Incidence of Antibiotic-Resistant *Escherichia coli* Bacteriuria According to Age and Location of Onset: A Population-Based Study From Olmsted County, Minnesota

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Abstract

Objective: To better understand the epidemiology of drug-resistant *Escherichia coli* across health care and community settings.

Patients and Methods: We conducted a population-based cohort study of the incidence of antibiotic-resistant *E coli* bacteriuria among different patient groups. All urine cultures with monomicrobial growth of *E coli* obtained from Olmsted County, Minnesota, residents from January 1, 2005, through December 31, 2009, were identified. The initial isolate per patient per year was included. Analyses were stratified by patient age and location of infection onset (ie, nosocomial, health care associated, and community associated).

Results: We evaluated 5619 *E coli* isolates and the associated patients. During the study period, the incidence of drug-resistant bacteriuria did not change among children but increased significantly among adults of all ages, most markedly among elderly patients older than 80 years. In elderly patients, the incidence of bacteriuria with isolates resistant to fluoroquinolones increased from 464 to 1116 per 100,000 person-years ($P<.001$), and the incidence of bacteriuria with isolates resistant to fluoroquinolones plus trimethoprim-sulfamethoxazole increased from 274 to 512 per 100,000 person-years ($P<.05$). When analyzed by location of infection onset, incidence of bacteriuria with isolates resistant to trimethoprim-sulfamethoxazole, fluoroquinolones, trimethoprim-sulfamethoxazole plus fluoroquinolones, extended-spectrum cephalosporins, and more than 3 drug classes increased significantly among community-associated but not among nosocomial or health care–associated cases.

Conclusion: In this population-based study, the incidence of antibiotic-resistant *E coli* bacteriuria nearly doubled during the 5-year study period among elderly patients and those with community-associated isolates. These patient groups should be targets of interventions to slow the emergence and spread of antibiotic-resistant *E coli*.

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Escherichia coli is the most common gram-negative pathogen in patients of all ages and the most common cause of urinary tract infections (UTIs). In recent years, there has been rapid, worldwide emergence of antibiotic-resistant *E coli*.[1-6] These resistant strains are a significant public health threat, causing infections that are difficult and costly to treat,[7,8] and are associated with poor outcomes.[9-11]

Community-associated (CA) *E coli* infections have become increasingly drug resistant, particularly to fluoroquinolones and trimethoprim-sulfamethoxazole, reducing options for outpatient treatment of UTI.[2,6] In addition, extended-spectrum β-lactamase and carbapenemase-producing *E coli* strains, such as were historically associated with nosocomial or health care–associated (HA) infections, are now prevalent in the community.[2,6,12-14] Most studies that have examined antibiotic resistance among *E coli* isolates have included convenience samples,[1,2,4,5,15-19] and only 2 have been population based.[20,21] Thus, it is unclear whether the increase in antibiotic-resistant *E coli* infections is disproportionately affecting specific patient groups. The sources, risk factors, and transmission pathways of antimicrobial-resistant *E coli* remain unclear, making design of interventions to slow their emergence and spread challenging.

Olmsted County, Minnesota, has experienced a rapid increase in the prevalence of antimicrobial resistance among *E coli* clinical isolates in recent years.[20] To better understand the epidemiology of drug-resistant *E coli*, we conducted a retrospective, population-based cohort study to determine and compare incidence of antibiotic-resistant *E coli* bacteriuria among different patient groups from 2005 through 2009.

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PATIENTS AND METHODS

Study Setting

The Rochester Epidemiology Project is a unique medical records linkage system that provides nearly complete enumeration of the population of Olmsted County and presents a unique opportunity to conduct population-level epidemiologic studies. Olmsted County is located in southeastern Minnesota, had an estimated population of 143,962 in 2009,[22] and is served by only 2 medical centers (Mayo Clinic and Olmsted Medical Center). The population characteristics of Olmsted County residents are similar to those of US non-Hispanic whites, as described elsewhere.[23,24]

