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Escherichia coli ST131: Variations on a theme of clonal expansion

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The worldwide emergence and spread of the antimicrobial-resistant *Escherichia coli* clonal group ST131 represents a pandemic (1). Since ST131 was first identified in 2008 it has disseminated rapidly and has contributed, in large part, to the rising prevalence of antimicrobial-resistant *E. coli* throughout the world (2, 3). The ST131 clonal group is associated with serotype O25b:H4, contains numerous virulence factors and a diversity of PFGE profiles, and typically exhibits a multidrug-resistant phenotype (4, 5). Specifically, most ST131 isolates are resistant to fluoroquinolones, and many are co-resistant to aminoglycosides, trimethoprim-sulfamethoxazole, and/or extended-spectrum cephalosporins via extended-spectrum beta-lactamase (ESBL) production, usually of CTX-M-15 (6).

Although the molecular epidemiology of ST131 is well characterized, the prevalence of ST131 in different settings and its sources, predictors, and transmission pathways remain unclear. ST131 has been described in ambulatory and hospitalized patients of all ages and has been reported to be spread via both person-to-person (7) and foodborne routes (8). However, since most epidemiological studies of ST131 have utilized convenience or highly selected samples, the true prevalence of ST131 and risk factors for ST131 infection or colonization are undefined. Only recently have studies using unbiased sampling strategies identified ST131 to be a healthcare-associated strain associated with elderly hosts (9, 10).

In this issue of EIMC, Lopez-Cerero and colleagues describe a population-based study of ST131 prevalence, resistance, and clonality in Southern Spain. These investigators evaluated over 4000 consecutive *E. coli* isolates from two clinical microbiology laboratories in their region over a 30-week period in 2010. These isolates were primarily from urine specimens and were collected both from outpatients and from inpatients admitted to tertiary care or long-term care hospitals. Over 500 ST131 isolates were identified by PCR, yielding an ST131 prevalence of 12.5%. Importantly, most (93%) ST131 isolates were ESBL-negative. Among the minority of ST131 isolates that were ESBL-positive, all but 1 isolate harbored CTX-M-15, whereas ESBL-positive non-ST131 isolates had other ESBL types. Resistance to all antibiotic classes was significantly more prevalent among ST131 isolates compared to non-ST131 isolates, regardless of ESBL status. Fluoroquinolone resistance, in particular, was strongly associated with ST131, occurring in 97% of ESBL-positive and 73% of ESBL-negative ST131 isolates. PFGE analysis of 88 ST131 isolates revealed 50 different pulsotypes, including 37 single-isolate pulsotypes and 3 different high-prevalence pulsotypes containing 4, 8, and 10 isolates each. Notably, these 3 high-prevalence pulsotypes accounted for ¼ of all ST131 isolates. In contrast, the non-ST131 isolates were

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more heterogeneous; 83% were single-isolate pulsotypes and no pulsotypes contained greater than 3 isolates.

This study yielded several novel findings. Through unbiased sampling of a large number of isolates the investigators were able to determine that the true prevalence of ST131 among *E. coli* clinical isolates in their region is 12.5%, which is comparable to a previous national survey from Spain (11), but lower than documented in other regions (1, 5, 10, 12). It is likely that the ST131 prevalence in Spain is slightly higher than this because the investigators relied on PCR detection of the O25b *rfb* variant and *papB* to identify ST131, and therefore did not capture the minor subset of ST131 isolates that express the O16 and H5 antigens (13, 14). However, the lower reported prevalence for ST131 in Spain as compared to other areas, and other reported prevalence differences between locales, may reflect true geographical differences in the distribution of the clonal group. Alternatively, they may reflect bias related to distribution of specimen types, resistance phenotypes, or patient populations included in the various studies.

