Molecular Epidemiology of Escherichia coli Causing Urinary Tract Infections in United States and In vitro Activity of Tebipenem, Including against Strain Lineage and Resistant Subsets (2018–2020)

R.E. Mendes1, T.B. Doyle2, I.A. Critchley3, N. Cotroneo3, J.M. Stefl2, M. Castanheira4

1JM Laboratories, North Liberty, IA, USA; 2Spero Therapeutics, Cambridge, MA, USA

Introduction

- Urinary tract infections (UTIs) are among the most common bacterial infections and the great majority of these infections are caused by Escherichia coli.
- The treatment of UTIs has become complex due to the high percentage of resistance, and approximately 20% and 25% of E. coli resistant for UTI in the United States are not susceptible to fluoroquinolones and cephalosporins, respectively (see Figure 1).
- The increase in antimicrobial resistance among isolates of E. coli has been driven mostly by the dissemination of the extraintestinal lineages belonging to sequence types (ST) 131. In general, these isolates are characterized by:
  - Serotype O157:H7
  - Fluoroquinolone resistance due to double mutations in gyrA, and
  - Plasmid-mediated resistance to antimicrobial agents such as β-lactams.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Materials and Methods

Bacterial organisms
- A total of 2,305 E. coli collected from 58 medical centers in 9 US Census Divisions were received from urine samples during the 2018–2020 STARTRAC Surveillance Program and included in the study.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing
- Isolates were tested for susceptibility to beta-lactam antibiotics following the Clinical and Laboratory Standards Institute (CLSI) (2019) guidelines.
- Phenotypic antimicrobial susceptibility patterns were produced using the automated systems according to the manufacturer’s instructions and were interpreted using CLSI-recommended quality control references.
- Isolates displaying MIC (mg/L) of ≤2 for carbapenem, aminoglycosides, and cephalosporins were selected for molecular screening of extended-spectrum β-lactamases (ESBL), plasmid-mediated AmpC, carbapenemases, and carbapenemase gene typing (MLST).
- Screening of β-lactamase genes
  - Isolates selected had their genomic DNA extracted by the fully automated Thermo Fisher Scientific’s KingFisher Flex Magnetic Particle Processor (Chesterfield, OH, USA), which was used as input material for bacterial identification and was an SG4S Sequencing platform at the JM Laboratories.
- KPC-2 formal sequencing was performed on each sample set as assembled independently for KPC-2 non-constitutively (SNAPs 3.1.0). An inhouse software was assembled to align the assembled sequences against a comprehensive KPC database containing known KPC-2 sequences.

Epidemiologic typing
- Multilocus sequence typing (MLST) was performed by extracting a defined set of housekeeping gene fragments (~500 bp). Each fragment was compared to known allelic variants for each locus.
- An allele sharing 100% genetic identity with a known variant received a numeric designation.
- For each number (1 to 6) for each housekeeping gene generated an allelic profile, defined as sequence type (ST).
- Isolates containing alleles that do not match an existing sequence in the MLST database were submitted for allele(s) and/or ST assignments.

Results

- A total of 15.0% (360/2,035) of the isolates had the MIC criteria for screening of β-lactamases and most isolates (74.7%; 269/360) carried β-lactamases and the ST131 subset (Table 2). ST131, 55 ST types were noted in isolates that met the MIC criteria for screening of β-lactamases, with most isolates belonging to ST131 (53.1%; 191/360). Carbapenem agents, including tebipenem, showed consistent activity against the isolates.
- One isolate carried β-lactamases and most isolates (74.7%; 269/360) carried β-lactamases, with most isolates belonging to ST131 (53.1%; 191/360).

Conclusions

- In general, the isolates that met the MIC criteria for screening of β-lactamases and caused UTI in the US belong to ST131.
- Isolates used to carry beta-lactamase. However, an additional subset carrying β-lactamase genes associated with group 9 were almost half of ST131 isolates.
- Carbapenem agents, including tebipenem, showed consistent activity against all isolates, regardless of resistance genotypes or strains. In addition, the tebipenem selection is dependent on β-lactamase genes (MIC > 32 mg/L) and extended-spectrum β-lactamase (ESBL) or ST131 isolate was greater than other options (MIC > 1 mg/L). This approach is effective for selecting a carbapenem as a clinical treatment option for UTI caused by E. coli in the US.

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References


Table 1. Antimicrobial activity of tebipenem and comparator agents tested against E. coli isolates included in this study

Table 2. Antimicrobial activity of tebipenem and comparator agents tested against E. coli isolates included in this study

Contact

R.E. Mendes
JM Laboratories
345 Beaver Knob Centre, Suite A
North Liberty, IA 52257
Phone: (319) 605-3370
Fax: (319) 605-3340
Email: rmendes@jm-labs.com

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