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Seasonal variation in *Escherichia coli* bloodstream infection: a population-based study

M. N. Al-Hasan[1,2], B. D. Lahr[3], J. E. Eckel-Passow[3] and L. M. Baddour[2]

1) *Division of Infectious Diseases, Department of Medicine, University of Kentucky, Lexington, KY,* 2) *Division of Infectious Diseases, Department of Medicine and* 3) *Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN, USA*

Abstract

Seasonal variation in the rates of infection with certain Gram-negative organisms has been previously examined in tertiary-care centres. We performed a population-based investigation to evaluate the seasonal variation in *Escherichia coli* bloodstream infection (BSI). We identified 461 unique patients in Olmsted County, Minnesota, from 1 January 1998 to 31 December 2007, with *E. coli* BSI. Incidence rates (IR) and IR ratios were calculated using Rochester Epidemiology Project tools. Multivariable Poisson regression was used to examine the association between the IR of *E. coli* BSI and average temperature. The age- and gender-adjusted IR of *E. coli* BSI per 100 000 person-years was 50.2 (95% CI 42.9–57.5) during the warmest 4 months (June through September) compared with 37.1 (95% CI 32.7–41.5) during the remainder of the year, resulting in a 35% (95% CI 12–66%) increase in IR during the warmest 4 months. The average temperature was predictive of increasing IR of *E. coli* BSI (p 0.004); there was a 7% (95% CI 2–12%) increase in the IR for each 10-degree Fahrenheit (*c.* 5.5°C) increase in average temperature. To our knowledge, this is the first study to demonstrate seasonal variation in *E. coli* BSI, with a higher IR during the warmest 4 months than during the remainder of the year.

Keywords: Bacteraemia, epidemiology, *Escherichia coli*, incidence, seasonal variation
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Corresponding author and reprint requests: M. N. Al-Hasan, University of Kentucky Chandler Medical Center, 800 Rose Street, Room MN 672, Lexington, KY 40536, USA
E-mail: majdi.alhasan@uky.edu

Introduction

Seasonal variation in rates of infection with certain Gram-negative organisms including *Acinetobacter* species [1], *Aeromonas hydrophila* [2] and *Burkholderia pseudomallei* [3] has been previously described. A more recent study described seasonal variation in the incidence rates (IR) of infections due to *Acinetobacter baumannii*, *Enterobacter cloacae*, *Escherichia coli* and *Pseudomonas aeruginosa* in hospitalized patients [4]. In addition, seasonal variation in bloodstream infection (BSI) due to *Acinetobacter* spp. [1] and *Klebsiella pneumoniae* [5] has been reported in studies from tertiary care centres.

To our knowledge, seasonal variation in *E. coli* BSI has not been previously described; therefore, we performed a population-based investigation to examine the association between seasonal variation and the IR of *E. coli* BSI. The primary aims of the study were two-fold: (i) to compare the IR of *E. coli* BSI in the population of Olmsted County, Minnesota, between the warmest 4 months of the year (June through September) with that during the remainder of the year, and (ii) to examine the association between IR and average temperature.

Methods

Setting

Olmsted County is located in south-eastern Minnesota with a population of 124 277 according to the 2000 census (US Census Bureau, Olmsted County QuickFacts (http://quickfacts.census.gov), accessed April 21, 2008). With the exception 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 US non-Hispanic Whites [6,7]. The Rochester Epidemiology Project is a unique medical records-linkage system that encompasses care delivered to residents of Rochester and Olmsted County, Minnesota. The microbiology laboratories at Mayo Medical Center and Olmsted Medical

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Center are the only two laboratories in Olmsted County. These two medical centres are geographically isolated from other urban centres as previously described [6,8,9]; therefore, local residents are able to obtain healthcare within the community rather than seeking it at a distant geographical location.

Case ascertainment

We used complete enumeration of the Olmsted County, Minnesota, population from 1 January 1998 through 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, and obtain baseline clinical features. Patients with *E. coli* BSI who were living outside Olmsted County at the time of diagnosis were excluded. Blood cultures were performed using standard microbiology techniques according to CLSI. Both laboratories are certified by the College of American Pathologists. The study was approved by the institutional review boards of both institutions. The detailed case ascertainment and blood culture methods used were described previously [9,10].

Case definition

Monomicrobial BSI was defined as growth of only one organism in a blood culture, excluding coagulase-negative staphylococci, *Corynebacterium* spp., and *Propionibacterium* spp. Cases were classified according to the site of acquisition into nosocomial, healthcare-associated and community-acquired, as previously defined [11]. The primary source of BSI was defined using the Centers for Disease Control and Prevention criteria [12].