Case Definitions and Ascertainment

We identified urine cultures with growth of *E coli* from January 1, 2005, through December 31, 2009, using records of the microbiology laboratories at Mayo Clinic and Olmsted Medical Center, the 2 main medical centers in the county. We excluded polymicrobial cultures, cultures that had fewer than 10^5 colony-forming units per milliliter, cultures without drug susceptibility test results, and cultures from patients who did not reside in Olmsted County or provide research authorization. The initial isolate per patient per year was included. Isolates were classified as nosocomial (collected from inpatients at >72 hours after hospitalization), HA (collected from outpatients who had been hospitalized 90 days before culture collection; were residents of a nursing home or long-term care facility; or had received home intravenous therapy, wound care, specialized nursing, urinary catheterization, dialysis, or chemotherapy within 30 days before culture collection), and CA (collected from outpatients or inpatients hospitalized for <72 hours without any HA risk factors).[25] Clinical Laboratory Standards Institute–recommended methods were used to determine in vitro antimicrobial susceptibility results. Pre-2010 Clinical Laboratory Standards Institute cephalosporin breakpoints were used. Fluoroquinolone resistance was defined as resistance to levofloxacin or ciprofloxacin. Extended-spectrum cephalosporin resistance was defined as resistance to at least one of the following: ceftriaxone or cefotaxime, ceftazidime, and cefepime. Resistance to more than 3 drug classes was defined as resistance to 3 or more of the following: fluoroquinolones, trimethoprim-sulfamethoxazole, gentamicin, piperacillin-tazobactam, carbapenems, or extended-spectrum cephalosporins.[1] Isolates with intermediate susceptibility were considered resistant. The study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

Statistical Analyses

Age was classified into 4 categories (0-17 years, 18-64 years, 65-79 years, and ≥80 years). These age groups were based on a preliminary analysis that found significantly higher rates of *E coli* drug resistance in adults older than 65 years compared with younger adults and adults older than 80 years compared with those 65 to 79 years of age. Trends were evaluated using the Poisson distribution. Annual incidence rates, expressed as the number of first-episode *E coli* urine isolates per 100,000 person-years, were calculated, assuming that the entire population of Olmsted County was at risk each year. Some patients had multiple isolates during the study period; the first isolate per patient per calendar year was included to calculate annual incidence rates. Incidence rates were age adjusted to the US white population in 2009. The statistical analysis was performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC).

TABLE. Demographic Characteristics of Patients With *Escherichia coli* Urine Isolates, Olmsted County, Minnesota, 2005-2009

Characteristic	No. (%) (N=5619 isolates)
Age (y)	
0-17	892 (15.9)
18-64	2709 (48.2)
65-79	945 (16.8)
≥80	1073 (19.1)
Female	4920 (87.6)
Outpatient	4908 (87.4)
Site of acquisition	
Community associated	4135 (73.6)
Health care associated	1235 (22.0)
Nosocomial	249 (4.4)
Long-term care facility	41 (0.7)

RESULTS

Demographic Characteristics

A total of 5619 urine isolates from 4736 unique patients were included in the study. The Table lists the demographic characteristics of the study population. Most patients were female (88%) and outpatients (87%), and nearly half were 18 to 64 years of age (48%). Overall, 74% of the isolates were CA, 22% were HA, and 4% were nosocomial. Pediatric patients accounted for 19% of the CA isolates, 9% of HA isolates, and only 2% of nosocomial isolates. In contrast, patients older than 80 years accounted for 13% of CA, 36% of HA, and 37% of nosocomial isolates. Extremely few patients (0.7%) were long-term care facility residents.

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Prevalence of Antimicrobial Resistance Among *E coli* Urine Isolates

We first examined the proportion of isolates with antibiotic resistance for each year of the study period. The number of isolates was 1129 (20%) in 2005, 1170 (21%) in 2006, 1116 (20%) in 2007, 1112 (20%) in 2008, and 1092 (19%) in 2009. Between 2005 and 2009 statistically significant increases were found in resistance to ampicillin (39%-43%; $P=.02$), cefazolin (4%-7%; $P<.001$), trimethoprim-sulfamethoxazole (17%-25%; $P<.001$), fluoroquinolones (7%-16%; $P<.001$), fluoroquinolone plus trimethoprim-sulfamethoxazole (4%-10%; $P<.001$), gentamicin (3%-7%; $P<.001$), extended-spectrum cephalosporins (1%-3%; $P<.001$), and more than 3 drug classes (2%-5%; $P=.003$). Uniquely, nitrofurantoin resistance did not increase during the study period. These trends were significant among adults but not children (data not shown), prompting us to further stratify the adult population in subsequent analyses of incidence rates.

