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Antimicrobial resistance of *Escherichia coli* urinary isolates in the Veterans Affairs Healthcare System

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**Running title:** *Escherichia coli* Resistance

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Abstract

We reviewed almost 300,000 clinical *E. coli* urine isolates (2009-2013) from 127 facilities to assess antibiotic resistance among Veterans Affairs healthcare system patients using Clinical Laboratory Standards Institute and Centers for Disease Control and Prevention National Healthcare Safety Network definitions/guidance. Resistance to fluoroquinolones and trimethoprim/sulfamethoxazole approached 30%. Resistance to nitrofurantoin, anti-pseudomonal penicillin/beta-lactamase inhibitors, and carbapenems remained less than 10%. The percentage of isolates that were considered multidrug-resistant varied (4.1% to 36.5%) depending on definition used.
Escherichia coli is the most clinically relevant and multiply-drug resistant bacterial pathogen causing urinary tract infections (UTI). (1, 2) Monitoring resistance is important to support clinical decision-making and public health safety. The Clinical Laboratory Standards Institute (CLSI) guidelines for clinical laboratories provide standardized methodology in the preparation and presentation of cumulative susceptibility data through use of an antibiogram. (3-5) Data from Centers for Diseases Control and Prevention (CDC’s) National Healthcare Safety Network (NHSN), are also of great value for tracking antimicrobial resistance. (6) Limited data are available to provide a comprehensive description of E. coli resistance nationally in inpatient and outpatient settings.

The Veterans Affairs’ (VA) is the nation’s largest integrated healthcare system, providing care to over 9 million Veterans in over 140 medical centers and 1200 outpatient clinics throughout the United States (US). (7) Antimicrobial susceptibility data are captured in the VA’s electronic datasets, and provide a unique opportunity to assess resistance nationally. Our intent is to describe national antimicrobial resistance rates in clinical E. coli urine isolates and to highlight differences in resistance rates using CLSI and NHSN criteria.

We retrospectively evaluated adult (age ≥18 years) VA patients with urine cultures growing E. coli between January 2009 to December 2013. We utilized three different criteria for assessing resistance: CDC’s NHSN criteria which captures the first isolate per-patient per-month; (8) CLSI guidance which recommends including only the first isolate per-patient per-year for antibiogram presentation; (3, 5) and a third method using the most resistant isolate per-person per-facility per-year since the first two approaches may underestimate overall resistance rates. (9) We removed all same day duplicate antibiotic susceptibility test results (same patient, same isolate, same day) keeping the most resistant result. (8, 10)
To classify antibiotic resistance rates, individual antibiotic agents were further categorized based on international standard definitions of the European Centre for Disease Prevention and Control (ECDC) and the CDC for Enterobacteriaceae and the CDC’s Antibiotic Resistance Patient Safety Atlas (AR Atlas) E. coli phenotype definitions.\(^{(11, 12)}\) The CDC’s AR Atlas includes data on healthcare-associated infections reported to the CDC’s NHSN. Multidrug-resistance (MDR) was defined as non-susceptibility to at least one drug in at least 3 categories, using the ECDC/CDC international standard and the CDC’s AR Atlas definitions.\(^{(11, 12)}\)

During the 5-year study, 297,046 E. coli isolates were identified from 127 sites in all 9 CDC regions using the NHSN methods (first isolate per month). Most isolates were obtained from white (74.8%) males (77.8%) in the outpatient setting (76.4%). Resistance was 34.3% for fluoroquinolones, 28.2% for trimethoprim/sulfamethoxazole, and under 10% for extended spectrum cephalosporins (6.9%), nitrofurantoin (6.2%), anti-pseudomonal penicillin/beta-lactamase inhibitors (5.3%), and carbapenems (0.4%; Table 1). Resistance rates were higher for inpatient versus outpatient isolates for all antibiotic categories assessed (Table 2) and varied by CDC region and treatment setting (Figures 1 and 2).

