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## Clonal distribution and associated characteristics of *Escherichia coli* clinical and surveillance isolates from a military medical center



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### ABSTRACT

Antimicrobial-resistant *Escherichia coli* are a concern for military health services. We studied 100 extended-spectrum beta-lactamase (ESBL)-producing and non-producing *E. coli* clinical and surveillance isolates from military personnel and civilians at Brooke Army Medical Center (2007–2011). Major *E. coli* lineages, most prominently ST10 (24%), ST131 (16%), and ST648 (8%), were distributed much as reported for other North American populations. ST131, represented mainly by its resistance-associated ST131-H30 clonal subset, was uniquely associated with a clinical origin, regardless of ESBL status. Thus, clonal background predicted resistance phenotype and clinical versus surveillance origin, and these findings could assist military clinicians and epidemiologists.

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## 1. Introduction

Extraintestinal pathogenic *Escherichia coli* (ExPEC) cause most community and hospital-associated extraintestinal *E. coli* infections (Johnson and Russo, 2005). Specific ExPEC lineages, or sequence types (STs), are commonly multidrug-resistant (MDR), and have been associated with international travel and medical care. The acquisition of difficult-to-treat, antimicrobial-resistant ExPEC is therefore a concern for military health services.

In this study, we examined the distribution of *E. coli* genotypes identified among clinical and surveillance (e.g. skin colonization) isolates from deployed and non-deployed active duty US military personnel and civilians, collected as part of routine medical care at a US military medical center. Stool surveillance isolates were not included in this study. We sought to determine whether military personnel (especially

those with a history of international deployment or injury), when infected or colonized cutaneously with *E. coli*, were at an increased risk of having specific extensively drug-resistant major lineages of ExPEC. In addition, we attempted to define the characteristics of these lineages as they occur among military personnel. We focused specifically on the presence of sequence type 131 (ST131) and its resistance-associated H30 and H30Rx subclones within this population, and compared these strains' prevalence with data collected from veterans receiving care within the Veterans Health Administration in 2011 (Colpan et al., 2013).

## 2. Materials and methods

### 2.1. Isolates and subjects

The study isolates included 100 de-identified archival *E. coli* clinical and surveillance isolates, which were obtained along with associated information (specimen type, collection date, collection site, isolate source, injury during deployment, etc.) from the Molecular Biology Laboratory at Brooke Army Medical Center, JBSA Fort Sam Houston, TX. The isolates had been recovered

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**Table 1**Extraintestinal pathogenic *Escherichia coli* source and characteristics.

Host characteristic, phylogroup, or ST <sup>a</sup>	Prevalence of trait, No. of isolates (%)					
	Total (n = 100)	Clinical (n = 25)		Surveillance (n = 25)		P value <sup>b</sup>
		ESBL-producing	Non-ESBL-producing	ESBL-producing	Non-ESBL-producing	
Active duty	84 (84)	18 (72)	20 (80)	22 (88)	24 (96)	0.11
Deployment injury	65 (65)	11 (44)	1 (4)	19 (76)	18 (72)	<0.001
Group A	30 (30)	8 (32)	4 (16)	10 (40)	8 (32)	0.31
Group B1	13 (13)	2 (8)	3 (12)	3 (12)	5 (20)	0.73
Group B2	31 (31)	8 (32)	14 (56)	2 (8)	7 (28)	0.003
Group C	2 (2)	1 (4)	1 (4)	0 (0)	0 (0)	n.a. <sup>c</sup>
Group D	16 (16)	5 (20)	1 (4)	5 (20)	5 (20)	0.26
Group F	8 (8)	1 (4)	2 (8)	5 (20)	0 (0)	0.08
ST10 (group A)	24 (24)	8 (32)	1 (4)	7 (28)	8 (32)	0.06
ST131 (group B2)	16 (16)	8 (32)	6 (24)	1 (4)	1 (4)	0.01
ST131 H30	14 (14)	6 (24)	6 (24)	1 (4)	1 (4)	0.60
ST131 H30Rx	8 (8)	4 (16)	3 (12)	0 (0)	1 (4)	n.a. <sup>c</sup>
ST131 non-H30	2 (2)	2 (8)	0 (0)	0 (0)	0 (0)	n.a. <sup>c</sup>
ST648 (group F)	8 (8)	1 (4)	2 (8)	5 (20)	0 (0)	n.a. <sup>c</sup>