Incidence by Age

We determined and compared trends in the incidence of *E coli* bacteriuria among different age cohorts. In 2009 the incidence (per 100,000 person-years) of bacteriuria (due to susceptible and resistant isolates) was 413 in children 17 years or younger, 588 in patients 18 through 64 years old, 1628 in patients 65 through 79 years old, and 3879 in patients 80 years and older. The incidence of drug-susceptible bacteriuria decreased significantly ($P<.001$) among all age groups during the study period (Figure 1, A and Supplemental Table, avail-

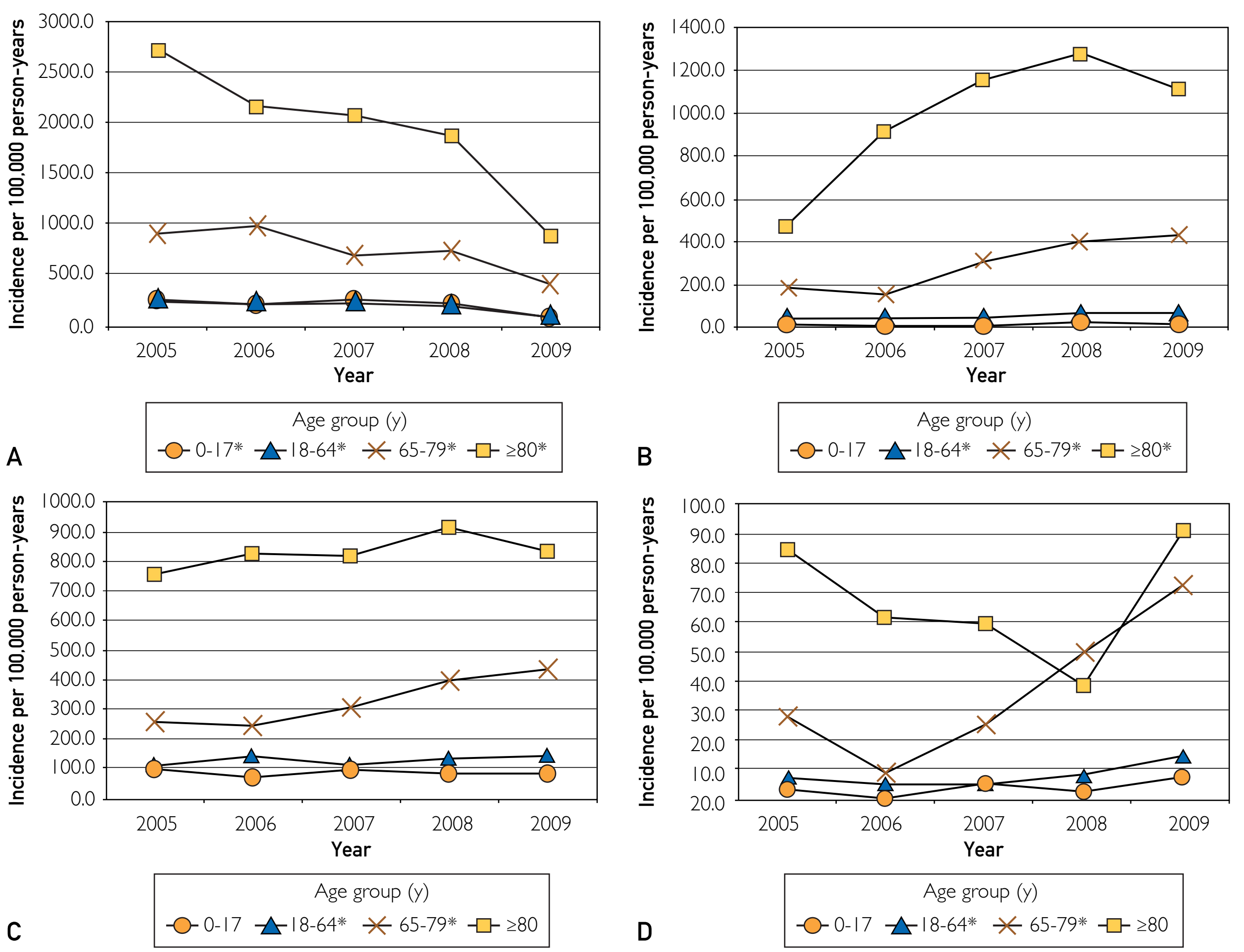

FIGURE 1. Incidence of *Escherichia coli* bacteriuria by age, Olmsted County, Minnesota, 2005-2009. A, Drug-susceptible isolates. B, Fluoroquinolone-resistant isolates. C, Trimethoprim-sulfamethoxazole–resistant isolates. D, Extended-spectrum cephalosporin–resistant isolates. Asterisk indicates $P<.05$.

able online at mayoclinicproceedings.org). In contrast, the incidence of bacteriuria resistant to fluoroquinolone or trimethoprim-sulfamethoxazole plus fluoroquinolone increased significantly ($P<.05$) in all 3 adult groups but did not change in children (Figure 1, B). The incidence of fluoroquinolone-resistant bacteriuria increased most rapidly in patients 80 years and older (from 464 to 1116; $P<.001$) and increased more slowly in those 65 to 79 years of age (from 187 