Seasonal variation in *Escherichia coli* bloodstream infections in northern Israel

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Abstract

Seasonal variation in the infection rate with certain Gram-negative organisms has been previously described, but few studies have been published regarding *Escherichia coli*. The aim of this study was to investigate the incidence rate of *E. coli* bloodstream infection (BSI) and the association with temperature in different seasons in the Yizrael Valley. Positive blood cultures sent to the microbiology laboratory of Ha’Emek Medical Centre over a period of 8 years (January 2001 to December 2008) were included. The mean monthly temperature in the Yizrael Valley in the same period was compared with the monthly *E. coli* BSI rate. We divided the year into three periods: winter (December to February: mean temperature <15°C), transitional (March, April and November: mean temperature 15–19°C) and summer (May to October: mean temperature ≥20°C). In addition, we correlated the mean monthly antibiotic use in the same period measured as total defined daily doses for the whole regional population with *E. coli* BSI. During the study period, 2810 BSIs were recorded (35% *E. coli*). In 67.4% of the cases of *E. coli* bacteraemia, the source was urinary tract infection. The crude incidence of *E. coli* BSI was 4.1/1000 admissions. There was no difference in the number of cultures/month (mean: 29 ± 6). However, *E. coli* BSI was 19% and 21% more frequent in summer than in the transitional and winter seasons, respectively (p 0.01). The antibiotic consumption was significantly higher in the winter period. We found significantly higher rates of *E. coli* BSI in the summer period. Host, bacterial and ecological factors, together with high consumption of antibiotics during the winter season, could partially explain these findings.

Keywords: *E. coli*, *E. coli* and temperature, *E. coli* bacteraemia, *E. coli* incidence rate, *E. coli* seasonal variation

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Introduction

Bacteraemia is a leading cause of morbidity and mortality [1]. Gram-negative rods in general and *Escherichia coli* in particular are the most prevalent isolates in community-acquired bloodstream infection (BSI) [2]. The epidemiology, reservoir and principal routes by which humans are exposed to these pathogenic strains of *E. coli* remain poorly understood [3].

Recognition of seasonal trends in infectious diseases may improve diagnosis, use of empirical therapy, and infection control interventions [4].

Seasonal variation in rates of infection with certain Gram-negative organisms has been previously described [4–7]; furthermore, a seasonal variation in *E. coli* BSI was recently demonstrated in a population-based study [5]. The aims of the study were:

1. To compare the incidence rates (IRs) of *E. coli* BSI at Ha’Emek Medical Centre, between the winter, transitional and summer seasons, during a 96-month period (January 2001 to December 2008).
2. To examine the association between the IRs of *E. coli* BSI and average temperature in the same seasons and periods.
3. To examine the association between the IRs of *E. coli* BSI and average monthly antimicrobial use in the community in the same seasons and periods, as a possible factor that could influence the number of hospitalized patients suffering from an infectious disease.
Materials and Methods

The study was conducted at Ha’Emek Medical Centre, a community university-affiliated medical centre in northern Israel (500 beds), serving a population of ~500,000 inhabitants.

From January 2001 to December 2008, all positive E. coli blood cultures obtained from adult patients (≥18 years old) were prospectively recorded, as part of an ongoing BSI surveillance programme conducted in our hospital. Only one isolate was included for each bacteraemic episode. The crude IR of E. coli BSI was calculated per 1000 hospital admissions.

The temperature in the Yizrael Valley in the same period was obtained from the Israeli Meteorological Service, who provide a monthly report of minimal, maximal and average temperatures at two locations in northern Israel, Nir Ha’Emek and Nave Yaar, which are representative of the regional weather.

In order to discriminate warm from cold months, we divided the year into three ‘seasons’: winter (December to February: mean temperature <15°C), transitional (March, April and November: mean temperature 15–19°C) and summer (May to October: mean temperature ≥20°C).

