COMMENTARY

Who Is Leading This Dance? Understanding the Spread of *Escherichia coli* Sequence Type 131

Benjamin A. Rogers, MBBS, FRACP;[1] Yohei Doi, MD, PhD[2]

(See the article by Banerjee et al, on pages 361–369.)

Escherichia coli is part of our normal intestinal flora and a ubiquitous human pathogen. It causes a wide range of disease, including intestinal infection (from diarrhea to hemolytic uremic syndrome) and extraintestinal infection (from uncomplicated urinary tract infection to bacteremia and meningitis). Although wild-type *E. coli* is intrinsically susceptible to most antimicrobials, extraintestinal *E. coli* strains have shown the ability to develop resistance to every class of agents introduced for human use. This trend goes back to the development of sulfonamide and ampicillin resistance in the mid-twentieth century and seems unlikely to abate in the foreseeable future.[1,2]

The previous decade has heralded some changes in the dynamics of resistance in *E. coli.* Resistance to sulfamethoxazole-trimethoprim and fluoroquinolones has skyrocketed worldwide, which is a significant trend, because it compromises 2 valuable oral treatment options for infections caused by *E. coli.* Equally alarming has been a rapid increase in the incidence of *E. coli*–producing extended-spectrum β-lactamase enzymes (ESBL-EC), and the expansion of ESBL-EC from nosocomial to community acquisition that has occurred in many regions.

A breakthrough in understanding these epidemiologic shifts in resistance came in the mid-2000s, when researchers used multilocus sequence typing (MLST) to identify the dominance of a particular bacterial clone, sequence type (ST) 131, among ESBL-EC strains.[3,4] Subsequently, ST131 *E. coli* has been shown to have worldwide distribution. It spans not only clinical strains of ESBL-EC, in which ST131 frequently accounts for greater than 25% of those isolates recovered, but also a significant proportion of fluoroquinolone-resistant strains and even asymptomatic carriage of ciprofloxacin-resistant ST131 *E. coli* among healthy individuals.[5] Overall, ST131 is now regarded as the single most important clone driving multidrug resistance in the community setting.

With this in mind, the work by Banerjee et al[6] reported in this issue of *Infection Control and Hospital Epidemiology* urges us to redefine the epidemiology of *E. coli* ST131. Here, the authors conducted a population-based, molecular epidemiologic analysis of 299 consecutive clinical isolates of extraintestinal *E. coli* identified in Olmstead County, Minnesota. Because of this study design, the isolates represented a relatively unbiased sample of community-associated, healthcare-associated, and hospital-acquired infections without regard to antimicrobial susceptibility. It should be pointed out that 39% of the isolates were from individuals with healthcare-associated or hospital-acquired infections; thus, the sample represented a relatively "medicalized" population.

In this context, ST131 accounted for 27% of the isolates. The most intriguing finding was that ST131 accounted for a much greater proportion of healthcare-associated than community-associated isolates (49% vs 15%). A whopping 76% of the isolates from long-term care facility (LTCF) residents were ST131. As expected, ST131 accounted for a much bigger share of antimicrobial-resistant isolates, including over 80% of isolates that were nonsusceptible to fluoroquinolones and approximately half of isolates resistant to trimethoprim-sulfamethoxazole; however, only 11% of the ST131 isolates were nonsusceptible to ceftriaxone, which is most commonly due to production of ESBL. The independent predictors for ST131 included residence in a LTCF, urinary tract infection in the previous month, complex infection due to *E. coli*, and previous antimicrobial exposure (extended-spectrum cephalosporin, macrolides, and fluoroquinolones). These predictors could all be considered potential markers of healthcare-associated infection, although only residence in a LTCF is included in the most commonly adopted definition.[7]

In summary, the data presented by Banerjee et al[6] yield compelling odds ratios for these medical risk factors that are in favor of ST131, not against it. Although these findings seemingly contradict the largest body of work on this clone, which strongly delineates its community-associated nature,[5]

Affiliations: 1. University of Queensland, UQ Centre for Clinical Research, Herston, Queensland, Australia; 2. Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Received December 21, 2012; accepted December 24, 2012; electronically published February 13, 2013.