<sup>a</sup> ST = sequence type. Only the three most prevalent STs are shown. Other STs that accounted for  $\geq 3\%$  of isolates each, in order of descending overall prevalence (no. of isolates), included: ST38 (5%), ST95 (5%), ST69 (4%), ST405 (4%), and ST73 (3%).

<sup>b</sup> By Fisher's exact test (two-tailed), for four-group comparisons.

<sup>c</sup> n.a., not applicable (number too small for statistical analysis).

between 2007 and 2011 from 100 unique military personnel and civilians attending the same military medical center (Table 1) and had been tested for extended-spectrum beta-lactamase (ESBL) production, as described below. The archival collections included isolates from patients with a suspected infection (clinical) or who were being screened for antimicrobial-resistant *E. coli* from nares or groin skin sites (surveillance). The 100 study isolates were selected randomly as four groups of 25 isolates each: (i) ESBL-producing clinical isolates, (ii) non-ESBL-producing clinical isolates, (iii) ESBL-producing surveillance isolates, and (iv) non-ESBL-producing surveillance isolates (Table 1). Specimen type and the subject's military versus civilian status and deployment history did not influence isolate selection.

The study was approved by research oversight committees at the participating institutions. It did not qualify for review by the respective institutional review boards due to its use of archived isolates that had been collected for routine monitoring purposes, along with generic deidentified epidemiological data.

## 2.2. Laboratory analysis

Antimicrobial susceptibilities and ESBL production was determined using the BD Phoenix Automated Microbiology System (Becton Dickinson and Company, Sparks, MD, USA) per manufacturer guidelines utilizing NMIC/ID-123 panels. Minimum inhibitory concentration (MIC) results were interpreted according to the Clinical Laboratory and Standards Institute criteria (Clinical and Laboratory Standards Institute, 2013). In addition, isolates were assessed molecularly for *bla*<sub>CTX-M-15</sub>, major *E. coli* phylogenetic group (phylogroup) (Clermont et al., 2013), ST or ST complex (STc; as determined by *fumC-fimH* typing (Weissman et al., 2012), full or partial MLST (Maiden et al., 1998), or STc-specific PCR assays (Clermont et al., 2014; Johnson et al., 2009; Matsumura et al., 2012)), membership in the ST131-H30 clonal subset or its sublineage ST131-H30Rx (Banerjee et al., 2013), O type (O16 and O25b only) (Johnson et al., 2014), and extended virulence genotype (for 50 markers) (Johnson et al., 2015). Resistance scores were defined as the number of antibiotic classes to which an isolate exhibited resistance. Virulence scores were defined based on the raw count of detected virulence genes.

## 2.3. Statistical analysis

Comparisons of proportions were tested using Fisher's exact or chi-squared tests. Comparisons of scores were tested using the Wilcoxon rank-sum test.

## 3. Results

### 3.1. Clinical and epidemiological data

The 100 source subjects included 84 (84%) active duty military personnel and 16 (16%) civilians receiving care at Brooke Army Medical Center (Table 1). Of 65 subjects with a known injury, 49 (75%) were injured during military deployment, which occurred exclusively in Iraq and/or Afghanistan. *E. coli* isolates recovered from these 49 deployed and injured military members included 10 isolates from wound sites, 2 from blood and 37 collected from the groin area, as part of surveillance sampling. The 50 clinical isolates were from urine ( $n = 18$ ), blood ( $n = 8$ ), wound ( $n = 23$ ), and body fluid ( $n = 1$ ). The 50 surveillance isolates were from groin ( $n = 49$ ) and nares ( $n = 1$ ).

