The Niche for *Escherichia coli* Sequence Type 131 Among Veterans: Urinary Tract Abnormalities and Long-Term Care Facilities

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**Background.** Antimicrobial resistance among *Escherichia coli* is increasing, driven largely by the global emergence of sequence type 131 (ST131). However, the clinical significance of ST131 status is unknown. Among veterans, we assessed whether ST131 causes more severe, persistent, or recurrence-prone infections than non-ST131 *E. coli*.

**Methods.** Isolates were assessed by polymerase chain reaction for membership in ST131 and relevant subclones thereof (H30R and H30Rx) and by broth microdilution for susceptibility to 11 antibiotics. Clinical and epidemiological data were systematically abstracted from the medical record. Between-group comparisons were made using t tests and Fisher’s exact test.

**Results.** Of the 311 unique *E. coli* isolates, 61 (19.6%) represented ST131. Of these, most (51 of 61, 83.6%) represented the H30R subclone; only 5 of 51 (9.8%) represented H30Rx. Relative to non-ST131 and non-H30R isolates, neither ST131 nor H30R were associated with more severe disease, worse clinical outcomes, or more robust hosts. Instead, both were more likely to be isolated from patients without manifestations of infection (for ST131, 36.1% vs 21.2% \(P=0.008\); for H30R, 39% vs 21% \(P=0.002\)) and who had prior healthcare contact or long-term care facility (LTCF) exposure (for ST131, 33% vs 14% \(P<0.001\)). Despite a greater likelihood of discordant initial therapy, outcomes did not differ between ST131 and H30R isolates vs other *E. coli* isolates.

**Conclusions.** Among veterans, ST131 and its H30R subclone were associated with LTCF-exposed hosts but not with worse outcomes.

**Keywords.** antimicrobial resistance; epidemiology; *Escherichia coli*; virulence.
Consequently, further study that accounts for host status is needed to determine whether ST131 truly is a more aggressive pathogen than non-ST131 *E. coli*.

In this study, we sought to test the hypotheses that ST131 causes infections that are more severe, persistent, and recurrent, and that occur in less compromised hosts than those caused by non-ST131 *E. coli*. For this experiment, we (1) collected clinical information from consecutive patients at the Minneapolis Veterans Affairs Medical Center (MVAMC) from whom *E. coli* was isolated, (2) characterized the corresponding *E. coli* isolates for ST131, H30R, and H30Rx status, and (3) then compared clonal background with disease severity and underlying host characteristics.

**METHODS**

**Patients and Isolates**
Consecutive *E. coli* isolates from unique patients, as recovered by the MVAMC microbiology laboratory between December 10, 2010 and April 25, 2011 from any specimen type, were retrieved and characterized by the research laboratory for membership in ST131, H30R, and H30Rx by using established polymerase chain reaction-based assays that detect single-nucleotide polymorphisms that are specific for each of the nested clonal lineages, with fluoroquinolone-resistant H30-positive isolates being regarded as H30R [18]. Antimicrobial susceptibility results, as generated by the clinical laboratory using a Vitek-2 instrument, were recorded. Of the present study isolates and source patients, 100 were included in a recently published multicenter study that explored similar epidemiologic associations in a broader population [17]. The present study was independently conceived and designed to assess the effects of ST131 in a predominantly male veteran population; a predetermined number of the present records obtained from the MVAMC clinical microbiology laboratory were included in this study. The Institutional Review Board of the MVAMC approved all study procedures and granted a waiver of informed consent for this study.

**Clinical and Epidemiological Data**
Study personnel reviewed each source patient’s medical record in the VA Computerized Patient Record System to abstract demographic, epidemiological, and clinical information. Demographic data included age, race, and gender. Epidemiological information included hospitalization, dialysis, or LTCF residence in the previous year, both within the VA system and elsewhere. Clinical information included characteristics of the presenting illness, its management and outcome, and underlying host status, as detailed below.

Specific clinical data included the presence or absence of any signs or symptoms of infection (both systemic and localized to the site of isolation), comorbid conditions, and (for patients with a urine isolate) any complicating factors known to predispose patients to more frequent or difficult to manage UTIs (obstruction, neurogenic bladder, urinary instrumentation, recent urologic surgery, calculi, and indwelling drainage device).