 0899-823X/2013/3404-0006$15.00. DOI: 10.1086/669874

TABLE 1. Key Information on Molecular Epidemiology Methods Used in Characterizing Sequence Type (ST) 131 *Escherichia coli*

Method	Typing targets	Resolution for ST131	Key characteristics
Multilocus sequence typing	Genomic sequence of 7 conserved housekeeping genes present in all *E. coli*. Gene functions are unrelated to bacterial virulence and pathogenesis.	First identified ST131 as a global epidemic clone.[3,4] By definition, all strains type as ST131 under the Achtman scheme (http://mlst.ucc.ie/mlst/dbs/Ecoli).	Provides very broad molecular epidemiological characterization. Given STs may contain a large range of bacteria of quite diverse genetic makeup.
Pulsed-field gel electrophoresis	DNA restriction sites (arbitrary sequences of 4–8 base-pairs of DNA) scattered throughout the *E. coli* genome.	Types ST131 into a variety of pulsotypes (subclones). Distinguishes human and animal clones and demonstrates geographical variation in circulating ST131 clones.[16]	Highly discriminatory typing method often used for spatially and temporally related outbreaks (eg, within a given healthcare network). May fail to identify spread of less closely related strains when used alone (eg, ST131 separates into a large number of pulsotypes).
fimH typing[17]	Genomic sequence of a 469-base-pair fragment of the gene encoding a subunit of the type 1 fimbriae, which is used by *E. coli* to adhere to urothelium (the gene is occasionally absent in nonuropathogenic strains).	ST131 show a variety of *fimH* types. Some of these correlate closely with other characteristics, including fluoroquinolone resistance.[18]	Given the functional nature of this gene, potentially identifies genetic traits that play a role in bacterial pathogenesis.

a number of historical[8,9] and contemporary[10,11] studies have also demonstrated high rates of healthcare-associated and hospital-acquired ST131. However, none demonstrate these findings with the weight of the study by Banerjee et al.[6]

This contrast in epidemiology warrants further consideration. Simple explanations may be geographical and methodological. First, the epidemiology of this clone undoubtedly varies by location.[5] Second, the methodology of published studies varies. Many investigators set out to find ST131 in the context of community-associated ESBL-EC infection and carefully surveyed this particular group.[12] Others have not stratified community-onset infections by healthcare association at all. In retrospect, these studies may have been examining only the tip of the iceberg (ie, community-associated, ESBL-producing *E. coli* ST131) while largely ignoring the much more substantial remainder under the water (ie, healthcare-associated, fluoroquinolone-resistant *E. coli* ST131). Another possibility is also in play. We may be seeing a change in the epidemiology of ST131, with this unwanted resident increasingly moving from the community into acute care settings, which is a path already travelled by predecessors such as community-associated methicillin-resistant *Staphylococcus aureus*.[13]

Regardless of the "when" and "where," the question of "why" ST131 has become a resident of our healthcare system is important. Some portals of entry are clear. Banerjee et al[6] and a number of other researchers have identified LTCFs as a reservoir of ST131. Two-way traffic of patients and resistant organisms between LTCFs and acute care facilities is almost invariable, with the term "revolving door" used by some to characterize this.[11] Heavy use of fluoroquinolones should likely shoulder some blame, although the true nature of their effect is not defined. Other than correlating individuals' previous fluoroquinolone exposure to infection with fluoroquinolone-resistant ST131 clones, we have no information on the broader ecological impact of fluoroquinolone use on the spread of ST131. We do know from other settings that overall population fluoroquinolone use closely correlates with rates of resistance amongst all *E. coli*[14] and that, once established, gastrointestinal carriage of fluoroquinolone resistance is prolonged compared with the carriage of resistance to other agents, such as ESBLs.[15] It is also increasingly clear among ST131 that animals and human clones are genetically distinct.[16] This suggests that problematic fluoroquinolone use driving this particular epidemic could be in the human population rather than the result of often-cited veterinary use and food contamination.

The most elusive component of "why" relates to the molecular characteristics of the clone. Although not extensively discussed in this study, Baterjee et al[6] offer some intriguing

data. Although ST131 was originally identified as an epidemic clone using MLST, the molecular-epidemiological equivalent of a 40,000-foot view, drilling down on ST131s with the other methods gives interesting insights (Table 1). Pulsed-field gel electrophoresis (PFGE), which is traditionally used within a defined spatial and temporal context, demonstrates that approximately half of the ST131 fluoroquinolone-resistant isolates in the Banterjee et al[6] study belonged to 2 specific PFGE pulsotypes. However, the more specific method to define the core subclone of fluoroquinolone-resistant ST131 appeared to be *fimH* typing, which is a recently defined single-locus sequence typing method that uses a section of the *fimH* gene.[17] Unlike the benign housekeeping genes of MLST, *fimH* is a virulence gene that codes for a subunit of type I fimbriae crucial for bacterial adhesion to urotheleium. Here, 99% of the fluoroquinolone-resistant ST131 isolates shared a specific allele, *fimH*30, whereas this allele was absent from any of the fluoroquinolone-susceptible ST131 isolates. This allele is likely more than just an epidemiological marker. In-depth examination of *fimH30*-carrying strains by other investigators has suggested a positively selected patho-adaptive trait. These strains appear to have augmented urovirulence via an enhanced ability to bind to urothelium.[18] In essence, this fluoroquinolone-resistant ST131 *fimH30* subclone is now fine-tuned for its host and environment and appears to be out-competing other ST131 subclones and non-ST131 strains.