### 3.2. Phylogroups

The 4 most common *E. coli* phylogroups overall, in descending frequency, were B2 (31%), A (30%), D (16%), and B1 (13%) (Table 1). Phylogroup B2 isolates were uniquely over-represented among the clinical isolates. Phylogroup A isolates (specifically ST10), although somewhat more common among surveillance than clinical isolates, were more common among clinical isolates than expected based on prior work (Salipante et al., 2015).

### 3.3. Sequence Types

The 8 most common STs, in descending frequency, were ST10 (24%), ST131 (16%), ST648 (8%), ST38 (5%), ST95 (5%), ST69 (4%), ST405 (4%), and ST73 (3%). Collectively, these 8 predominant STs accounted for 69% of the population. No temporal prevalence trends were apparent for any specific STs (not shown).

Statistical comparisons were done only with the 3 most common STs. ST10 was under-represented among non-ESBL-producing clinical isolates, whereas ST648 was over-represented among ESBL-producing surveillance isolates and absent among non-ESBL surveillance isolates. The combined prevalence of the three most common STs (ST10, 131, and 648) varied by host group, i.e., 36/84 (43%) for active duty subjects (including 24/49 [49%] for subjects with deployment-related wounds), versus 12/16 (75%) for civilian subjects ( $p = 0.02$ ).

ST131, the most prevalent ST among clinical isolates, was the only ST that was significantly over-represented among clinical isolates as

compared with surveillance isolates, regardless of ESBL status (Table 1). Fourteen (88%) of the 16 ST131 isolates belonged to the H30 subclone, with 8 (50%) of the H30 isolates belonging to the H30Rx sublineage. All ST131 isolates were O25b-positive except for one, which was non-H30 and O16-positive. ST131, H30, and H30Rx isolates were similarly prevalent among clinical isolates from active duty personnel versus civilians, and from subjects with deployment-related injuries versus other sources (not shown).

### 3.4. *bla*<sub>CTX-M-15</sub>

Overall, 31 (62%) of the 50 ESBL-producing isolates contained *bla*<sub>CTX-M-15</sub>, which was similarly prevalent among clinical and surveillance isolates (14/25 [56%] versus 17/25 [68%];  $p = 0.38$ ). *bla*<sub>CTX-M-15</sub> was not associated with active duty status or deployment injury (not shown). ST131 accounted for 7 (14%) ESBL-producing and 5 (16%) *bla*<sub>CTX-M-15</sub>-carrying isolates, with the majority of these belonging to the H30Rx ST131 subclone. In contrast, ST10 accounted for 15 (30%) ESBL-producing and 12 (39%) *bla*<sub>CTX-M-15</sub>-carrying isolates.

### 3.5. Virulence Scores

Overall, virulence scores were higher among non-ESBL-producers than ESBL-producers (median, 8.5 versus 6, respectively;  $P = 0.02$ ), regardless of clinical versus surveillance source. In contrast, they were similar among isolates from active duty personnel (median 7, range 1–24), including those with deployment-related injuries (median 7, range 1–22), and civilians (median 6.5, range 2–24).

Median virulence scores varied greatly between the 3 most common STs, with ST131 highest (11, range 6–15), ST648 intermediate (7.5, range 6–11), and ST10 lowest (4, range 2–12). They also varied greatly by phylogroup, with group B2 highest (12, range 6–24), groups D (8, range 4–16) and F (7.5, range 6–11) intermediate, and groups A (4, range 2–12) and B1 (2, range 1–8) lowest.

### 3.6. Antimicrobial resistance

The proportions of isolates exhibiting resistance to specific antimicrobial agents and classes varied significantly by study group (Table 2). Whether assessed by prevalence or resistance scores, resistance to the studied antimicrobial agents was associated closely with ESBL status, but minimally with clinical versus surveillance source. All but one of the isolates with a resistance score  $\geq 6$  ( $n = 39$ ) was ESBL-positive. Resistance scores were slightly higher among isolates from civilians (median, 5.5) versus active duty personnel (median, 5.0) ( $P = 0.09$ ). Among clinical isolates from active duty personnel, resistance scores were similar regardless of the subject's deployment-related injury history ( $P = 0.45$ ).