Statistical analysis

The IR, expressed as the number of new cases of BSI per 100 000 person-years, was calculated assuming that the entire population of Olmsted County was at risk of BSI. The 2000 Olmsted County census figures were used to compute the age-, gender- and calendar year-specific person-year denominator with a projected population growth rate after 2000 of 1.9% per year. The 2005 census figures for Olmsted County confirmed this annual projected growth rate as an accurate estimate. The 10-year study period was categorized into five 2-year intervals (1998–1999, 2000–2001, 2002–2003, 2004–2005, and 2006–2007) and age was categorized into five groups (0–18, 19–39, 40–59, 60–79, and ≥80 years). The IR was directly adjusted to the US 2000 White population. The 95% CIs for the IR were estimated using a Poisson distribution.

To evaluate the association between seasonal variation and IR of *E. coli* BSI, the IR for the four warmest months (June through September) and the IR for the eight remaining months were each calculated; the person-year denominator was multiplied by 1/3 and 2/3, respectively. The incidence rate ratio (IRR) is the ratio of the IR for the four warmest months relative to the IR for the remaining 8 months. The 95% CIs for the IRR were constructed using the bootstrap method.

Multivariable Poisson regression was used to evaluate the association between IR of *E. coli* BSI and average monthly temperatures for Rochester, Minnesota, adjusting for gender, age, and calendar year. Average monthly temperatures were obtained from historic city records [Weatherbase Historical Weather for Rochester, Minnesota, USA (http://www.weatherbase.com), accessed 24 July 2008]. The IR was calculated for each of the 12 months assuming a fixed population within a given year. The SAS procedure GENMOD (version 8; SAS Institute Inc., Cary, NC, USA) was used for all Poisson regression analyses. The two-sided level of significance for statistical testing was defined as $p < 0.05$.

Results

The median age of patients with *E. coli* BSI was 69 (interquartile range 50–81) years and 66% were female. Most cases were community-acquired (59%); the remaining 9% and 32% were nosocomial and healthcare-associated, respectively. The urinary tract was the most common primary source of infection (80%), followed by the gastrointestinal tract (9%) and the respiratory tract (4%). Seven percent of patients with *E. coli* BSI had an unknown primary source of infection.

The overall age- and gender-adjusted IR of *E. coli* BSI was 41.4 per 100 000 person-years (95% CI 37.6–45.3; Table 1). The IR increased at a quadratic rate with age ($p < 0.001$) and was higher in women than in men; the age-adjusted IR was 48.0 per 100 000 person-years (95% CI 42.5–53.4) for women and 34.1 per 100 000 person-years (95% CI 28.6–39.6) for men. There was no change in IR detected over calendar years 1998–2007 (p 0.487 for linear trend).

Fig. 1. displays the relationship between the IR of *E. coli* BSI and average monthly temperature. There was a significant association between seasonal variation and the IR of *E. coli* BSI. The age- and gender-adjusted IR of *E. coli* BSI per 100 000 person-years was 50.2 (95% CI 42.9–57.5) during the warmest 4 months of the year (June through September) compared with 37.1 (95% CI 32.7–41.5) during the remaining 8 months, resulting in a 35% (95% CI 12–66%) increase in IR during the warmest 4 months (Table 2). When considering

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TABLE 1. Incidence rates of *Escherichia coli* bloodstream infection by age group and gender, 1998–2007

Gender	Age group (years) 0–18	19–39	40–59	60–79	≥80	Age-adjusted[a]	Age- and gender-adjusted[a]
Female	12 (6.7)	50 (25.1)	55 (31.1)	94 (120.1)	95 (329.1)	48.0 (42.5–53.4)	
Male	7 (3.7)	10 (5.1)	26 (15.5)	78 (116.4)	34 (263.6)	34.1 (28.6–39.6)	
Overall	19 (5.1)	60 (15.3)	81 (23.5)	172 (118.4)	129 (308.9)	41.6 (37.8–45.4)	41.4 (37.6–45.3)

Data are given as counts (incidence rates per 100 000 person-years), unless otherwise indicated.
[a]Incidence rates (95% CIs) are adjusted for US White 2000 census. There is a quadratic increase in the incidence rate of *E. coli* bloodstream infection with increasing age (p <0.001).

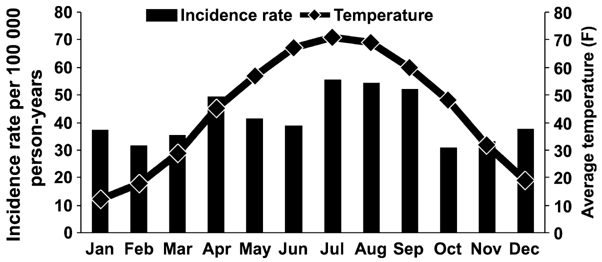

FIG. 1. Monthly age- and gender-adjusted incidence rates of *Escherichia coli* bloodstream infection and average monthly temperatures, 1998–2007.