The study was performed in a rather rural county in North America, and the generalizability of the authors' findings remains to be seen. However, they will prompt us to redefine the way we think about this emerging and expanding epidemic, which has the potential to deprive us of most oral treatment options for infections due to this exceedingly common bacteria in the near future.

ACKNOWLEDGMENTS

We thank David Paterson for his review of the manuscript of this article.

Financial support. B.A.R. is supported by an Australian Postgraduate Award Scholarship from the University of Queensland. Y.D. is supported in part by a career development award from the National Institutes of Health (K22AI080584).

Potential conflicts of interest. Y.D. has received research grants from Merck and served on an advisory board for Pfizer. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Address correspondence to Yohei Doi, Division of Infectious Diseases, Department of Medicine, University of Pittsburgh School of Medicine, S829 Scaife Hall, 3550 Terrace Street, Pittsburgh, PA 15261 (yod4@pitt.edu).

REFERENCES

1. Datta N, Kontomichalou P. Penicillinase synthesis controlled by infectious *R* factors in Enterobacteriaceae. *Nature* 1965; 208(5007):239–241.
2. Mitsuhashi S, Harada K, Hashimoto H, Egawa R. Drug-resistance of enteric bacteria. 5. Drug-resistance of *Escherichia coli* isolated from human being. *Jpn J Exp Med* 1961;31:53–60.
3. Coque TM, Novais A, Carattoli A, et al. Dissemination of clonally related *Escherichia coli* strains expressing extended-spectrum β-lactamase CTX-M-15. *Emerg Infect Dis* 2008;14(2):195–200.
4. Nicolas-Chanoine MH, Blanco J, Leflon-Guibout V, et al. Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15. *J Antimicrob Chemother* 2008; 61(2):273–281.
5. Rogers BA, Sidjabat HE, Paterson DL. *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. *J Antimicrob Chemother* 2011;66(1):1–14.
6. Banerjee R, Johnston B, Lohse C, et al. *Escherichia coli* sequence type 131 is a dominant, antimicrobial-resistant clonal group associated with healthcare and elderly hosts. *Infect Control Hosp Epidemiol* 2013;34:361–369(in this issue).
7. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 2002;137(10):791–797.
8. Lau SH, Reddy S, Cheesbrough J, et al. Major uropathogenic *Escherichia coli* strain isolated in the northwest of England identified by multilocus sequence typing. *J Clin Microbiol* 2008;46(3): 1076–1080.
9. Blanco M, Alonso MP, Nicolas-Chanoine MH, et al. Molecular epidemiology of *Escherichia coli* producing extended-spectrum β-lactamases in Lugo (Spain): dissemination of clone O25b:H4-ST131 producing CTX-M-15. *J Antimicrob Chemother* 2009; 63(6):1135–1141.
10. Brisse S, Diancourt L, Laouenan C, et al. Phylogenetic distribution of CTX-M- and non-extended-spectrum-β-lactamase-producing *Escherichia coli* isolates: group B2 isolates, except clone ST131, rarely produce CTX-M enzymes. *J Clin Microbiol* 2012;50(9):2974–2981.
11. Burke L, Humphreys H, Fitzgerald-Hughes D. The revolving door between hospital and community: extended-spectrum β-lactamase-producing *Escherichia coli* in Dublin. *J Hosp Infect* 2012;81(3):192–198.
12. Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum-β-Lactamase (ESBL)-producing *Escherichia coli* infection in the United States. *Clin Infect Dis* 2012.
13. Seybold U, Kourbatova EV, Johnson JG, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections. *Clin Infect Dis* 2006;42(5):647–656.
14. Cheng AC, Turnidge J, Collignon P, Looke D, Barton M, Gottlieb T. Control of fluoroquinolone resistance through successful regulation, Australia. *Emerg Infect Dis* 2012;18(9):1453–1460.
15. Rogers BA, Kennedy KJ, Sidjabat HE, Jones M, Collignon P, Paterson DL. Prolonged carriage of resistant *E. coli* by returned travellers: clonality, risk factors and bacterial characteristics. *Eur J Clin Microbiol Infect Dis* 2012;31(9):2413–2420.
16. Johnson JR, Nicolas-Chanoine MH, DebRoy C, et al. Comparison of *Escherichia coli* ST131 pulsotypes, by epidemiologic traits, 1967–2009. *Emerg Infect Dis* 2012;18(4):598–607.
17. Weissman SJ, Johnson JR, Tchesnokova V, et al. High-resolution two-locus clonal typing of extraintestinal pathogenic *Escherichia coli*. *Appl Environ Microbiol* 2012;78(5):1353–1360.
18. Paul S, Linardopoulou EV, Billig M, et al. Role of homologous recombination in adaptive diversification of extra-intestinal *Escherichia coli*. *J Bacteriol* 2012;195:231–242.