The Spanish investigators also found that ST131 accounted for only 12.5% of 295 ESBL isolates in the study region. This is in marked contrast to previous studies of ESBL *E. coli* from other parts of the world, which found that one-third to one-half (or more) of ESBL isolates are ST131 (5, 15–18). Another novel finding was that certain fluoroquinolone-resistant and fluoroquinolone-susceptible ST131 isolates exhibited highly similar or indistinguishable PFGE profiles. This differs from a prior study in which no fluoroquinolone-susceptible ST131 isolates were identified within PFGE clusters comprising fluoroquinolone-resistant ST131 isolates (19), and suggests possible recent acquisition or loss of fluoroquinolone resistance by certain of the Spanish isolates.

This study illustrates that although there is probably geographic variation in ST131's prevalence, association with ESBLs, and population structure, several consistent, locale-independent themes can be identified regarding ST131. First, throughout the world, ST131 is strongly associated with fluoroquinolone resistance and, among isolates that are co-resistant to extended-spectrum beta-lactams, with CTX-M-15. Second, a few pulsotypes of ST131 exhibit a very high-prevalence compared with ST131's many other pulsotypes, implying a much greater clonal expansion (2, 5, 19). The high-prevalence pulsotypes identified in this study may be the same as those previously described elsewhere (19), although this remains uncertain since, in the absence of uniform methodologies and interpretive criteria, PFGE profiles cannot be reliably compared across laboratories.

Third, this and other molecular epidemiological studies suggest possible mechanisms of ST131 dissemination. The strong association between ST131 and fluoroquinolone resistance suggests that fluoroquinolone use has driven the emergence and spread of ST131. In contrast, extended-spectrum beta-lactams are less plausible as important selectors for ST131 at the population level since in this study (and multiple others) most ST131 isolates were not ESBL-producers, and the most prevalent ST131 pulsotypes were not associated with ESBL carriage (19). The widespread global distribution of a few prominent pulsotypes of ST131 suggests ongoing clonal spread rather than sporadic emergence of heterogeneous strains. At the same time, however, the existence of geographically restricted ST131 pulsotypes also suggests local or endemic transmission of low-prevalence pulsotypes. The dramatic clonal spread of certain pulsotypes may be mediated through international travel or person-to-person spread within healthcare facilities or the community. Presumably the high-prevalence ST131 pulsotypes have a fitness advantage over less prevalent pulsotypes. It will be important to determine whether this advantage stems from enhanced virulence, transmissibility, or ability to colonize hosts.

Since both antibiotic selection pressure and clonal spread appear to be promoting the success of ST131, a combination of enhanced antimicrobial stewardship and infection control interventions will be needed to halt the further emergence and spread of this highly successful antimicrobial-resistant clonal group. Stewardship efforts that focus on reducing overuse and misuse of fluoroquinolones, in particular, are likely to have the greatest impact on ST131 prevalence. Recent evidence that clonal expansion of ST131 is occurring primarily in healthcare and long-term care facilities (9, 10) indicates an urgent need for improved antimicrobial stewardship and infection control practices within such institutions, both to reduce selection for ST131 and to block further transmission.

Lastly, the high prevalence of ST131, especially among fluoroquinolone-resistant *E. coli* isolates, has implications for management and diagnosis of extraintestinal *E. coli* infections. Many patients infected with ST131 have persistent or recurrent symptoms, probably at least in part because they receive empiric therapy with fluoroquinolones, which are largely ineffective against this clonal group (10). This suggests that prescribers require education about the rising prevalence of fluoroquinolone-resistant *E. coli* and risk factors for ST131. Additionally, development of rapid molecular tests that identify ST131 prior to the availability of culture and susceptibility results could lead to more effective initial antibiotic therapy and better outcomes.

In summary, clonal expansion of ST131 has dramatically changed the population structure, antimicrobial resistance profile, and therapeutic management of infections caused by *E. coli*, much as the expansion of the USA300 clone did for methicillin-resistant *Staphylococcus aureus* in the U.S. over 10 years ago. Both of these pathogens are reminders that antimicrobial-resistant clones will continue to emerge and threaten public health, obliging us to respond with effective antimicrobial stewardship and infection control practices combined with heightened surveillance for such strains.

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