Urinalysis results were not used as a sign of infection. Details of antimicrobial therapy were recorded, including whether the initial therapy was active against the *E. coli* isolate. Outcomes assessed included clinical recurrence, microbiologic recurrence (ie, repeated isolation of *E. coli* from the same clinical site), *Clostridium difficile* infection, escalation in level of care (defined as transfer to a higher-acuity setting), use of advanced imaging (defined as computerized tomography, magnetic resonance imaging, or ultrasonography), and mortality, both in-hospital and overall. Source patients were followed for 30 days. The Institutional Review Board of the MVAMC approved all study procedures and granted a waiver of informed consent for this study.

**Statistical Methods**
Between-group comparisons were made using SPSS, t tests for continuous variables, and Fisher’s exact test for categorical variables. The criterion for statistical significance was *P* < .05.

**RESULTS**

**Study Isolates**
Three hundred eleven unique (by patient) *E. coli* isolates were obtained from the MVAMC clinical microbiology laboratory during the study period. Of these, 61 (19.6%) were identified as ST131, most of which (51, 83.6%) represented the H30R subclone. Only 5 (9.8%) of the 51 H30R isolates represented the H30Rx subclone; accordingly, further analysis was limited to ST131 and H30R status.

**Clinical Source**
Among the 311 total isolates, urine was the most common source (260, 83.6%), followed by wound (36, 11.6%), blood (6, 1.9%), respiratory (5, 1.6%), peritoneal fluid (4, 1.3%), and unclassified (1, 0.3%). No differences in ST131 or H30R subclone status by source were identified.

**Demographic and Epidemiologic Associations**
Source patients were predominantly male (86.2%), as expected in a VA population, and elderly, with a mean age of 67.8 years (standard deviation, 15.1). Most patients (78.8%) were seen in the outpatient setting. Race was most commonly white (78.5%), unknown (15.4%), or African American (3.5%). Prior contact with healthcare facilities in the past year was common, with more than 30% of patients having been hospitalized and 43.1% having had 1 of the assessed exposures (Table 1). The only significant demographic or epidemiologic correlate of having an ST131 or ST131-H30R isolate was LTCF exposure, which was over twice as common in association with ST131 and H30R isolates as with other isolates (for ST131, 32.8% vs 14.4% [*P* = .002]; for H30R, 37.3% vs 14.2% [*P* < .001]).

**Medical Comorbidities**
Comorbid conditions were common in the source patients, as were known urologic complicating factors (Tables 2 and 3). Diabetes was present in approximately 50% of patients, and...
chronic kidney disease was present in approximately 20%. Among the 260 patients with urine-source isolates, obstruction was the most common complicating factor (28.1%), followed closely by indwelling drainage devices (25.8%). Of the patients with urine-source isolates, a numerically greater proportion of patients with an ST131 isolate had an underlying urological condition compared with those with a non-ST131 isolate (61.1% vs 51.5%; \( P = .07 \)) (Table 3). Likewise, a significantly greater proportion of patients with an H30R isolate had an underlying urological condition compared with those with a non-H30R isolate (73.9% vs 50.5%; \( P = .005 \)).

**Clinical Manifestations**

Clinical manifestations consistent with infection were documented in 236 (75.9%) of the 311 source patients. Manifestations included urinary frequency and dysuria (assessed for urine isolates), wound erythema (assessed for wound isolates), cough (assessed for respiratory isolates), and/or vital sign abnormalities and peripheral blood leukocytosis (assessed for any isolate). Sequence type 131 and H30R status were associated with colonization rather than symptomatic infection, with infectious manifestations present in association with only 39 (63.9%) of 61 ST131 isolates, vs 197 (78.8%) of 250 non-ST131 isolates (\( P = .02 \)), and with only 31 (60.8%) of 51 H30R isolates, vs 205 (78.8%) of 260 non-H30R isolates (\( P = .008 \)). Systemic manifestations were infrequent, the most common being leukocytosis (18.0%) and fever (9.3%); no differences in these were observed between ST131 or H30R isolates and non-ST131 or H30R isolates.

For specific clinical manifestations, only 2 (both, urinary tract-specific) were significantly associated with ST131 and the H30R subclone, both negatively so (Table 4). That is, compared with patients with non-ST131 urine isolates, patients with ST131 urine isolates had a lower likelihood of both dysuria (10.7% vs 31.4%; \( P = .002 \)) and urinary frequency (8.9% vs 22.1%; \( P = .03 \)). Likewise, patients with H30R subclone isolates, compared with patients with non-H30R isolates, had a lower likelihood of both dysuria (8.7% vs 30.8%; \( P = .003 \)) and frequency (6.5% vs 22.0%; \( P = .02 \)).

