EDITORIAL COMMENTARY

Flying Under the Radar: The Stealth Pandemic of *Escherichia coli* Sequence Type 131

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(See the Major Article by Colpan et al on pages 1256–65.)

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Escherichia coli plays a prominent role in the etiology of both healthcare-acquired and community-acquired bacterial infections. Of the >7 million uncomplicated outpatient urinary tract infections that occur in the United States annually, *E. coli* accounts for 80%–90% [1, 2]. Urinary tract infections are also the most common healthcare-acquired infection [3], and *E. coli* also comprises the majority of these infections. When complicated by bloodstream involvement, *E. coli* infections are associated with considerable morbidity and mortality [4].

The emergence of antimicrobial resistance has complicated the therapeutic approach to *E. coli*. The prevalence of resistance to first-line agents such as ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) has increased steadily over time [1]. Enthusiasm surrounding the introduction of newer broader-spectrum antimicrobials such as the third-generation cephalosporins and fluoroquinolones was quickly tempered by emergence of resistance to these agents. Over the past 20 years, fluoroquinolone-resistant *E. coli* (FQREC) and extended-spectrum β-lactamase–producing *E. coli* (ESBL-EC) have emerged globally [5, 6] (Lautenbach et al, manuscript in preparation). These organisms are typically resistant to multiple antimicrobials, severely limiting treatment options [7–10]. Not surprisingly, FQREC and ESBL-EC infections have been associated with significant morbidity, mortality, and cost [11–13].

A major advance in the understanding of these global trends occurred in 2008 when a specific clone of *E. coli*, *E. coli* sequence type 31 (ST131), was identified among ESBL-EC isolates [14, 15]. ST131 has since been identified worldwide in community and healthcare settings [16–20]. Indeed, numerous studies have now shown that ST131 accounts for a significantly greater proportion of ESBL-EC and FQREC compared to their susceptible counterparts [16, 17, 19]. ST131 strains are also more likely to be resistant to ampicillin, TMP-SMX, and the aminoglycosides [18, 20]. In a very short time frame, ST131 has taken its place as the most important driver of multidrug resistance in *E. coli*.

With this background, Colpan and colleagues report in this issue of *Clinical Infectious Diseases* their experience from a network of 24 Veterans Affairs (VA) medical centers [21]. This large, geographically diverse, and comprehensive effort represents an important advance in our understanding of this emerging pathogen. The authors estimated that ST131 accounts for more than one-quarter of all *E. coli* isolates from VA sites nationally, is geographically widespread, and is found consistently across various anatomic sites of infection and healthcare settings. A total of 595 *E. coli* isolates were divided into 3 groups based on antimicrobial resistance characteristics: (1) FQREC; (2) ESBL-EC; and (3) fluoroquinolone-susceptible *E. coli* (FQSEC). ST131 accounted for 78% and 64% of FQREC and ESBL-EC infections, respectively, but only 7% of FQSEC infections. The disparity between resistant and susceptible isolates increased further when focusing specifically on the H30 subclone of ST131.

Colpan and colleagues also rigorously assessed the relationship between virulence and antimicrobial resistance specific to the ST131 clonal group [21]. Within each of the 3 resistance groups noted above, a greater proportion of ST131 than non-ST131 met criteria for extraintestinal pathogenic *E. coli*. Virulence profiles were fairly consistent across the 3 resistance groups when focusing specifically on ST131. However, among non-ST131 isolates, virulence

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was much less pronounced among the FQREC and ESBL-EC groups compared to the FQSEC group.

The authors' work represents an important contribution as both clinical and laboratory studies have debated the controversial link between ST131 and virulence [18–20, 22, 23]. Indeed, the long-standing assumption in the field of antimicrobial resistance has been that the acquisition of resistance determinants, such as those seen in ST131, typically comes at some cost to the organism with regard to fitness or virulence [18]. Colpan and colleagues however, convincingly demonstrate a strong association between ST131 and enhanced virulence. More importantly, this relationship is consistent regardless of whether the isolate manifests a resistant phenotype. This finding suggests a unique place for ST131 in the long line of emerging resistant pathogens, and may help to explain its rapid and widespread dissemination.

