·9%) vME, compared to only 2 (0·4%) vME with ARMIA [7].

In vitro susceptibility rates may vary significantly, depending on the aminoglycoside resistance mechanisms, which are frequently co-transferred along with other resistance genes on mobile genetic elements [3]. It is reported that aminoglycoside resistance mechanisms, such as 16S rRNA methylase, coexist with other resistance mechanisms including extended-spectrum β-lactamase, carbapenemase, and plasmid-mediated quinolone resistance determinants [9]. Thus, it is important to detect the underlying aminoglycosides resistance mechanisms to prevent co-selection of these resistance mechanisms. The ARMIA developed by Mancini and colleagues would be useful for this purpose to avoid misidentification of the aminoglycoside resistance mechanisms.

Declaration of Competing Interest

None to declare.

References

[1] Mohr KI. History of antibiotics research. Curr Top Microbiol Immunol 2016;398:237–72. https://doi.org/10.1007/82_2016_499.
[2] Mingeot-Leclercq MP, Glupczynski Y, Tulkens PM. Aminoglycosides: activity and resistance. Antimicrob Agents Chemother 1999;43:727–37.
[3] Karaiskos I, Lagou S, Pontikis K, Rapti V, Poulakou G. The "old" and the "new" antibiotics for MDR gram-negative pathogens: for whom, when, and how. Front Public Health 2019;7:151. https://doi.org/10.3389/fpubh.2019.00151.
[4] Serio AW, Keepers T, Andrews L, Krause KM. Aminoglycoside revival: review of a historically important class of antimicrobials undergoing rejuvenation. EcoSal Plus 2018;8. https://doi.org/10.1128/ecosalplus.ESP-0002-2018.
[5] Livermore DM, Winstanley TG, Shannon KP. Interpretative reading: recognizing the unusual and inferring resistance mechanisms from resistance phenotypes. J Antimicrob Chemother 2001;48(Suppl. 1):87–102. https://doi.org/10.1093/jac/48.suppl_1.87.
[6] The EUCAST guideline on detection of resistance mechanisms v 2.0 (2017-07-11). http://www.eucast.org/resistance_mechanisms/; 2019. (n.d.).
[7] Mancini S, Marchesi M, Imkamp F, Wagner K, Keller PM, Quiblier C, et al. Population-based inference of aminoglycoside resistance mechanisms in *Escherichia coli*. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.07.020.
[8] Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. Clin Infect Dis 2009;49:1749–55. https://doi.org/10.1086/647952.
[9] Wei D-D, Wan L-G, Yu Y, Xu Q-F, Deng Q, Cao X-W, et al. Characterization of extended-spectrum beta-lactamase, carbapenemase, and plasmid quinolone determinants in *Klebsiella pneumoniae* isolates carrying distinct types of 16S rRNA methylase genes, and their association with mobile genetic elements. Microb Drug Resist 2015;21:186–93. https://doi.org/10.1089/mdr.2014.0073.

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