**Antimicrobial Resistance**

The ST131 isolates exhibited a greater prevalence of resistance to multiple antimicrobials compared with the non-ST131 isolates. In addition to the expected association with fluoroquinolone resistance (85.2% vs 8.4%; \( P < .001 \)), ST131 isolates also were significantly more often resistant to trimethoprim/sulfamethoxazole (TMP/SMZ), ampicillin, ampicillin/sulbactam, and gentamicin. The H30R isolates exhibited an even stronger association with fluoroquinolone resistance (100% [by definition] vs 8.5% for non-H30R isolates; \( P < .001 \)), plus significant associations

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### Table 2. Comorbid Medical Conditions Present in 311 Veteran Source Patients, Overall and Stratified by ST131 and H30R Status

| Medical Condition       | Overall (n = 311) | ST131 (n = 61) | Non-ST131 (n = 250) | \( P \) Value, ST131 vs Non-ST131 | H30R (n = 51) | Non-H30R (n = 260) | \( P \) Value, H30R vs Non-H30R |
|-------------------------|------------------|---------------|---------------------|----------------------------------|-------------|---------------------|----------------------------------|
| Diabetes                | 142 (45.7)       | 24 (39.3)     | 118 (47.2)          | .32                              | 19 (37.3)   | 123 (47.3)          | .22                              |
| Chronic kidney disease  | 53 (17.0)        | 7 (11.5)      | 46 (18.4)           | .25                              | 6 (11.8)    | 47 (18.1)           | .32                              |
| Dementia                | 32 (10.3)        | 8 (13.1)      | 24 (9.6)            | .48                              | 8 (15.7)    | 24 (9.2)            | .20                              |
| Immune suppression      | 31 (10.0)        | 4 (6.6)       | 27 (10.8)           | .45                              | 4 (7.8)     | 27 (10.4)           | .63                              |
| Cirrhosis               | 7 (2.3)          | 2 (3.3)       | 5 (2.0)             | .63                              | 2 (3.9)     | 5 (1.9)             | .60                              |
| Neutropenia             | 4 (1.3)          | 0 (0)         | 4 (1.6)             | .59                              | 0 (0)       | 4 (1.5)             | .61                              |
| Any of above            | 190 (61.1)       | 35 (57.4)     | 155 (62.0)          | .56                              | 30 (58.8)   | 160 (61.5)          | .75                              |

**Abbreviations:** H30R, ST131 subclone H30R; ST131, sequence type 131.
with resistance to ampicillin, ampicillin/sulbactam, and gentamicin, and a numerically greater prevalence of TMP/SMZ resistance that approached significance (29.4% vs 18.1%; \( P = .08 \)).

**Clinical Outcomes**

Among patients who had documented manifestations of infection, the ST131 isolates’ more extensive and prevalent antimicrobial resistance resulted in a significantly greater likelihood of discordant initial antimicrobial therapy for them, compared with non-ST131 isolates (11 of 39 [28.2%] vs 6 of 197 [3.0%]; \( P < .001 \)). Patients with H30R isolates were even more likely to receive discordant initial therapy, relative to patients with non-H30R isolates (35.5% vs 2.9%; \( P < .001 \)). Despite this, assessed outcomes did not differ significantly between patients with ST131 vs non-ST131 isolates or between those with H30R versus non-H30R isolates. All assessed outcomes were rare, limiting our power to detect between-group differences. Although 7 of 8 assessed outcomes were numerically less common among ST131 or H30R source patients, there were no statistically significant differences, and the overall rates were similar to those of non-ST131 source patients (Table 5).