TABLE 2. Age-adjusted incidence rates of *Escherichia coli* bloodstream infection for the warmest 4 months compared with the remainder of the year, 1998–2007

Gender	IR (95% CI) June–September	Rest of the year	IRR (95% CI)
Female	58.8 (48.3–69.2)	42.6 (36.3–48.8)	1.38 (1.09–1.75)
Male	40.5 (30.2–50.8)	30.9 (24.4–37.3)	1.31 (0.95–1.81)
Overall[a]	50.2 (42.9–57.5)	37.1 (32.7–41.5)	1.35 (1.12–1.66)

IR, incidence rate per 100 000 person-years; IRR, incidence rate ratio.
[a]Overall incidence rates are gender-adjusted for US White 2000 census.

only the warmest two months (July and August), there was a 44% (95% CI 16–79%) increase in the IR in comparison with the remaining 10 months. Similarly, there was an association between the average monthly temperature and the IR of *E. coli* BSI (p 0.004). More specifically, there was a 7% (95% CI 2–12%) increase in the IR for each 10-degree Fahrenheit (c. 5.5°C) increase in average temperature.

Discussion

To our knowledge, this is the first study to describe a seasonal variation in *E. coli* BSI. We found a 35% increase in the IR of *E. coli* BSI during the warmest 4 months of the year (June through September) compared with that for the remainder of the year and a 7% increase in the IR of *E. coli* BSI for each 10-degree Fahrenheit (c. 5.5°C) increase in average temperature.

The high IR of *E. coli* BSI during the four warmest months and the association between the IR and average temperature is intuitive because they characterize the *in vitro* temperature requirements for growth of *E. coli*. It has been shown that the doubling rate of *E. coli* increases with increasing temperature until an optimal growth temperature of 35–36°C is reached [13]. This growth pattern of *E. coli* was also seen in our local environment. Researchers at the University of Minnesota reported a higher density of *E. coli* in temperate soils from Lake Superior watersheds in Northern Minnesota during the warmest months compared with the remainder of the year [14]. This ecological association may provide a logical hypothetical explanation for our study results with an increased risk of human colonization with pathogenic strains of *E. coli* during the warmest months and hence an increased rate of infection. According to this hypothesis, the age- and gender-adjusted IR of *E. coli* BSI should continue to increase as the average temperatures approach the optimal growth temperature of *E. coli*. It would be interesting to compare the IR of *E. coli* BSI in other population-based settings with relatively similar population characteristics to ours, but at geographical locations with differing average temperatures.

A recent report from four tertiary-care centres in four continents described a seasonal variation in the IR of *K. pneumoniae* BSI and an association between the IR of *K. pneumoniae* BSI and average temperature [5]. It is conceivable that we would observe a similar pattern in the IR of *E. coli* BSI because the *in vitro* temperature requirements for growth of both *E. coli* and *K. pneumoniae* are relatively uniform. Due to the relatively small number of patients with BSI due to *K. pneumoniae* and other Gram-negative bacilli in our local population over the 10-year study period, an examination of seasonal variation for these organisms was not conducted.

The IR of *E. coli* BSI increased with age, similar to what we have previously observed in *P. aeruginosa* BSI in the same population [9]. In contrast to *P. aeruginosa* BSI, which was more common in men and more likely to be nosocomial or healthcare-associated [9], *E. coli* BSI was more common in women and more likely to be community-acquired.

There are a few limitations to our study. First, 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. Second, because of the relatively cold weather in Olmsted County, during the winter months, some retirees travel to spend the winter in warmer geographical locations. It is conceivable that *E. coli* BSIs in these individuals would not have been captured by our local microbiology laboratories, and therefore we could have underestimated the IR of *E. coli* BSI during winter months. Nevertheless, it is highly unlikely that this phenomenon in such a small portion of the general population explains the 35% increase in the IR of *E. coli* observed during the summer months.

In summary, we have demonstrated higher IRs of *E. coli* BSI during the four warmest months than during the remainder of the year as well as an association between the IR of *E. coli* BSI and average temperature. These novel epidemiological observations should stimulate hypothesis-generated investigations to evaluate further the impact of climate on infectious diseases.

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Transparency Declaration

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. The study received funding from the Small Grants Program and the Baddour Family Fund at the Mayo Clinic, Rochester, MN, USA. The funding source had no role in the study design. This work was made possible by research grant R01-AR30582 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (National Institutes of Health, US Public Health Service). The authors declare no conflicts of interest.

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