to 429; $P<.001$) and 18 to 64 years of age (from 36 to 63; $P<.001$) (Figure 1, B and Supplemental Table, available online at http://www.mayoclinicproceedings.org). The incidence of bacteriuria with isolates resistant to cefazolin, gentamicin, trimethoprim-sulfamethoxazole, or extended-spectrum cephalosporins increased significantly ($P<.05$) among patients 18 to 64 and 65 to 79 years of age but did not change among children or those =80 years and older (Figure 1, C and D, and Supplemental Table, available online at http://www.mayoclinicproceedings.org). No change was found in the incidence of ampicillin or nitrofurantoin resistance in any age group.

Incidence by Location of Onset

Trends in the incidence of antibiotic-resistant *E coli* bacteriuria also differed by CA, HA, or nosocomial onset. In all 3 groups, the incidence (per 100,000 person-years) of drug-susceptible bacteriuria decreased significantly (Figure 2, A and Supplemental Table, available online at http://www.mayoclinicproceedings.org), whereas the incidence of fluoroquinolone-resistant bacteriuria increased (Figure 2, B and Supplemental Table, available online at http://www.mayoclinicproceedings.org), most significantly among the CA isolates (from 31 to 80 per 100,000; $P<.001$). Likewise, the incidence of bacteriuria resistant to fluoroquinolone plus trimethoprim-sulfamethoxazole nearly tripled among