### 3.7. ST131 prevalence comparison with 2011 data from US veterans

A recent study determined that among *E. coli* clinical isolates from 24 VA medical centers across the U.S. *E. coli* ST131 (predominantly ST131-H30) accounted for 7% of fluoroquinolone-susceptible, 78% of fluoroquinolone-resistant, and 64% of ESBL-producing isolates, and for 28% of *E. coli* isolates overall (Colpan et al., 2013). Based on the 2% overall prevalence of ceftriaxone resistance (a proxy for ESBL production) in that study's source population (Colpan et al., 2013), back calculations indicated that ST131 accounted for 26% of that study's non-ESBL producing *E. coli* isolates. Thus, the estimated prevalence of ST131 among clinical *E. coli* isolates in that study versus the present study was 64% versus 32% for ESBL-producing isolates, and 26% versus 24% for non-ESBL-producing isolates.

## 4. Discussion

In this study we analyzed the clonal background, resistance characteristics, and virulence genotypes of 100 clinical and surveillance *E. coli* isolates collected from military personnel and civilians at a US military medical center. We sought to determine whether distinctive lineages

**Table 2**  
Proportion of *Escherichia coli* isolates resistant to specific antimicrobial classes and agents.

Antimicrobial class or agent <sup>b</sup>	Resistance prevalence, no. isolates (%)				
	Total ( $n = 100$ )	ESBL <sup>a</sup> -producers		ESBL <sup>a</sup> -non-producers	
		Clinical ( $n = 25$ )	Surveillance ( $n = 25$ )	Clinical ( $n = 25$ )	Surveillance ( $n = 25$ )
Any aminoglycoside	43 (43)	16 (64)	15 (60)	7 (28)	5 (20)
Gentamicin	36 (36)	15 (60)	11 (44)	5 (20)	5 (20)
Amikacin	3 (3)	1 (4)	0 (0)	2 (8)	0 (0)
Tobramycin	35 (35)	14 (56)	13 (52)	6 (24)	2 (8)
Any penicillin	83 (83)	25 (100)	25 (100)	19 (76)	14 (56)
Ampicillin	83 (83)	25 (100)	25 (100)	19 (76)	14 (56)
Ampicillin-sulbactam	68 (68)	25 (100)	25 (100)	12 (48)	6 (24)
Piperacillin-tazobactam	7 (7)	3 (12)	3 (12)	1 (4)	0 (0)
Monobactam (aztreonam)	48 (48)	25 (100)	23 (92)	0 (0)	0 (0)
Any cephalosporin	59 (59)	25 (100)	23 (92)	8 (32)	3 (12)
Cefazolin	59 (59)	25 (100)	23 (92)	8 (32)	3 (12)
Cefepime	49 (49)	25 (100)	23 (92)	1 (4)	0 (0)
Cefoxitin	5 (5)	2 (8)	2 (8)	1 (4)	0 (0)
Ceftazidime	48 (48)	25 (100)	23 (92)	0 (0)	0 (0)
Ceftriaxone	48 (48)	23 (92)	22 (88)	3 (12)	n.d. <sup>e</sup>
Cefuroxime	52 (52)	25 (100)	23 (92)	4 (16)	0 (0)
Any quinolone	58 (58)	21 (84)	16 (64)	13 (52)	8 (32)
Ciprofloxacin	58 (58)	21 (84)	16 (64)	13 (52)	8 (32)
Levofloxacin	57 (57)	21 (84)	16 (64)	12 (48)	8 (32)
Nitrofurans (nitrofurantoin)	2 (2)	1 (4)	1 (4)	0 (0)	0 (0)
Tetracyclines (tetracycline)	68 (68)	18 (72)	24 (96)	12 (48)	14 (56)
Anti-folate agents (TMP-SMZ) <sup>c</sup>	67 (67)	23 (92)	22 (88)	12 (48)	10 (40)
$\geq 3$ antibiotic classes (MDR) <sup>d</sup>	77 (77)	25 (100)	25 (100)	14 (56)	13 (52)

<sup>a</sup> ESBL, extended-spectrum beta-lactamase.

