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Antimicrobial resistance trends of *Escherichia coli* bloodstream isolates: a population-based study, 1998–2007

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***Background*: There have been contradictory results regarding temporal changes in the antimicrobial resistance of *Escherichia coli* from tertiary care centres. Therefore, we performed a population-based investigation to examine *in vitro* antimicrobial resistance trends of *E. coli* bloodstream isolates.**

***Methods*: In this retrospective population-based incidence study, we identified 461 unique patients with first episodes of *E. coli* bloodstream infection (BSI) from 1 January 1998 to 31 December 2007 through microbiology records at the two laboratories in Olmsted County, Minnesota. Logistic regression was used to examine temporal changes in antimicrobial resistance and Poisson regression for changes in incidence rates.**

***Results*: The median age of patients with *E. coli* BSI was 69 years; 306 (66.4%) were female. The age-adjusted incidence rate of *E. coli* BSI per 100 000 person-years was 48.0 (95% CI: 42.5–53.4) in females and 34.0 (95% CI: 28.6–39.6) in males. The urinary tract was the most common primary source of infection (79.8%). During the study period, resistance rates of *E. coli* bloodstream isolates increased from 32% to 53% for ampicillin, from 23% to 45% for ampicillin/sulbactam, from 9% to 28% for trimethoprim/sulfamethoxazole and from 0% to 12% for ciprofloxacin. Resistance rates to carbapenems, cephalosporins and piperacillin/tazobactam remained low and stable.**

***Conclusions*: To our knowledge, this is the first population-based study on antimicrobial resistance trends of *E. coli* bloodstream isolates in the USA. We demonstrated linear trends of increasing resistance among these isolates to three different classes of antimicrobial over the past decade.**

Keywords: bacteraemia, *E. coli*, epidemiology, fluoroquinolones

Introduction

Escherichia coli is the most common cause of bloodstream infection (BSI) in population-based settings.[1–5] There are conflicting results in the literature regarding antimicrobial resistance trends of *E. coli*. Although some studies have reported trends of increasing antimicrobial resistance, others have not.[6–13] These studies, for the most part, have been performed at tertiary care centres where referral bias could overestimate the true antimicrobial resistance rates.[14] In addition, some studies have included urinary and respiratory *E. coli* isolates that may not be of clinical significance, particularly in hospitalized patients.[6,9–11]

To our knowledge, population-based studies that examine the antimicrobial resistance trends of *E. coli* bloodstream isolates in the USA are lacking. Therefore, we performed a population-based study to examine antimicrobial resistance trends of *E. coli* bloodstream isolates in Olmsted County, Minnesota, over the past decade. We hypothesized that there was a trend of increasing resistance among these isolates to three different types of antimicrobial (ampicillin, trimethoprim/sulfamethoxazole and ciprofloxacin) from 1998 to 2007.

Materials and methods

Setting

Olmsted County is located in southeastern Minnesota with a population of 124 277 according to the 2000 census.[15] With the exception

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of a lower prevalence of injection drug use, a higher prevalence of middle-class individuals and a higher proportion being employed in the healthcare industry, the population characteristics of Olmsted County residents are similar to those of USA non-Hispanic whites.[16,17] The Rochester Epidemiology Project (REP) is a unique medical records-linkage system that encompasses care delivered to residents of Rochester and Olmsted County, Minnesota. The microbiology laboratories at the Mayo Medical Center and Olmsted Medical Center are the only two laboratories in Olmsted County. These two medical centres are geographically isolated from other urban centres as described previously;[14,16,18] therefore, local residents are able to obtain healthcare within the community, rather than seeking healthcare at a distant geographic location.