In addition, we correlated the mean monthly antibiotic use between January 2001 and December 2008, measured as total defined daily dose (DDD) for the whole regional population insured in ‘Clalit Health Services’, the largest medical health organization in Israel, with 70% coverage for the population in our region.

The study was approved by the institutional ethics committee.

All statistical analyses were performed with SPSS software, version 16 (SPSS Inc., Chicago, IL, USA). Poisson generalized linear models were used to estimate the association of the number of E. coli BSIs per month with season. The log of the number of hospital admissions in each month was treated as an offset in the model, and a constant dispersion over time was assumed. The association of the number of E. coli infections per month with season was adjusted for the number of months since January 2001, in order to account for long-term trends and unmeasured time-related variables. The Wald $\chi^2$-test was used to assess seasonality. The association of the number of E. coli BSIs per month with temperature was assessed by stratifying the data into summer and non-summer months. This was also adjusted for the number of months since January 2001. The Wald $\chi^2$-test was used to assess temperature. One-way ANOVA was performed to assess whether there was a seasonal variation in the number of admissions or the number of cultures. Similarly, one-way ANOVA was performed to assess whether there was a monthly variation in the number of cultures. Linear, quadratic and cubic curves were fitted to the data in order to assess the existence of a time trend. Spearman correlations were performed between monthly DDD and monthly temperature and E. coli incidence.

Results

From January 2001 to December 2008, 239,232 patients were hospitalized. The mean number of admissions per month was similar in each season: 2540 in the winter season, 2475 in the transitional season, and 2476 in the summer season (difference not significant). In this 96-month period, 2810 positive blood cultures were recovered (only the first blood culture for each patient/episode was included). Sixty-five per cent of them ($n=1827$) were non-E. coli, and 35% ($n=983$) were E. coli isolates; 72.4% of them were E. coli acquired in the community, and 27.6% were hospital-acquired BSIs. The most common source of E. coli BSI was the urinary tract (67.4%).

The mean number of BSIs was 29 ± 6/month; there was no statistically significant difference in the number of cultures per month.

The incidence of E. coli BSI (per 1000 admissions) per month plotted over time, among hospitalized patients at Ha’Emek medical centre, appeared to be stable over time (Fig. 1), with a crude IR of E. coli BSI of 4.1/1000 hospital admissions.

The mean temperature during the years 2001–2008 was 20.4 ± 5.9°C (median: 20.6°C). The hottest month was
August, with a mean temperature of 28 ± 0.3°C, and the coldest month was January, with a mean temperature of 11.8 ± 1.2°C. The temperatures measured in the defined ‘seasons’ were as follows: winter, <15°C; transitional, 15–19°C; and summer, ≥20°C.

The number of E. coli BSIs was significantly higher in the summer season than in either the winter season (31 ± 6 vs. 27 ± 4, respectively; p <0.01) or the transitional season (31 ± 6 vs. 28 ± 6, respectively; p <0.03).

The IR ratio (IRR) for E. coli BSI according to season was 1.19 (95% CI 1.12–1.26) for comparison of the summer with the transitional season, and 1.21 (95% CI 1.16–1.28) for comparison of the summer season with the winter season; that is, a means of 19% and 21% higher frequency in the summer than in the transitional and the winter seasons, respectively (p 0.01) (Fig. 2). No difference was found between the transitional and winter seasons. Temperature was positively correlated with the rate of E. coli BSI (Spearman r = 0.299; p <0.003). However, within seasons, no association between temperature and E. coli BSI rates were found (p >0.60).

The average monthly antimicrobial use in the community was 214 893 DDD; the highest use was in January (258 324 DDD), and the lowest in July (191 595 DDD). The expectedly higher use during the winter period was significantly negatively correlated with temperature (Spearman \( r = -0.453 \), p <0.03), but was not correlated with the incidence of all E. coli BSIs (Spearman \( r = -0.12 \), p >0.58) (Fig. 3).

**Discussion**

There have been few reports of seasonal variation in the incidence of BSI in hospitalized patients, and most of them have been limited to intensive-care units [4].