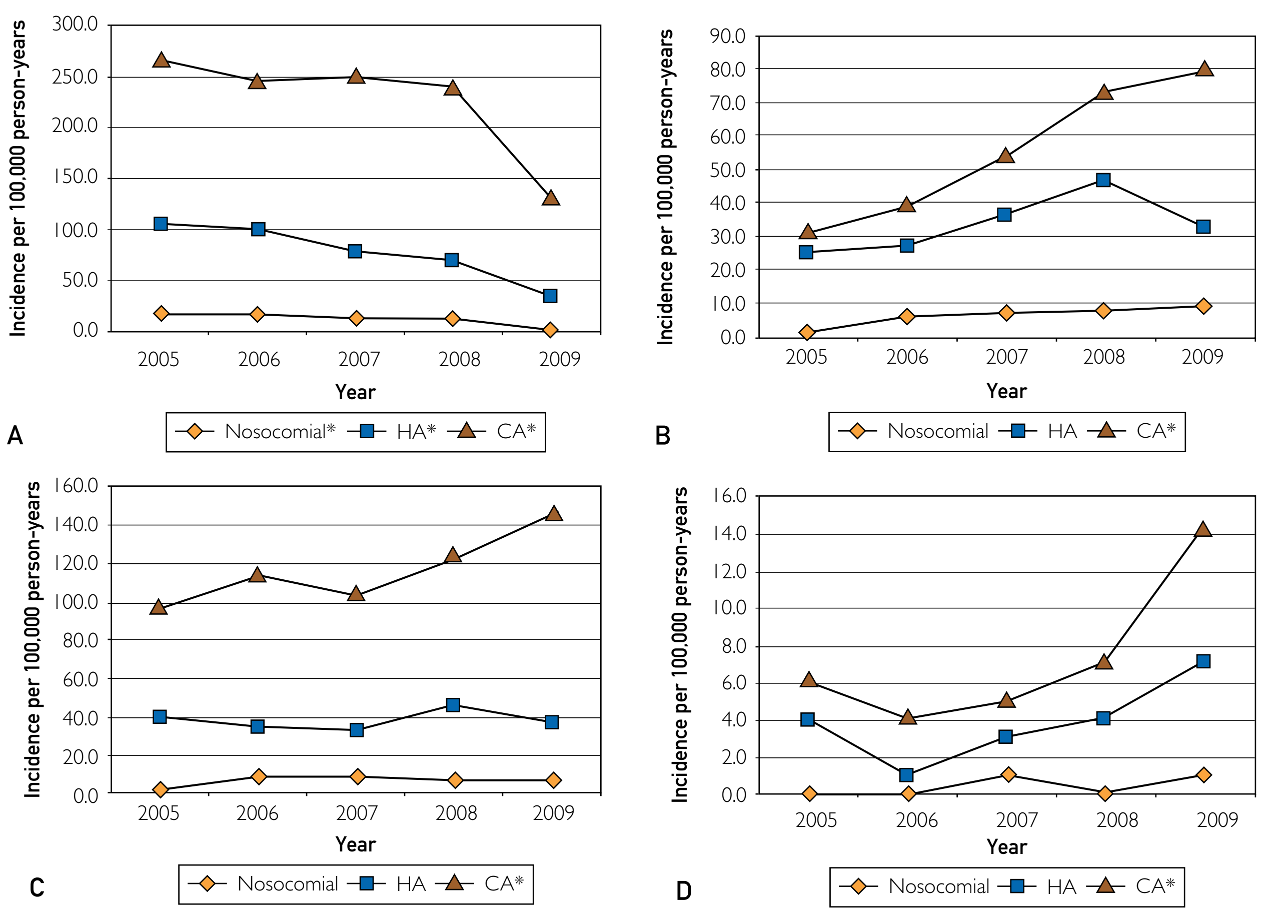

FIGURE 2. Incidence of *Escherichia coli* bacteriuria by location of onset, Olmsted County, Minnesota, 2005-2009. A, Drug-susceptible isolates. B, Fluoroquinolone-resistant isolates. C, Trimethoprim-sulfamethoxazole–resistant isolates. D, Extended-spectrum cephalosporin–resistant isolates. CA = community associated; HA = health care associated. Asterisk indicates $P<.05$.

CA isolates (from 18 to 49; $P<.001$). In addition, although the incidence of bacteriuria with isolates resistant to trimethoprim-sulfamethoxazole, gentamicin, extended-spectrum cephalosporins, or more than 3 drug classes did not change significantly among the nosocomial or HA groups (Figure 2, C and D, and Supplemental Table, available online at http://www.mayoclinicproceedings.org), it increased significantly among CA isolates (from 97 to 145 [$P=.002$] for trimethoprim-sulfamethoxazole, 15 to 37 [$P<.001$] for gentamicin, 6 to 14 [$P=.01$] for extended-spectrum cephalosporins, and 8 to 25 [$P<.001$] for >3 drug classes). Notably, the incidence of ampicillin and nitrofurantoin resistance did not change significantly in any group.

DISCUSSION

In this 5-year, population-based study of *E coli* bacteriuria in Olmsted Country, Minnesota, we found that the incidence of antibiotic-resistant bacteriuria increased most significantly among elderly patients and residents in the community but did not change among children or those with HA or nosocomial bacteriuria. This is the first population-based study conducted in the current era of widespread CA, drug-resistant *E coli.* We compared incidences across ages and hospital and community settings, in contrast to prior population-based studies, which restricted their analyses to only community-onset *E coli* infections[21,26] or infections in elderly patients[27] or evaluated the overall prevalence of antimicrobial resistance without stratifying by patient characteristics.[20,21]

