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

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

3

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

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1 **Abstract**

2 **Word Count: 75 words**

3 We reviewed almost 300,000 clinical *E. coli* urine isolates (2009-2013) from 127 facilities to
4 assess antibiotic resistance among Veterans Affairs healthcare system patients using Clinical
5 Laboratory Standards Institute and Centers for Disease Control and Prevention National
6 Healthcare Safety Network definitions/guidance. Resistance to fluoroquinolones and
7 trimethoprim/sulfamethoxazole approached 30%. Resistance to nitrofurantoin, anti-pseudomonal
8 penicillin/beta-lactamase inhibitors, and carbapenems remained less than 10%. The percentage
9 of isolates that were considered multidrug-resistant varied (4.1% to 36.5%) depending on
10 definition used.

11

1 **Word Count: 996** words

2 *Escherichia coli* is the most clinically relevant and multiply-drug resistant bacterial pathogen
3 causing urinary tract infections (UTI).(1, 2) Monitoring resistance is important to support clinical
4 decision-making and public health safety. The Clinical Laboratory Standards Institute (CLSI)
5 guidelines for clinical laboratories provide standardized methodology in the preparation and
6 presentation of cumulative susceptibility data through use of an antibiogram.(3-5) Data from
7 Centers for Diseases Control and Prevention (CDC's) National Healthcare Safety Network
8 (NHSN), are also of great value for tracking antimicrobial resistance.(6) Limited data are available
9 to provide a comprehensive description of *E. coli* resistance nationally in inpatient and outpatient
10 settings.

11
12 The Veterans Affairs (VA) is the nation's largest integrated healthcare system, providing care to
13 over 9 million Veterans in over 140 medical centers and 1200 outpatient clinics throughout the
14 United States (US).(7) Antimicrobial susceptibility data are captured in the VA's electronic
15 datasets, and provide a unique opportunity to assess resistance nationally. Our intent is to
16 describe national antimicrobial resistance rates in clinical *E. coli* urine isolates and to highlight
17 differences in resistance rates using CLSI and NHSN criteria.

18
19 We retrospectively evaluated adult (age ≥ 18 years) VA patients with urine cultures growing *E. coli*
20 between January 2009 to December 2013. We utilized three different criteria for assessing
21 resistance: CDC's NHSN criteria which captures the first isolate per-patient per-month;(8) CLSI
22 guidance which recommends including only the first isolate per-patient per-year for antibiogram
23 presentation;(3, 5) and a third method using the most resistant isolate per-person per-facility per-
24 year since the first two approaches may underestimate overall resistance rates.(9) We removed
25 all same day duplicate antibiotic susceptibility test results (same patient, same isolate, same day)
26 keeping the most resistant result.(8, 10)

1
2 To classify antibiotic resistance rates, individual antibiotic agents were further categorized based
3 on international standard definitions of the European Centre for Disease Prevention and Control
4 (ECDC) and the CDC for Enterobacteriaceae and the CDC's Antibiotic Resistance Patient Safety
5 Atlas (AR Atlas) *E. coli* phenotype definitions.(11, 12) The CDC's AR Atlas includes data on
6 healthcare-associated infections reported to the CDC's NHSN. Multidrug-resistance (MDR) was
7 defined as non-susceptibility to at least one drug in at least 3 categories, using the ECDC/CDC
8 international standard and the CDC's AR Atlas definitions.(11, 12)

9
10 During the 5-year study, 297,046 *E. coli* isolates were identified from 127 sites in all 9 CDC regions
11 using the NHSN methods (first isolate per month). Most isolates were obtained from white
12 (74.8%) males (77.8%) in the outpatient setting (76.4%). Resistance was 34.3% for
13 fluoroquinolones, 28.2% for trimethoprim/sulfamethoxazole, and under 10% for extended
14 spectrum cephalosporins (6.9%), nitrofurantoin (6.2%), anti-pseudomonal penicillin/beta-
15 lactamase inhibitors (5.3%), and carbapenems (0.4%; **Table 1**). Resistance rates were higher
16 for inpatient versus outpatient isolates for all antibiotic categories assessed (**Table 2**) and varied
17 by CDC region and treatment setting (**Figures 1 and 2**).

18
19 We identified 297,046 *E. coli* isolates when we included only the first (per CLSI recommendations)
20 or most resistant isolate per patient per facility per year (**Table 1**). Resistance rates were similar
21 with both methods (first isolate vs. most resistant).

22
23 In a sub-analysis, we overlaid the two different global MDR definitions. (11, 12) The percentage
24 of MDR isolates was 36.5% (108,500/297,046) using the ECDC/CDC international standard and
25 4.1% (12,293/297,046) using the CDC's AR Atlas definitions. We further classified the prevalence
26 of MDR for inpatient and outpatient isolates using both methods (ECDC/CDC: 46.6% and 33.4%,

1 CDC AR Atlas: 7.2% and 3.2%, respectively).

2

3 Antimicrobial resistance among *E. coli* urinary isolates is increasing in the US.(6, 13) Confusion
4 exists when local facilities compare their CLSI-based antibiogram with national surveillance data.

5 We identified high rates of antimicrobial resistance to several commonly used *E. coli* UTI
6 treatment options. The overall rate of fluoroquinolone resistance using NHSN methods was
7 34.3%, with resistance reaching almost 50% among inpatients and 30% for outpatients similar to
8 previous findings.(6, 13-16) These findings are concerning as fluoroquinolones are frequently
9 used empirically to treat UTIs, especially complicated infections.

