Comparison of the VITEK2 Advanced Expert System Phenotyping and Genetic Characterization of β-Lactamase Genes for Enterobacterales Isolates from North and Latin America

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Introduction

- β-Lactam agents are commonly used as the primary therapeutic option for serious infections caused by Enterobacterales isolates.
- The rapid detection of β-lactam resistant phenotypes such as transferable AmpC (tAmpC), ESBL, and carbapenemase is important for appropriate antimicrobial therapy administration and infection control measures.
- The VITEK2 Advanced Expert System (AES) provides standardized phenotypic interpretation of MIC results based on an extensive database of MIC distributions and prevalent resistance mechanisms in Enterobacterales isolates.
- In this study, the AES resistant phenotypes for β-lactams were compared to the molecular characterization of 488 Enterobacterales from North and Latin America.

Materials and Methods

Bacterial isolates

- Among the 488 Enterobacterales isolates (1/patient), 384 were collected from medical centers located in North America (274 isolates from 61 centers in the US) or Latin America (110 isolates from 11 centers in 6 countries) as part of the SENTRY Antimicrobial Surveillance Program during 2015–2019 (**Figure 1**).
- Additionally, 104 molecularly characterized isolates from the CDC & FDA Antibiotic Resistance Bank were included.
- *Klebsiella pneumoniae* (34.8%) was the most common organism, followed by *Escherichia coli* (26.6%), *Enterobacter cloacae* species complex (13.3%), and other Enterobacterales (25.2%; **Figure 2**).

Susceptibility testing

- Broth microdilution (BMD) susceptibility testing was conducted according to CLSI M07 guidelines using frozen-form 96-well plates produced by JMI Laboratories.
- All isolates were tested by the VITEK 2 system using N802 and XN15 AST cards. MIC results were generated using the Advanced Expert System (AES) in the Global Clinical and Laboratory Studies Institute (CLSI)-based + Natural Resistance (NATR) mode and reviewed by a microbiologist.
- CLSI clinical breakpoints were applied.
- Whole genome sequencing (WGS) was performed on isolates that met the following criteria by BMD:
  - *E. coli* and *K. pneumoniae* isolates displaying MIC values ≥2 mg/L for at least 2 of the following β-lactams: aztreonam, cefepime, ceftazidime, or ceftriaxone; and/or
  - Enterobacterales isolates displaying meropenem and/or imipenem MIC results >1 mg/L.
- Enterobacterales isolates that did not meet the criteria for molecular characterization were considered wildtype.

AES assessment

- The accuracy, sensitivity, and specificity of AES report for β-lactam resistant phenotype were compared to resistant genotypes confirmed by WGS, where:
  - Accuracy rate was calculated as: the number of AES and molecular categories in agreement/total number of AES reports × 100%
  - Sensitivity: ability of AES report to correctly identify a truly positive condition
  - Specificity: ability of AES report to correctly identify a truly negative condition

Results

- The AES provided phenotypic reports for 447/488 (91.6%) Enterobacterales isolates. The remaining 41 isolates were not a match to any AES phenotype.
- Among the 447 Enterobacterales isolates, 191 (42.7%) were characterized by WGS as isolates harboring at least 1 carbapenemase gene, 107 (23.9%) as harboring ESBL genes, 28 (6.3%) as harboring tAmpC genes, and 121 (27.1%) as wildtype.
- Overall, the AES report was accurate for 429/447 isolates (96.0%).
- The AES accurately reported carbapenemase, ESBL, and tAmpC phenotypes for 93.5%, 96.4%, and 98.7% of isolates, respectively (**Figure 3**).
- All wildtype isolates were correctly categorized by the AES as either wildtype or displaying an acquired penicillinase.
- The AES sensitivity/specificity rates were 96.3%/91.4%, 94.4%/97.1%, 82.1%/99.8%, and 100%/98.8% for reporting carbapenemase, ESBL, tAmpC, and wildtype, respectively (**Figure 3**).
- Only 18 isolates harboring carbapenemase (7 total; 3 KPC, 2 MBL, 2 OXA-48), ESBL (6), and tAmpC (5) genes were not correctly detected by AES (**Table 1**).
- Among the 41 isolates for which an AES phenotype was not reported, 20 harbored a carbapenemase, 15 an ESBL, 4 a tAmpC gene, and 2 displayed a wildtype genotype.

Figure 1. Distribution of Enterobacterales isolate collection by country of origin or source

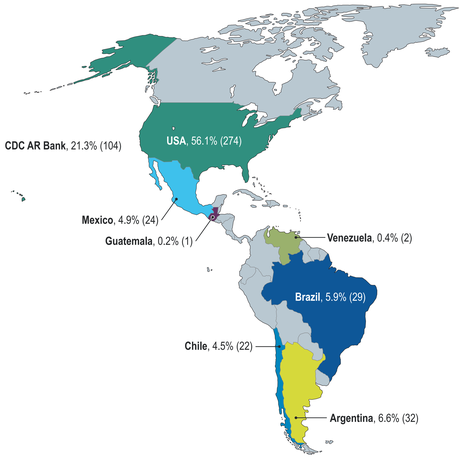


Table 1. AES phenotype and WGS genotype discordances

	WGS genotype				
AES report	**ESBL**	**Carba-penemase**	**tAmpC**	**Wild-type**	**Total**
Acquired penicillinase, wild (cephalosporinase)		2	2		4
Carbapenemase (+ or – ESBL)	4				4
ESBL + impermeability (cephamycins), ESBL		5	3		8
AmpC	2				2
Total	**6**	**7**	**5**	**0**	**18**

Figure 2. Characterization of Enterobacterales isolates by species and β-lactam resistant genotype

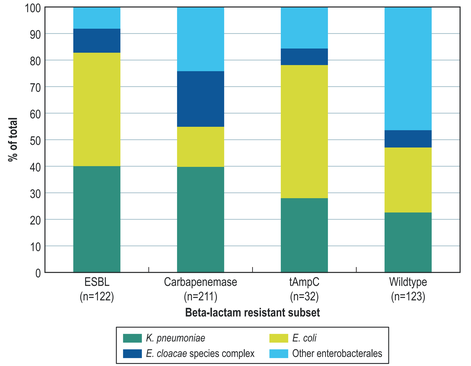
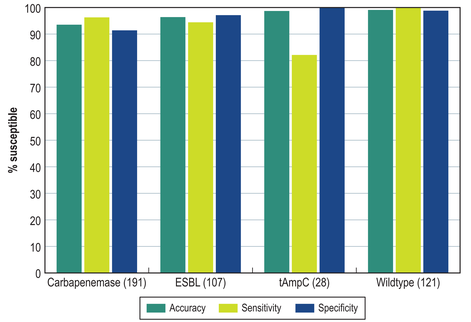


Figure 3. Accuracy, sensitivity, and specificity rates for AES β-lactam phenotype report compared to β-lactam resistant genotype



Conclusions

- VITEK2 AES correctly displayed resistance phenotypes for 96.0% (429/447) of isolates from this challenging collection of Enterobacterales harboring a variety of β-lactamase genes.
- The AES phenotypic report can be accurately applied as a rapid tool for the detection of resistance mechanisms among Enterobacterales, which could significantly aid future antimicrobial stewardship initiatives and improve patient care.

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