Although these virulence data are highly compelling, their clinical relevance remains unclear. Specifically, are clinical outcomes worse in patients with infections due to *E. coli* ST131? Some early evidence suggests this may be the case. A recent study compared the virulence gene profile of ST131 isolates from patients with pyelonephritis, cystitis, and fecal samples [24]. These authors found a prevalence gradient of virulence profiles, with greatest virulence gene prevalence in pyelonephritis and lowest in fecal isolates, providing evidence of a link between high prevalence of virulence genes and more invasive infection [24].

Building on this work, a recent study demonstrated a higher rate of persistent or recurrent symptoms in patients with ST131 infections compared to non-ST131 infections [16]. Elucidating the relationship between ST131 infections and clinical outcomes is complicated by the fact that ST131 infections are typically multidrug resistant and, thus, patients with such infections are less likely to receive adequate empiric antibiotic therapy. Given the well-known relationship between adequate empiric therapy and outcomes, it will be critical to determine the specific effect of virulence on outcomes. Virulence characteristics may also play a role in the duration of colonization with ST131. Indeed, recent data suggest that patients may remain colonized with resistant gram-negative pathogens for prolonged periods (eg, months) [25–27]. Whether the virulence profile of ST131 predicts prolonged colonization is unclear. Given the likely relationship between prolonged colonization and risk of both subsequent infection and transmission [19], answering these questions will be critical in more clearly defining the impact of ST131.

Given the remarkable emergence of ST131 and its association with antimicrobial resistance and virulence, efforts to curb further emergence of this pathogen are urgently needed. Critical to designing such preventive strategies is the identification of the forces driving emergence of this pathogen. Although the clinical epidemiology of ST131 remains poorly described, recent progress has been made. Earlier this year, Banerjee and colleagues analyzed 299 consecutive *E. coli* isolates submitted to Olmsted County laboratories from all healthcare settings [16]. ST131 accounted for 49% of healthcare-associated isolates, 15% of community isolates, and 76% of long-term care facility (LTCF) isolates. In multivariable analyses, LTCF residence was the strongest risk factor for ST131. This is consistent with recent work showing high rates of ST131 infection in the LTCF setting [28] and other studies demonstrating LTCF residence to be an independent risk factor for fluoroquinolone-resistant and/or ESBL-producing Enterobacteriaceae [11, 29].

These findings suggest that the LTCF setting may play a unique role in the emergence of ST131. LTCFs represent an increasingly important setting for healthcare delivery in the United States. Currently, there are >16 000 LTCFs in the United States caring for an estimated 1.5 million residents [30]. The importance of focusing future research on this population specifically is highlighted by several considerations. First, immune function decreases with aging [31], and older persons suffer more chronic diseases that affect the integrity of host resistance [32]. Second, LTCF residents live in an institutional environment that may increase the risk for person-to-person spread of infection due to frequent contact with other residents and less attention to infection control [32, 33]. Third, rates of antimicrobial use are significant in LTCFs in the United States, with up to 70% of residents receiving at least 1 antimicrobial over the course of a year [34]. Even more concerning is that up to 75% of antimicrobials prescribed in the LTCF setting are inappropriate [34]. Finally, LTCF residents colonized with resistant pathogens may, because of frequent transfer to and from acute care facilities, serve to introduce and propagate the dissemination of resistant pathogens across a variety of other healthcare settings [8]. For these reasons, investigation of the epidemiology of ST131 in the LTCF setting is urgently needed.

The work of Colpan and colleagues was conducted in a VA network [21]. Although one may question the generalizability of the VA healthcare system, this study included sites from a broad geographic region and the results are consistent with prior studies conducted in non-VA settings. In addition, one must acknowledge that only those patients for whom a clinical culture was obtained were included in this study. Many patients are likely to be treated for urinary tract infections empirically, with a culture obtained only if clinical response is inadequate. As such, clinical cultures are likely to overrepresent the prevalence of antimicrobial resistance. For this reason, future studies should evaluate the epidemiology and impact of ST131 gastrointestinal tract colonization.

Coplan and colleagues have provided important new insights into the continued emergence of ST131, thereby putting

this pathogen squarely on the radar of clinicians and investigators. This organism poses an important threat to our ability to treat both community- and healthcare-acquired infections. The recent identification of an ST131 strain harboring a New Delhi metallo-β-lactamase (which confers carbapenem resistance) serves to further highlight the threat posed by this emerging pathogen [35]. Future work is needed to better define the clinical epidemiology and impact of ST131 if we hope to devise effective strategies for prevention and treatment.

Note

Potential conflicts of interest. Author certifies no potential conflicts of interest.

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