Case ascertainment

We used complete enumeration of Olmsted County, Minnesota, population from 1 January 1998 to 31 December 2007. Using the microbiology databases at the Mayo Medical Center Rochester and Olmsted Medical Center, we identified 461 unique patients with first episodes of monomicrobial *E. coli* BSI. Medical records were reviewed by the primary investigator (M. N. A.) to confirm the diagnosis, determine patient residency status, obtain baseline clinical features and obtain *in vitro* antimicrobial susceptibility data. Blood cultures were identified using standard microbiology techniques according to the CLSI. Both laboratories are certified by the College of American Pathologists. CLSI methods were employed to evaluate *in vitro* antimicrobial susceptibility results of *E. coli* isolates. The study was approved by the institutional review boards of both institutions. The detailed case ascertainment and blood culture methods used were described elsewhere.[5,14]

Case definition

Monomicrobial *E. coli* BSI was defined as growth of only *E. coli* in a blood culture, excluding coagulase-negative staphylococci, *Corynebacterium* species and *Propionibacterium* spp. Cases were classified according to the site of acquisition into nosocomial, healthcare-associated and community-acquired, as previously defined.[19] The primary source of BSI was defined using the Centers for Disease Control and Prevention criteria.[20] Fluoroquinolone-resistant *E. coli* isolates were defined as isolates that are resistant *in vitro* to ciprofloxacin. All aspects of the study were prespecified in the study protocol prior to data collection.

Statistical analysis

Descriptive statistics were used to summarize the data: medians and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. The χ^2 or Fisher's exact test, as appropriate, was used to evaluate associations between categorical variables.

Incidence rate (IR), expressed as the number of new cases of *E. coli* BSI per 100000 person-years, was calculated assuming that the entire population of Olmsted County was at risk of *E. coli* BSI. Age-, gender- and calendar year-specific IRs were estimated by using the number of patients in each age, gender and calendar year group as the numerator, with corresponding denominators obtained from the 2000 Olmsted County census. A projected population growth rate of 1.9% per year after 2000 was assumed. The rates were directly adjusted to the USA 2000 white population.[15] To calculate the rates, the 10 year study period was divided into five 2 year intervals (1998–99, 2000–01, 2002–03, 2004–05 and 2006–07) and age was categorized into five groups (0–18, 19–39, 40–59, 60–79 and ≥80 years). Ninety-five per cent confidence intervals (95% CIs) were derived using the Poisson distribution.

Poisson regression was used to test for a linear trend in IR for each antimicrobial separately. To examine temporal changes in antimicrobial resistance, *E. coli* isolates that were resistant or had intermediate susceptibility to a particular antimicrobial were classified as being resistant to that antimicrobial; otherwise, the isolate was classified as being susceptible. Logistic regression was used to test for a linear increase in the log odds of *E. coli* isolates that are resistant to each antimicrobial throughout the study period; the 10 year study period was divided into five 2 year intervals as described previously. Goodness of fit was evaluated using deviance and the Hosmer–Lemeshow test for each Poisson and logistic regression model, respectively. For testing goodness of fit, a significance threshold was defined as $P<0.01$. The GENMOD procedure in SAS (version 8, SAS Institute Inc, Cary, NC, USA) was used to perform Poisson regression, and the LOGISTIC procedure for logistic regression. The level of significance for all statistical testing was defined as $P<0.05$ (two-sided) unless otherwise noted.

Results

We identified 461 unique patients with *E. coli* BSI during the study period. The median age of patients with *E. coli* BSI was 69 (IQR: 50–81) years. Three hundred and six (66.4%) were female. Gender-specific IRs for each age group are illustrated in Figure 1. Age-adjusted IR per 100000 person-years was higher in females than in males [48.0 (95% CI: 42.5–53.4) versus 34.0 (95% CI: 28.6–39.6)]. The age- and gender-adjusted IR of *E. coli* BSI remained relatively stable across the 10 year study period (ranging from 37 to 47 per 100000 person-years; Figure 2) with an overall age- and gender-adjusted IR of 41.4 per 100000 person-years (95% CI: 37.6–45.3).

Most cases were community-acquired (59.4%); the remainder were healthcare associated (31.7%) or nosocomial (8.9%). The urinary tract was the most common primary source of infection (79.8%), followed by the gastrointestinal tract (8.7%), the respiratory tract (3.0%) and other sites (1.3%). Thirty-three patients (7.2%) had primary BSI of unknown primary source. Females were more likely to have a urinary primary source of infection than males (85.6% versus 68.4%, $P<0.001$).