We identified 297,046 E. coli isolates when we included only the first (per CLSI recommendations) or most resistant isolate per patient per facility per year (Table 1). Resistance rates were similar with both methods (first isolate vs. most resistant).

In a sub-analysis, we overlaid the two different global MDR definitions. \(^{(11, 12)}\) The percentage of MDR isolates was 36.5% (108,500/297,046) using the ECDC/CDC international standard and 4.1% (12,293/297,046) using the CDC’s AR Atlas definitions. We further classified the prevalence of MDR for inpatient and outpatient isolates using both methods (ECDC/CDC: 46.6% and 33.4%,
Antimicrobial resistance among *E. coli* urinary isolates is increasing in the US.\(^\text{6, 13}\) Confusion exists when local facilities compare their CLSI-based antibiogram with national surveillance data. We identified high rates of antimicrobial resistance to several commonly used *E. coli* UTI treatment options. The overall rate of fluoroquinolone resistance using NHSN methods was 34.3%, with resistance reaching almost 50% among inpatients and 30% for outpatients similar to previous findings.\(^\text{6, 13-16}\) These findings are concerning as fluoroquinolones are frequently used empirically to treat UTIs, especially complicated infections.

Our study also demonstrated trimethoprim/sulfamethoxazole resistance approaching 30%. Several studies, including *E. coli* urinary isolates from US outpatients, have reported greater than 20% resistance to trimethoprim/sulfamethoxazole.\(^\text{15, 16}\) Trimethoprim/sulfamethoxazole should not be used for empiric treatment of acute cystitis when local antibiograms reveal 20% or greater resistance according to Infectious Diseases Society of America (IDSA) guidelines.\(^\text{2}\)

Similar to previous findings, we demonstrated that resistance to nitrofurantoin continues to remain low and this may be an appropriate option for patients with uncomplicated cystitis.\(^\text{15, 16}\) For empiric inpatient treatment options, our data suggests that anti-pseudomonal penicillin/β-lactamase inhibitors and carbapenems remain among the most active agents, similar to recent nationwide surveillance data.\(^\text{6, 13}\)

We found vast differences in the number of isolates considered MDR depending on the definition used. According to the CDC’s AR Atlas definition, 7.2% of our inpatient isolates were MDR. Similarly, 5.5-8.1% of *E. coli* causing a CAUTI reported to the CDC’s NHSN from 2011 to 2014 were MDR.\(^\text{6}\) Using the international standard MDR definition, over 45% and 30% of inpatient and outpatient isolates, respectively, were considered MDR. Our results suggest these definitions
may overestimate resistance compared to the methods used by the CDC AR Atlas.

There are several limitations to our study. We did not distinguish colonization versus true symptomatic infection. Our data represents all positive microbiologic *E. coli* urine cultures and thus represents the full ecological resistance among all cultures in the VA system. The heterogeneity among VA microbiology laboratories and the antibiotics tested also impacts our data. The CLSI MIC susceptibility breakpoints for Enterobacteriaceae have changed over time, and these changes may have been applied at different times by individual laboratories. As such, we applied the 2014 CLSI breakpoints to our data when MIC data was available. Finally, the generalizability of our results may be limited to the VA population.

In conclusion, among almost 300,000 urinary *E. coli* isolates collected from a predominately male VA outpatient population, resistance to fluoroquinolones and trimethoprim/sulfamethoxazole approached 30%. Resistance to extended-spectrum cephalosporins, nitrofurantoin, antipseudomonal penicillin/beta-lactamase inhibitors, and carbapenems remained low. Of note, the percentage of isolates that considered MDR varied considerably depending on definition used.
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Conflict of interest.

Haley J. Morrill is supported in part by a Career Development Award, Department of Veterans Affairs, and has received research funding from Merck (Cubist).

Jacob B. Morton has no conflicts.

Aisling R. Caffrey has received research funding from Pfizer Inc and Merck (Cubist).

Lan Jiang has no conflicts.