**DISCUSSION**

This observational study of 311 consecutive *E. coli* isolates (including 61 ST131 isolates, 51 representing the H30R subclone) and their corresponding source patients provides an in-depth assessment of the host epidemiology, clinical presentations, disease severity, and outcomes associated with this globally disseminated clone among veterans. Contrary to our prior hypotheses, ST131 and H30R were not associated with more severe disease, worse clinical outcomes, or more robust hosts. On the contrary, both ST131 and H30R were actually more likely to be isolated from source patients who lacked manifestations of infection and who had prior healthcare contact or LTCF exposure. Moreover, despite a greater likelihood of discordant initial therapy, ST131 and H30R isolates were numerically less likely than other *E. coli* isolates to be associated with adverse outcomes. These findings, which largely replicate those of a recent multicenter study that included 100 of the present study isolates [17], uniquely document a lack of association of ST131 with adverse outcomes, possibly related to the present study’s all-veteran, predominantly male population.

| Urological condition | Overall (n = 260) | ST131 (n = 56) | Non-ST131 (n = 204) | \( P \) Value, ST131 vs Non-ST131 | Overall (n = 260) | H30R (n = 46) | Non-H30R (n = 214) | \( P \) Value, H30R vs Non-H30R |
|----------------------|------------------|---------------|---------------------|----------------------------------|------------------|------------------|---------------------|----------------------------------|
| Obstruction          | 73 (28.1)        | 17 (30.4)     | 56 (27.5)           | .74                              | 16 (34.8)        | 57 (26.8)       | .28                              |
| Indwelling drainage device | 67 (25.8) | 17 (30.4)     | 50 (24.5)           | .39                              | 16 (34.8)        | 51 (23.8)       | .14                              |
| Neurogenic bladder   | 47 (18.1)        | 14 (30.4)     | 33 (16.2)           | .17                              | 13 (28.3)        | 34 (15.9)       | .06                              |
| Urinary instrumentation | 19 (7.3)    | 6 (10.7)      | 13 (6.3)            | .38                              | 6 (13.0)         | 13 (6.1)        | .12                              |
| Calculi              | 13 (5.0)         | 5 (8.9)       | 8 (3.9)             | .16                              | 5 (10.9)         | 8 (3.7)         | .06                              |
| Recent surgery       | 10 (3.8)         | 4 (7.1)       | 6 (2.9)             | .23                              | 3 (6.5)          | 7 (3.3)         | .39                              |
| Any abnormality      | 142 (54.6)       | 37 (66.1)     | 105 (51.5)          | .07                              | 34 (73.9)        | 108 (50.5)      | .005                             |

Abbreviations: H30R, ST131 subclone H30R; ST131, sequence type 131.

| Clinical Manifestation | Overall (n = 260) | ST131 (n = 56) | Non-ST131 (n = 204) | \( P \) Value, ST131 vs Non-ST131 | Overall (n = 260) | H30R (n = 46) | Non-H30R (n = 214) | \( P \) Value, H30R vs Non-H30R |
|-----------------------|------------------|---------------|---------------------|----------------------------------|------------------|------------------|---------------------|----------------------------------|
| Dysuria               | 70 (26.9)        | 6 (10.7)      | 64 (31.4)           | .002                             | 4 (8.7)          | 66 (30.8)       | .003                             |
| Frequency             | 50 (19.2)        | 5 (8.9)       | 45 (22.1)           | .03                              | 3 (6.5)          | 47 (22.0)       | .02                              |
| Urgency               | 40 (15.4)        | 6 (10.7)      | 34 (16.7)           | .31                              | 4 (8.7)          | 36 (16.8)       | .19                              |
| Hematuria             | 37 (14.2)        | 4 (7.1)       | 33 (16.2)           | .13                              | 3 (6.5)          | 34 (15.9)       | .11                              |
| Flank pain            | 17 (6.5)         | 6 (10.7)      | 11 (5.4)            | .22                              | 4 (8.7)          | 13 (6.1)        | .74                              |
| Suprapubic pain       | 12 (4.6)         | 4 (7.1)       | 8 (3.9)             | .47                              | 2 (4.3)          | 12 (5.6)        | 1.0                              |

Abbreviations: H30R, ST131 subclone H30R; ST131, sequence type 131.
Overall, our findings suggest that, despite ST131’s high prevalence and extensive virulence and resistance profiles, on a by-case basis ST131 may lead to more colonization than other E. coli, and it may favor hosts with urinary tract abnormalities and LTCF exposure. The H30R subclone accounted for the majority (51 of 61, 83.6%) of ST131 isolates; accordingly, the H30R isolates had largely similar associations, as did the ST131 isolates. Unfortunately, our study had too few H30Rx subclone isolates to meaningfully assess associations specifically with this subclone.