The *in vitro* antimicrobial resistance rates of *E. coli* bloodstream isolates to all tested antimicrobials are shown in Table 1.

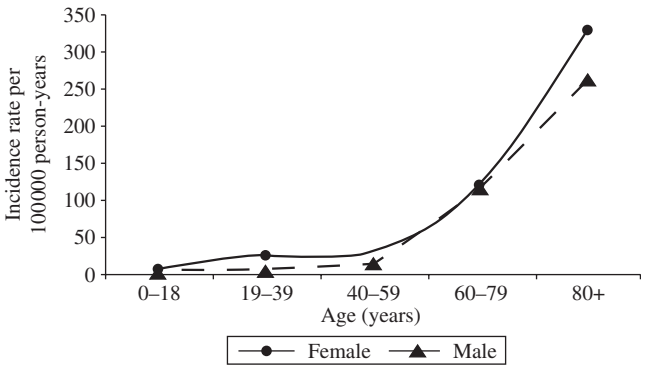

Figure 1. Incidence rate of *E. coli* bloodstream infection by age and gender, 1998–2007.

There was a linear trend of increasing resistance among *E. coli* bloodstream isolates to ampicillin ($P=0.004$), ampicillin/sulbactam ($P=0.002$), trimethoprim/sulfamethoxazole ($P=0.002$) and fluoroquinolones ($P=0.004$ and $P=0.003$ for levofloxacin and ciprofloxacin, respectively) during the 10 year study period (Figure 3). The increase in antimicrobial resistance rates was more prominent in 2006–07. Resistance rates to gentamicin, piperacillin/tazobactam and cephalosporins remained generally low during the study period with no statistically significant linear trends of increasing resistance (Table 1). Following the introduction of the extended-spectrum β-lactamase (ESBL) screen in our microbiology laboratory in 2000, only three ESBL-producing *E. coli* bloodstream isolates have been identified. No carbapenem-resistant *E. coli* bloodstream isolates were detected in our population over the past decade.

Although the age- and gender-adjusted IR of *E. coli* BSI remained relatively stable, there was an increase in the IR of antimicrobial-resistant *E. coli* BSI over the study period (Figure 2). The age- and gender-adjusted IR per 100 000 person-years increased from 14 to 20 for ampicillin-resistant *E. coli* BSI, from 4 to 10 for trimethoprim/sulfamethoxazole-resistant *E. coli* BSI and from 0 to 5 for ciprofloxacin-resistant *E. coli* BSI during the past decade ($P=0.095$, $P=0.009$ and $P=0.003$, respectively; test for linear trend across the 10 year study period).

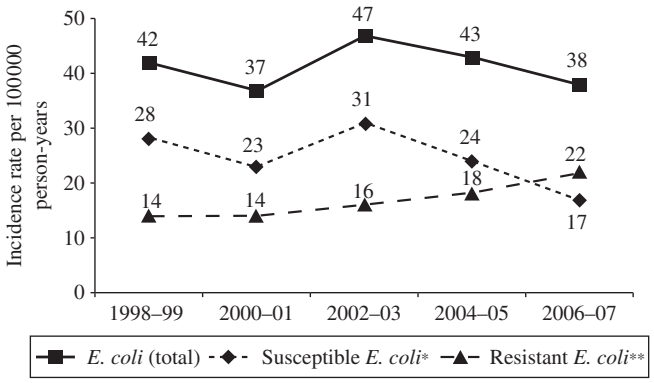

Figure 2. Age- and gender-adjusted incidence rates of antimicrobial-susceptible, antimicrobial-resistant and total *E. coli* BSI by each 2 year interval, 1998–2007. **E. coli* bloodstream isolates susceptible to all tested antimicrobials. ***E. coli* bloodstream isolates resistant to at least one tested antimicrobial.