<sup>b</sup> Antimicrobial classes are listed first, followed by the corresponding individual agents that were tested. No resistance was detected to carbapenems (imipenem, meropenem).

<sup>c</sup> TMP-SMZ, trimethoprim-sulfamethoxazole.

<sup>d</sup> MDR, multidrug-resistant.

<sup>e</sup> n.d., not done.

predominate among such isolates, the degree of similarity between surveillance versus clinical isolates or isolates from active duty personnel versus civilians, and the comparative prevalence of ST131-H30 in this population versus among military veterans. The observed clonal distribution largely resembled that expected for North American human *E. coli* isolates, with a marked predominance among clinical isolates of ST131, specifically its H30 subclone (Salipante et al., 2015). ST10 was more prevalent among clinical isolates than expected, which could be due to a greater frequency of cutaneous carriage (Table 1). Associations of resistance and virulence traits with clonal background and ecological source followed well-established patterns. Thus, ST131-H30 and ST10 contribute importantly to extraintestinal (especially MDR) *E. coli* infections among military personnel and associated civilians, possibly justifying special diagnostic and surveillance efforts directed toward them.

Notably, all 4 isolate groups (as defined based on clinical versus surveillance origin and ESBL phenotype) were quite diverse microbiologically, and their predominant STs were familiar contributors to infections and/or resistance. As such, we found no evidence of an unrecognized clonal outbreak or endemic focus, especially one involving a novel *E. coli* strain. Although the risk of multidrug-resistant *E. coli* and ExPEC acquisition from international settings clearly is high, and outbreaks stemming from military deployment are critical to the public health of active duty military members and civilians (CDC, 2004), our findings suggest that “the usual suspects”, led by ST131-H30, are also prevalent in the military health system. Thus, any future *E. coli* rapid diagnostics developed for general use should prove useful also within the military.

The third most common clonal group, ST648, is increasingly reported as an emerging MDR pathogen in the literature (Zhang et al., 2016). In our study, it accounted for all group F study isolates, and was linked to ESBL production among surveillance isolates. However, it contributed minimally to the clinical isolate population.

A comparison of the present data with the findings of Colpan et al. regarding clinical *E. coli* isolates from 24 Veterans Affairs medical centers in 2011 (Colpan et al., 2013) showed that, here, ST131 and ST131-H30 accounted for only half as great a proportion of ESBL-producing isolates (i.e., 32% versus 64%), but a fairly similar proportion of non-ESBL-producing or total isolates (26% versus 24%). Further study would be needed to clarify the basis for these findings.

Study limitations include the relatively small sample size and the limited availability of subject data, which restricted the range of epidemiological analyses. Study strengths include the unique study population and the isolates’ extensive molecular characterization.

## 5. Conclusion

We found a predominance of ST131-H30 and ST10 among clinical and surveillance *E. coli* isolates from a military medical center. ST131 and H30 were strongly – and uniquely – associated with a clinical origin, irrespective of ESBL status, supporting special pathogenicity for these lineages, and in comparison with clinical isolates from US military veterans were similarly common overall, although less common among ESBL-producing isolates. Resistance traits, virulence genes, and clonal/phylogenetic groups exhibited familiar associations. Our findings provide potentially useful insights into the clonal distribution and associated characteristics of *E. coli* from military personnel and civilians.

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## Conflicts of Interest

Dr. Johnson has received research funding from Merck, Actavis/Forest, and Tetrphase, is a consultant for Janssen/Crucell, and has patent applications for tests to detect *E. coli* strains. Dr. Sokurenko has patent applications to detect *E. coli* strains and is a major shareholder in IDGenomics. The other authors report no financial conflicts of interest.

## Prior Presentation

None.

## Disclaimer

The opinions expressed here are strictly those of the authors and do not necessarily reflect those of the author’s respective institutions, the Department of Veterans Affairs, the Department of the Army, the Department of Defense, or the National Institutes of Health.

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