Source patients with a history of LTCF exposure were significantly more likely to have an ST131 isolate; this was not true for other healthcare exposures (ie, hospitalization or dialysis). Whether this association of ST131 with LTCF exposure, which has been documented previously [17, 19], is due to the underlying comorbid conditions of patients with LTCF exposure—vs selective antimicrobial exposure, infection control lapses within LTCFs, or a combination of these—is unknown. However, the resistance characteristic of ST131, combined with the high level of antimicrobial use in such facilities, seems likely to provide ideal selection for the survival of ST131 and similarly resistant pathogens [15, 17]. The finding that, when present in a urine culture, ST131 was less likely than other E. coli to be associated with dysuria or frequency may reflect that it is well suited to asymptomatic colonization of the urinary tract, possibly aided by the factors discussed above, ie, resistance, antimicrobial use, and a population with numerous comorbid conditions, including underlying urinary tract abnormalities.

More than one third of source patients with an ST131 isolate received discordant initial antimicrobial therapy, compared with fewer than 3 percent of other patients, a greater than 10-fold difference, as observed also in the recent multicenter study [17]. This was largely driven by the high percentage of ST131 isolates resistant to fluoroquinolones, which are still widely used for empiric therapy of UTIs, even in hospitalized patients. The lack of demonstrable harm from this discordant therapy has several possible explanations, including that few patients were critically ill, active therapy was likely initiated within 1 to 2 days (once susceptibility results became available), there was insufficient analytical power to detect such harms, and there was an omission of other possibly relevant outcome variables (eg, quality of life).

Strengths of the study include the inclusion of consecutive E. coli isolates, which limits bias potentially associated with other sampling techniques, and consistent data abstraction using a standardized form. In addition, the all-veteran study population, which increases the applicability of the findings to veterans in general, was unique to this study; eg, veterans constituted <10% of patients in the recent multicenter study [17]. Weaknesses include reliance on clinician documentation, because clinical information could be abstracted only if providers documented their findings accurately and completely. In addition, although fully 61 (19.6%) of the 311 study isolates were ST131, a larger sample size for ST131, H30R, and especially H30Rx isolates would have permitted a more robust exploration of associations with these strains, including for severe disease. However, arguing against such an association was our failure to detect, among patients with an ST131 or H30R isolate, even a suggestive trend toward more severe disease or a greater likelihood of infection-associated clinical manifestations or persistence/recurrence.

**CONCLUSIONS**

Among veterans with ST131 isolated from a clinical specimen, disease severity and clinical outcomes were not appreciably worse compared with veterans with non-ST131 isolates. The ST131 and its H30R subclone were associated with asymptomatic

### Table 5. Assessed Outcomes, Overall and Stratified by ST131 and H30R Status, Among the 236 Patients With Documented Manifestations of Infection

| Outcome                        | No. of Isolates (Column %) | P Value, ST131 vs Non-ST131 | No. of Isolates (Column %) | P Value, H30R vs Non-H30R |
|-------------------------------|---------------------------|-----------------------------|---------------------------|---------------------------|
| Clinical recurrence           | 9 (3.8)                   | .65                         | 2 (6.5)                   | .61                       |
| Microbiological recurrence    | 3 (1.3)                   | 1                          | 0 (0)                     | 1                         |
| Clostridium difficile infection| 2 (0.8)                   | 1                          | 0 (0)                     | 2 (1.0)                   |
| Mortality, overall            | 8 (3.4)                   | .36                         | 0 (0)                     | 8 (3.9)                   |
| In-hospital mortality         | 8 (3.4)                   | .36                         | 0 (0)                     | 8 (3.9)                   |
| ICU admission                 | 15 (6.3)                  | 1                          | 2 (6.5)                   | 1                         |
| Escalation in level of care   | 14 (5.9)                  | .48                         | 1 (3.2)                   | 13 (6.3)                  |
| Use of advanced imaging       | 56 (23.7)                 | .68                         | 6 (19.4)                  | .65                       |
| Any of above                  | 77 (32.6)                 | .58                         | 9 (29.0)                  | .84                       |

**Abbreviations**: H30R, ST131 subclone; H30R, ICU, intensive care unit; ST131, sequence type 131.

*a* Computerized tomography, magnetic resonance imaging, or ultrasonography.
colonization and LTCF exposure. Future research should (1) further define the clinical and epidemiological correlates of this highly prevalent and extensively antimicrobial-resistant clone and (2) seek to identify opportunities for improved management and prevention.

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