Fluoroquinolone-resistant *E. coli* bloodstream isolates were more likely to be resistant to other antimicrobial agents than fluoroquinolone-susceptible isolates. Of 31 fluoroquinolone-resistant *E. coli* isolates, 23 (87.1%) were resistant to ampicillin, compared with only 147 (34.3%) of 428 fluoroquinolone-susceptible isolates ($P<0.001$). Similarly, 23 (74.2%) of 31 fluoroquinolone-resistant *E. coli* bloodstream isolates were resistant to trimethoprim/sulfamethoxazole, compared with only 64 (15.0%) of 428 fluoroquinolone-susceptible isolates ($P<0.001$).

Discussion

To our knowledge, this is the first population-based study of antimicrobial resistance trends of *E. coli* bloodstream isolates in the USA. We demonstrated trends of increasing resistance among these isolates to five different antimicrobials (ampicillin, ampicillin/sulbactam, trimethoprim/sulfamethoxazole, ciprofloxacin and levofloxacin) in three classes over the past decade. Resistance rates to gentamicin, piperacillin/tazobactam, cefazolin, ceftazidime and cefepime remained low and stable and there was no resistance to imipenem or meropenem among the isolates.

A previous study in the Danish population demonstrated an increase in resistance to ampicillin among *E. coli* bloodstream isolates from 17% to 28% between 1981 and 1997.[1] Our study showed that resistance to ampicillin continued to increase (from 32% to 53% between 1998 and 2007). Although the two studies were performed in different geographic locations, it appears that resistance rates to ampicillin among *E. coli* bloodstream isolates have tripled in the past three decades.

More recently, similar trends of increasing resistance were reported from a hospital-based study in Spain from 1997 to 2005.[12] Resistance rates among *E. coli* bloodstream isolates

Table 1. *In vitro* antimicrobial resistance rates of *E. coli* bloodstream isolates to antimicrobials, 1998–2007

Antimicrobial	1998–99	2000–01	2002–03	2004–05	2006–07	Overall	*P* value*
Ampicillin	28/87 (32)	27/80 (34)	35/103 (34)	36/98 (37)	48/91 (53)	174/459 (38)	0.004
Ampicillin/sulbactam	20/87 (23)	24/80 (30)	30/103 (29)	32/98 (33)	41/91 (45)	147/459 (32)	0.002
Cefazolin	2/87 (2)	1/80 (1)	3/103 (3)	3/98 (3)	5/91 (5)	14/459 (3)	0.239
Cefepime	1/86 (1)	0/75 (0)	0/95 (0)	1/89 (1)	0/82 (0)	2/427 (0)	0.614
Ceftazidime	1/87 (1)	1/80 (1)	0/103 (0)	1/98 (1)	2/91 (2)	5/459 (1)	0.514
Ciprofloxacin	0/87 (0)	4/80 (5)	9/103 (9)	7/98 (7)	11/91 (12)	31/459 (7)	0.003
Gentamicin	1/87 (1)	3/80 (4)	4/103 (4)	3/98 (3)	4/91 (4)	15/459 (3)	0.241
Imipenem	0/86 (0)	0/75 (0)	0/95 (0)	0/89 (0)	0/82 (0)	0/427 (0)	—
Levofloxacin	0/86 (0)	3/75 (4)	9/95 (9)	7/89 (8)	9/82 (11)	28/427 (7)	0.004
Meropenem	0/86 (0)	0/75 (0)	0/95 (0)	0/88 (0)	0/82 (0)	0/426 (0)	—
Piperacillin/tazobactam	0/86 (0)	0/75 (0)	4/95 (4)	0/89 (0)	1/83 (1)	5/428 (1)	0.515
Trimethoprim/sulfamethoxazole	8/87 (9)	17/80 (21)	22/103 (21)	15/98 (15)	25/91 (27)	87/459 (19)	0.002

Data are shown as number of non-susceptible isolates/number of isolates tested (%).
In vitro antimicrobial susceptibility results were not available for two *E. coli* bloodstream isolates.
**P* value denotes a one-degree of freedom test for linear trend using logistic regression.