David Dosa is a Veteran’s Affairs government employee. He has received research funding through the VA, The West Foundation, and National Institutes of Aging.

Leonard A. Mermel has served as a consultant for Medicines Company and has received research support from Astrellas.

Kerry L. LaPlante has received research funding, or acted as an advisor or consultant for BARD/Davol, Merck (Cubist), Forest, and Pfizer Inc.


Table 1. *Escherichia coli* Antibiotic Resistance Among Veterans Affairs Inpatient and Outpatient Facilities Nationally by Method Used to Describe Rates Determine Rates (2009-2013)

<table>
<thead>
<tr>
<th>Antibiotic Category</th>
<th>(NHSN Methods)</th>
<th>(CLSI Methods)</th>
<th>Most Resistant Isolate Per Patient Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Isolate Per Patient Per Facility Per Month</td>
<td>First Isolate Per Patient Per Year</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>12.6 (296,022)</td>
<td>10.9 (243,577)</td>
<td>11.5 (243,590)</td>
</tr>
<tr>
<td>Antipseudomonal penicillin/ beta-lactamase inhibitor</td>
<td>5.3 (206,707)</td>
<td>4.7 (170,013)</td>
<td>5.5 (170,342)</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>0.4 (231,153)</td>
<td>0.4 (189,809)</td>
<td>0.4 (190,017)</td>
</tr>
<tr>
<td>Extended spectrum cephalosporin</td>
<td>6.9 (264,519)</td>
<td>6.0 (217,513)</td>
<td>6.5 (217,886)</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>34.3 (291,674)</td>
<td>29.5 (240,005)</td>
<td>30.4 (240,086)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>6.2 (249,096)</td>
<td>5.4 (204,526)</td>
<td>6.1 (204,611)</td>
</tr>
<tr>
<td>Amoxicillin or ampicillin/ beta-lactamase inhibitor</td>
<td>39.6 (238,738)</td>
<td>37.2 (196,203)</td>
<td>39.0 (196,450)</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>28.2 (296,501)</td>
<td>25.2 (243,957)</td>
<td>26.3 (243,982)</td>
</tr>
<tr>
<td><strong>Total Number of Isolates</strong></td>
<td><strong>297,046</strong></td>
<td><strong>244,411</strong></td>
<td><strong>244,411</strong></td>
</tr>
</tbody>
</table>

CDC= Centers for Disease Control and Prevention; CLSI= Clinical and Laboratory Standards Institute; NHSN= National Healthcare Safety Network
Data are % non-susceptible (number of isolates tested)

Aminoglycoside category included amikacin, gentamicin, and tobramycin.

Antipseudomonal penicillin/ beta-lactamase inhibitor category included piperacillin/tazobactam and ticarcillin/clavulanic acid.

Carbapenem category included imipenem, meropenem, doripenem, and ertapenem.

Extended spectrum cephalosporin category included ceftriaxone, ceftazidime, cefotaxime, and cefepime.

Fluoroquinolone category included levofloxacin and ciprofloxacin.

Amoxicillin or ampicillin/ beta-lactamase inhibitor category included amoxicillin/clavulanic acid and ampicillin/sulbactam.
Table 2. *Escherichia coli* Antibiotic Resistance Among Veterans Affairs Inpatient and Outpatient Facilities Nationally by Healthcare Setting (2009-2013)*