In our study, the incidence of drug-susceptible or drug-resistant *E coli* bacteriuria increased with age and was 10 times higher in patients 80 years and older compared with children. This is consistent with the findings that rates of bacteriuria and UTI increase with age.[26,28-30] Risk factors for UTI in elderly individuals include cognitive impairment, urinary incontinence, and inability to perform activities of daily living.[30] Notably, during the study period, drug-resistant strains replaced drug-susceptible ones among patients older than 65 years because the incidence of overall bacteriuria did not change but the incidence of drug-resistant bacteriuria (with isolates resistant to fluoroquinolones, fluoroquinolone plus trimethoprim-sulfamethoxazole, or >3 drug classes) nearly doubled. Patients 80 years and older contributed nearly 40% of the nosocomial and HA *E coli* isolates in our study, suggesting that well-described risk factors, such as residence in long-term care facilities,[31,32] prior antimicrobial exposure,[33-36] or use of urinary catheters,[27,37,38] are likely contributing to emerging drug resistance in this group of patients.

The incidence of drug-resistant *E coli* also increased significantly among CA isolates, suggesting that younger adults (ages 18-64 years), who contributed half of the CA isolates in this study, are also at risk for drug-resistant *E coli*. This increase in resistance among *E coli* in the community has been reported in numerous studies[3,4,39-41] and may be due to several factors, including increasing reliance on outpatient medical management, increasing antimicrobial use in the outpatient setting, transmission of drug-resistant strains from the hospital into the community, or expansion of drug-resistant clones within the community.[3,14,18,42]

Because resistance to fluoroquinolone and fluoroquinolone plus trimethoprim-sulfamethoxazole increased more markedly than resistance to other antibiotics among our *E coli* isolates from 2005 through 2009, we hypothesize that there has been expansion of drug-resistant clones within Olmsted County. In the United States, more than half of *E coli* with resistance to fluoroquinolones or fluoroquinolones plus trimethoprim-sulfamethoxazole are sequence type 131,[1] a highly drug-resistant and globally disseminated clonal group first reported in 2008.[2,3,5,17] We are currently performing molecular epidemiology studies to determine whether clonal expansion of sequence type 131 or other clonal groups has contributed to the rapid increase in drug resistance we observed.

Results from this study and others[26,43,44] suggest that to accurately represent *E coli* resistance rates, antibiograms should be stratified by patient age and location of infection onset. Pooling susceptibility data from all *E coli* isolates in our study into a cumulative antibiogram resulted in overestimating resistance among pediatric isolates and underestimating resistance among isolates from elderly individuals (data not shown), both of which may lead to inappropriate empiric antibiotic selection. Furthermore, although monitoring antimicrobial resistance among both CA and nosocomial isolates is recommended,[45] few medical centers have done this routinely.

A strength of this study is that it was population based, with a large sample size. We had nearly complete enumeration of Olmsted County residents of all ages, eliminated referral bias, and included isolates from both health care and community settings. Limitations of this study include that findings are likely generalizable only to populations that are similar to that of Olmsted County. In addition, we relied on laboratory data and excluded individuals who did not have cultures obtained. This approach may have resulted in overrepresentation of patients with complicated UTIs and drug-resistant isolates because it is possible that some patients with UTIs did not have urine cultures obtained. Moreover, we lacked clinical presentation data and so could not distinguish *E coli* colonization from infection. It is likely that some *E coli* isolates that were included were from cases of asymptomatic bacteriuria, especially among elderly individuals; therefore, we quantified the incidence of bacteriuria rather than of UTI. To minimize the effects of individuals with multiple urine cultures per year who are more likely to have complicated UTIs, colonized indwelling urinary catheters, or asymptomatic bacteriuria, we included only one urinary isolate per person per year. Despite these limitations, the increasing incidence of antibiotic resistance among *E coli* isolates during our study period is noteworthy and should affect clinical practice. Clinicians should be aware of these trends and use nitrofurantoin as first-line therapy for uncomplicated cystitis in our county, as recommended in recent treatment guidelines.[46]

CONCLUSION

From 2005 through 2009 the incidence of drug-resistant *E coli* uropathogens increased significantly among the elderly and community residents of Olmsted County, Minnesota. Future research priorities include elucidating the risk factors and transmission pathways of resistant strains within these patient groups to design interventions that slow the emergence and spread of antibiotic-resistant *E coli*.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayclinicproceedings.org.

Abbreviations and Acronyms: **CA** = community associated; **HA** = health care associated; **UTI** = urinary tract infection

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