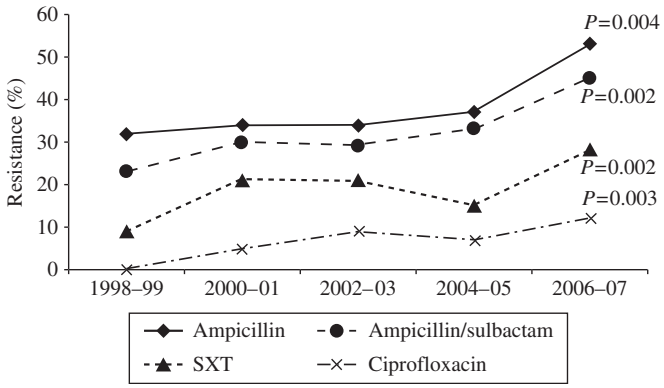

Figure 3. *In vitro* antimicrobial resistance rates of *E. coli* bloodstream isolates by each 2 year interval, 1998–2007. *P* value denotes a one-degree of freedom test for linear trend using logistic regression. SXT, trimethoprim/sulfamethoxazole.

increased from 47% to 63% for ampicillin, from 24% to 34% for trimethoprim/sulfamethoxazole and from 16% to 23% for ciprofloxacin. Although the higher rates of reported resistance in the latter study compared with ours may be due to higher rates of resistance in Spain than in the USA, it remains possible that referral bias also contributed. In contrast to this study from Spain, we did not detect a trend of increasing resistance to third-generation cephalosporins.

Our results were also consistent with those of a recent population-based study from Calgary, Canada, where increasing antimicrobial resistance rates among *E. coli* bloodstream isolates to ampicillin, amoxicillin/clavulanate and ciprofloxacin, and stable antimicrobial resistance rates to piperacillin/tazobactam and carbapenems were observed between 2000 and 2006.[21] *E. coli* bloodstream isolates in Calgary health region demonstrated trends of increasing resistance to cephalosporins as well.

There are several surveillance studies on *E. coli* antimicrobial resistance trends in the USA, but these studies, for the most part, are hospital based. In fact, many studies have exclusively examined nosocomial isolates.[6,9,13] Some studies have combined bloodstream with other clinical sources of isolates (urinary, respiratory, etc.).[6,9–11] Moreover, results of these studies have been conflicting. One study showed no trend of increasing resistance to ampicillin among nosocomial *E. coli* bloodstream isolates between 1995 and 2002.[13] Another study showed a trend of increasing resistance to third-generation cephalosporins among nosocomial *E. coli* isolates between 1986 and 2003.[9] A subsequent report demonstrated no increase in resistance to third-generation cephalosporins among intensive care unit *E. coli* isolates between 1992 and 2004.[6] Another study reported an increase in resistance to ciprofloxacin among intensive care unit *E. coli* isolates from 1% to 17% between 1993 and 2004.[11] To our knowledge, the only population-based study of *E. coli* antimicrobial resistance trends in the USA included only urinary tract isolates and, contrary to our study, showed no trends of increasing resistance to trimethoprim/sulfamethoxazole or ciprofloxacin between 1999 and 2005.[22]