<table>
<thead>
<tr>
<th>Antibiotic Category</th>
<th>Overall</th>
<th>Inpatient</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>12.6 (296,022)</td>
<td>17.4 (69,824)</td>
<td>11.1 (226,198)</td>
</tr>
<tr>
<td>Antipseudomonal penicillin/beta-lactamase inhibitor</td>
<td>5.3 (206,707)</td>
<td>8.0 (50,795)</td>
<td>4.5 (155,912)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>0.4 (231,153)</td>
<td>0.5 (55,643)</td>
<td>0.4 (175,510)</td>
</tr>
<tr>
<td>Extended-spectrum cephalosporin</td>
<td>6.9 (264,519)</td>
<td>11.3 (63,706)</td>
<td>5.4 (200,813)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>34.3 (291,674)</td>
<td>46.5 (68,659)</td>
<td>30.5 (223,015)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>6.2 (249,096)</td>
<td>7.0 (56,025)</td>
<td>6.0 (193,071)</td>
</tr>
<tr>
<td>Amoxicillin or ampicillin/beta-lactamase inhibitor</td>
<td>39.6 (238,738)</td>
<td>47.7 (56,168)</td>
<td>37.0 (182,570)</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>28.2 (296,501)</td>
<td>35.6 (69,958)</td>
<td>26.0 (226,543)</td>
</tr>
<tr>
<td><strong>Total Number of Isolates</strong></td>
<td><strong>297,046</strong></td>
<td><strong>70,101</strong></td>
<td><strong>226,945</strong></td>
</tr>
</tbody>
</table>

Results by healthcare setting include the first isolate per patient per facility per month (CDC NHSN Methods)*
 CDC= Centers for Disease Control and Prevention; CLSI= Clinical and Laboratory Standards Institute; NHSN= National Healthcare Safety Network

Data are % non-susceptible (number of isolates tested)

Aminoglycoside category included amikacin, gentamicin, and tobramycin.

Antipseudomonal penicillin/ beta-lactamase inhibitor category included piperacillin/tazobactam and ticarcillin/clavulanic acid.

Carbapenem category included imipenem, meropenem, doripenem, and ertapenem.

Extended spectrum cephalosporin category included ceftriaxone, ceftazidime, cefotaxime, and cefepime.

Fluoroquinolone category included levofloxacin and ciprofloxacin.

Amoxicillin or ampicillin/ beta-lacamase/beta-lactamase inhibitor category included amoxicillin/clavulanic acid and ampicillin/sulbactam.
Figure 1. *Escherichia coli* Antibiotic Resistance Among Veterans Affairs Inpatient Facilities Nationally by CDC Region (2009-2013)*

Results by CDC region include the first isolate per patient per facility per month (CDC NHSN Methods)*

CDC= Centers for Disease Control and Prevention; E N Central= East North Central Region; E S Central= East South Central Region; ES Ceph= Extended spectrum cephalosporin; FQ= Fluoroquinolone; Mid Atlantic= Middle Atlantic Region; Mountain=Mountain Region; New England= New England Region; Pacific= Pacific Region; S Atlantic= South Atlantic Region; W N Central= West North Central Region; W S Central= West South Central Region

Data are % non-susceptible (total number of isolates tested). Not every antibiotic category tested for every isolate tested.

Carbapenem category included imipenem, meropenem, doripenem, and ertapenem.

Extended-spectrum cephalosporin category included ceftriaxone, ceftazidime, cefotaxime, and cefepime.

Fluoroquinolone category included levofloxacin and ciprofloxacin.
Figure 2. *Escherichia coli* Antibiotic Resistance Among Veterans Affairs Outpatient Facilities Nationally by CDC Region (2009-2013)*

Results by CDC region include the first Isolate per patient per facility per month (CDC NHSN Methods)*

CDC= Centers for Disease Control and Prevention; E N Central= East North Central Region; E S Central= East South Central Region; ES Ceph= Extended spectrum cephalosporin; FQ= Fluoroquinolone; Mid Atlantic= Middle Atlantic Region; Mountain=Mountain Region; New England= New England Region; Pacific= Pacific Region; S Atlantic= South Atlantic Region; W N Central= West North Central Region; W S Central= West South Central Region

Data are % non-susceptible (total number of isolates tested). Not every antibiotic category tested for every isolate tested.

Carbapenem category included imipenem, meropenem, doripenem, and ertapenem.

Extended-spectrum cephalosporin category included ceftriaxone, ceftazidime, cefotaxime, and cefepime.

Fluoroquinolone category included levofloxacin and ciprofloxacin.