Seasonal peaks in the IR of BSI caused by some Gram-negative organisms during the summer have been previously described, including for Acinetobacter and Aeromonas [4,6,7]. Furthermore, seasonal variation of the most common Gram-negative rods causing human infection, such as E. coli [5] and Klebsiella pneumoniae [8], was recently reported. Interestingly, there have been no reports of summer peaks in the incidence of infection caused by Gram-positive pathogens [4]. Potential explanations for the summer and temperature-associated peaks in the incidence of infection caused by Gram-negative pathogens are many but unproven [4].

After 8 years of analysis of BSI in 239 232 hospitalized patients, we found 2810 positive blood cultures equally distributed over the year (29 ± 6/month); however, the IRR for E. coli according to season was significantly higher in the summer season, being 19% higher than in the transitional season, and 21% higher than in the winter season, similarly to what was reported by Perencevich et al. [4]. The temperature gaps between the summer season and transitional and winter seasons were 1–4°C, and ≥5°C, respectively. Al-Hasan et al. [5] estimated that a 7% increase in the average monthly incidence of E. coli BSI occurred for every 5.5°C
increase in average monthly temperature, which is similar to our findings.

The exact cause of the observed higher rates of *E. coli* BSI during warm months remains elusive [8]. It is reasonable to hypothesize that humans also have higher levels of colonization with environmental bacteria during warm months, and higher colonization levels may explain the observed increase in infection rate during the summer [8].

Researchers at the University of Minnesota reported a higher density of *E. coli* in template soils from Lake Superior during the warmest months than in the remainder of the year. This ecological association may provide a logical hypothetical explanation for the increased rate of human colonization with pathological strains of *E. coli* during the warmest months, and hence an increased rate of infection [9].

Although it is plausible that increased contamination of food and water sources with *E. coli* pathogenic strains during the summer could explain the seasonality of *E. coli*, this hypothesis may be very simplistic. Correlations between temperature and the incidence of disease may be confounded by a huge number of unmeasurable variables [3].

For example, Perencevich [4] suggested that, given the high incidence of urinary tract infection as the *E. coli* portal of entry, increased sexual activity during the summer months (a known risk factor for community-acquired urinary tract infection) could explain the seasonal variation found by us and other authors [4].

Therefore, a seasonal increase in exposure to *E. coli* is probably not the only mechanism by which the incidence of BSI might increase. Seasonal changes in vulnerability to disease within a population are also possible. These changes might result from seasonal changes in host immune function, or seasonal changes in the virulence factors of the microorganisms [3].

As expected, the community use of antimicrobials (measured as total DDD) was statistically significantly higher in the winter season; however, no statistical correlation was found between their lower use in summer and the high incidence of *E. coli* BSI.

Our study has some limitations. First, this is a study conducted in a community low-complexity centre, where two-thirds of the BSIs are community-acquired. Thus, conclusions from our study may not be generalizable to other hospitals. Second, although the Ha’Emek Medical Centre provides most of the medical and laboratory services in northern Israel, so we could compare BSI data with temperatures recorded in our area of influence, our data would probably not match the temperature registry in the central and southern regions of the country; therefore, until more studies are performed, our findings should be considered to be limited to our geographical area.

Third, we did not investigate numerous variables, such as travel, sexual activity, water consumption, recreational water exposure, or food preparation practices, that could be confounders and change the IR of *E. coli* BSI.

Future studies are needed to determine the reasons for the seasonal variation in *E. coli* BSI. Studies should include humidity, environmental and animal sources of *E. coli*, and human activities, in order to find cofactors for this phenomenon.

Awareness regarding seasonal variation in *E. coli* BSI, together with local profiles of antimicrobial susceptibility, could be of relevance at the time of starting empirical antimicrobial therapy for Gram-negative BSI.

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**Transparency Declaration**

There is no conflict of interest for all authors.

**References**