The increase in resistance to antimicrobial agents, particularly fluoroquinolones, among *E. coli* bloodstream isolates in our study is disturbing. Resistance rates to fluoroquinolones have increased to 12% in the 2006–07 interval of the study. This could have a significant impact on the empirical choice of antimicrobial regimen in patients who present with possible *E. coli* BSI or pyelonephritis. We have previously demonstrated a similar trend of increasing resistance to fluoroquinolones among *E. coli* bloodstream isolates in solid organ transplant recipients between 1998 and 2007.[23] An increase in resistance to fluoroquinolones in the general population carries more clinical and public health implications. Because 80% of *E. coli* bloodstream isolates in this study are from a urinary source, it is conceivable that the observed resistance trends in *E. coli* bloodstream isolates are reflective of resistance of *E. coli* urinary tract isolates in our population. Because fluoroquinolones, especially the newer ones, have the highest bioavailability among all available oral antimicrobials with Gram-negative activity, this trend of increasing resistance to fluoroquinolones will likely restrict availability of a reliable oral therapy for 'switch' therapy of serious *E. coli* infections. Additionally, because fluoroquinolone-resistant *E. coli* isolates are more likely to be resistant to ampicillin and trimethoprim/sulfamethoxazole, an increasing proportion of patients with *E. coli* urinary tract infections may require intravenous antimicrobial therapy for the duration of treatment, which could markedly increase the cost of therapy.[24]

Currently, ampicillin is rarely used for empirical therapy of *E. coli* BSI, and yet, ampicillin/sulbactam has remained listed as an option in some of these regimens.[25] The alarmingly high resistance rate to ampicillin/sulbactam among *E. coli* bloodstream isolates is a notable observation in our investigation. Only 55% of *E. coli* bloodstream isolates were susceptible to ampicillin/sulbactam during 2006–07; therefore, empirical use of this antimicrobial for treatment of possible *E. coli* BSI should be discouraged, at least in our local population. Fortunately, resistance rates to other β-lactam antibiotics, including piperacillin/tazobactam, carbapenems and third- and fourth-generation cephalosporins, have remained low.

Factors operative in the increase in resistance to antimicrobials in *E. coli* bloodstream isolates in our population over the past decade remain to be defined. We speculate that the increasing use of antimicrobials, particularly fluoroquinolones, may be associated with an increasing rate of fluoroquinolone resistance, as previously suggested in other populations.[26] Despite the availability of ciprofloxacin for human use in the USA since 1987, resistance rates to fluoroquinolones among *E. coli* bloodstream isolates remained very low at the beginning of our study in 1998. It is conceivable that resistance rates to fluoroquinolones have increased since the introduction of newer fluoroquinolones in the USA in 1996. A previous study of *Pseudomonas aeruginosa* isolates suggested that exposure to levofloxacin, but not ciprofloxacin, was associated with an increased risk of development of fluoroquinolone-resistant *P. aeruginosa* isolates.[27] Another possible explanation for increasing fluoroquinolone resistance is use of fluoroquinolones in animals. There is a temporal association between increasing fluoroquinolone resistance in *E. coli* bloodstream isolates in our population and the licensing of these antimicrobials for veterinary use in 1995. A similar ecological association has been shown in other enteric Gram-negative pathogens, such as *Salmonella* and *Campylobacter* species.[28–30] Clearly, additional studies that examine risk factors for the development of fluoroquinolone resistance among *E. coli* are warranted.

The major strength of our work is the large sample size with which to perform the proposed statistical analyses. Contrary to

some previous cross-sectional studies that examined antimicrobial resistance trends over multiple interrupted points in time, we provided a more complete view of antimicrobial resistance trends by including all *E. coli* bloodstream isolates over the past 10 years. Additionally, the population-based design added strength and uniqueness to our work.

Our study has limitations. First, we did not perform genetic or molecular testing on *E. coli* bloodstream isolates to examine for specific resistance genes or enzymes. Second, our data were derived from one geographic area. Since resistance patterns may vary from one geographic location to another, studies from multiple sites may provide a more comprehensive picture of resistance trends across the country. Other limitations include the retrospective design and the reliance on one source for case ascertainment. Finally, the population of Olmsted County consists mainly of middle-class whites; therefore, our study results may be generalized only to communities with similar population characteristics.

In summary, we demonstrated a trend of increasing resistance among *E. coli* bloodstream isolates to three different classes of antimicrobial over the past decade. Increasing resistance, particularly to fluoroquinolones, may have an impact on choice of empirical antimicrobial therapy in patients who present with *E. coli* BSI or serious upper urinary tract infections.

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Transparency declarations

None to declare.

M. N. A. and B. D. L. have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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