10

11 Our study also demonstrated trimethoprim/sulfamethoxazole resistance approaching 30%.
12 Several studies, including *E. coli* urinary isolates from US outpatients, have reported greater than
13 20% resistance to trimethoprim/sulfamethoxazole.(15, 16) Trimethoprim/sulfamethoxazole
14 should not be used for empiric treatment of acute cystitis when local antibiograms reveal 20% or
15 greater resistance according to Infectious Diseases Society of America (IDSA) guidelines.(2)
16 Similar to previous findings, we demonstrated that resistance to nitrofurantoin continues to remain
17 low and this may be an appropriate option for patients with uncomplicated cystitis.(15, 16) For
18 empiric inpatient treatment options, our data suggests that anti-pseudomonal penicillin/beta-
19 lactamase inhibitors and carbapenems remain among the most active agents, similar to recent
20 nationwide surveillance data.(6, 13)

21

22 We found vast differences in the number of isolates considered MDR depending on the definition
23 used. According to the CDC's AR Atlas definition, 7.2% of our inpatient isolates were MDR.
24 Similarly, 5.5-8.1% of *E. coli* causing a CAUTI reported to the CDC's NHSN from 2011 to 2014
25 were MDR.(6) Using the international standard MDR definition, over 45% and 30% of inpatient
26 and outpatient isolates, respectively, were considered MDR. Our results suggest these definitions

1 may overestimate resistance compared to the methods used by the CDC AR Atlas.

2

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

11

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

17

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5

6 *Conflict of interest.*

7 Haley J. Morrill is supported in part by a Career Development Award, Department of Veterans
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9 Jacob B. Morton has no conflicts.

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

11 Lan Jiang has no conflicts.

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18 .

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23 Resistance among Urinary Isolates from Female Outpatients in the United States in
24 2003 and 2012. *Antimicrob Agents Chemother* **60**:2680-2683.
25

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

4

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

5 CDC= Centers for Disease Control and Prevention; CLSI= Clinical and Laboratory Standards
 6 Institute; NHSN= National Healthcare Safety Network

7

- 1 Data are % non-susceptible (number of isolates tested)
- 2
- 3 Aminoglycoside category included amikacin, gentamicin, and tobramycin.
- 4 Antipseudomonal penicillin/ beta-lactamase inhibitor category included piperacillin/tazobactam
- 5 and ticarcillin/clavulanic acid.
- 6 Carbapenem category included imipenem, meropenem, doripenem, and ertapenem.
- 7 Extended spectrum cephalosporin category included ceftriaxone, ceftazidime, cefotaxime, and
- 8 cefepime.
- 9 Fluoroquinolone category included levofloxacin and ciprofloxacin.
- 10 Amoxicillin or ampicillin/ beta-lactamase inhibitor category included amoxicillin/clavulanic acid
- 11 and ampicillin/sulbactam.
- 12

1 **Table 2. *Escherichia coli* Antibiotic Resistance Among Veterans Affairs Inpatient and**
 2 **Outpatient Facilities Nationally by Healthcare Setting (2009-2013)***

3

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

4 Results by healthcare setting include the first Isolate per patient per facility per month (CDC NHSN
 5 Methods)*

6

1 CDC= Centers for Disease Control and Prevention; CLSI= Clinical and Laboratory Standards
2 Institute; NHSN= National Healthcare Safety Network
3
4 Data are % non-susceptible (number of isolates tested)
5
6 Aminoglycoside category included amikacin, gentamicin, and tobramycin.
7 Antipseudomonal penicillin/ beta-lactamase inhibitor category included piperacillin/tazobactam
8 and ticarcillin/clavulanic acid.
9 Carbapenem category included imipenem, meropenem, doripenem, and ertapenem.
10 Extended spectrum cephalosporin category included ceftriaxone, ceftazidime, cefotaxime, and
11 cefepime.
12 Fluoroquinolone category included levofloxacin and ciprofloxacin.
13 Amoxicillin or ampicillin/ beta-lactamase/beta-lactamase inhibitor category included
14 amoxicillin/clavulanic acid and ampicillin/sulbactam.
15

1 **Figure 1. *Escherichia coli* Antibiotic Resistance Among Veterans Affairs Inpatient Facilities Nationally by CDC Region (2009-**
2 **2013)***

3
4 Results by CDC region include the first Isolate per patient per facility per month (CDC NHSN Methods)*

5
6
7 CDC= Centers for Disease Control and Prevention; E N Central= East North Central Region; E S Central= East South Central Region;
8 ES Ceph= Extended spectrum cephalosporin; FQ= Fluoroquinolone; Mid Atlantic= Middle Atlantic Region; Mountain=Mountain Region;
9 New England= New England Region; Pacific= Pacific Region; S Atlantic= South Atlantic Region; W N Central= West North Central Region;
10 W S Central= West South Central Region

11
12 Data are % non-susceptible (total number of isolates tested). Not every antibiotic category tested for every isolate tested.

13
14 Carbapenem category included imipenem, meropenem, doripenem, and ertapenem.

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

16 Fluoroquinolone category included levofloxacin and ciprofloxacin.

1 **Figure 2. *Escherichia coli* Antibiotic Resistance Among Veterans Affairs Outpatient Facilities Nationally by CDC Region (2009-**
2 **2013)***

3
4 Results by CDC region include the first Isolate per patient per facility per month (CDC NHSN Methods)*

5
6
7 CDC= Centers for Disease Control and Prevention; E N Central= East North Central Region; E S Central= East South Central Region;
8 ES Ceph= Extended spectrum cephalosporin; FQ= Fluoroquinolone; Mid Atlantic= Middle Atlantic Region; Mountain=Mountain Region;
9 New England= New England Region; Pacific= Pacific Region; S Atlantic= South Atlantic Region; W N Central= West North Central Region;
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16 Fluoroquinolone category included levofloxacin and ciprofloxacin.