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Temporal Trends in *Enterobacter* Species Bloodstream Infection: A Population-Based Study, 1998-2007

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Abstract

Enterobacter species are the fourth most common cause of gram-negative bloodstream infection (BSI). We examined temporal changes and seasonal variation in the incidence rate of *Enterobacter* spp. BSI, estimated 28-day and 1-year mortality, and determined *in vitro* antimicrobial resistance rates of *Enterobacter* spp. bloodstream isolates in Olmsted County, Minnesota, from 1/1/1998 to 12/31/2007. Multivariable Poisson regression was used to examine temporal changes and seasonal variation in incidence rate and Kaplan-Meier method to estimate 28-day and 1-year mortality. The median age of patients with *Enterobacter* spp. BSI was 58 years and 53% were female. The overall age- and gender-adjusted incidence rate of *Enterobacter* spp. BSI was 3.3/100,000 person-years (95% confidence interval [CI]: 2.3-4.4). There was a linear trend of increasing incidence rate from 0.8 (95% CI: 0-1.9) to 6.2 (95% CI: 3.0-9.3) per 100,000 person-years between 1998 and 2007 (p=0.002). There was no significant difference in the incidence rate of *Enterobacter* spp. BSI during the warmest four months compared to the remainder of the year (incidence rate ratio 1.06 [95% CI: 0.47-2.01]). The overall 28-day and 1-year mortality rates of *Enterobacter* spp. BSI were 21% (95% CI: 8-34%) and 38% (95% CI: 22-53%), respectively. Up to 13% of *Enterobacter* spp. bloodstream isolates were resistant to third-generation cephalosporins. To our knowledge, this is the first population-based study to describe the epidemiology and outcome of *Enterobacter* spp. BSI. The increase in incidence rate of *Enterobacter* spp. BSI over the past decade, coupled with its associated antimicrobial resistance, dictate more investigation of this syndrome.

Keywords

bacteremia; epidemiology; mortality; seasonal variation; incidence; *Enterobacter*; antimicrobial resistance

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Transparency Declaration:
MNA and BDL 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.

Potential conflicts of interest. MNA, BDL, JEE, and LMB: No conflict.

Introduction

Enterobacter species are the fourth most common cause of gram-negative bloodstream infection (BSI) [1-3]. Population-based studies that specifically address the epidemiology, outcome, and *in vitro* antimicrobial resistance rates of *Enterobacter* spp. BSI are lacking and most surveys that have been published have been derived from referral tertiary care centers [4-10]. Therefore, we performed a population-based study to determine the incidence rate and examine temporal changes in the incidence rate of *Enterobacter* spp. BSI. In addition, we examined seasonal variation in incidence rate of *Enterobacter* spp. BSI because recent reports have demonstrated seasonal variation in both *Escherichia coli* [11] and *Klebsiella pneumoniae* BSI [12] and other syndromes of infections caused by gram-negative bacilli [13]. We also estimated the 28-day and 1-year mortality rates in patients with *Enterobacter* spp. BSI. Lastly, we examined the *in vitro* antimicrobial resistance rates of *Enterobacter* spp. bloodstream isolates in Olmsted County, Minnesota, from 1998 to 2007.

Methods

Setting

Olmsted County is located in southeastern Minnesota and has 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 USA non-Hispanic whites [14,15]. The Rochester Epidemiology Project (REP) is a unique medical records-linkage system that encompasses care delivered to residents of Olmsted County, Minnesota. The microbiology laboratories at Mayo Medical Center and Olmsted Medical Center are the only two laboratories in Olmsted County. These two medical centers are geographically isolated from other urban centers as previously described [14,16,17]; 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, from 1 January 1998 to 31 December 2007. Using the microbiology databases at the Mayo Medical Center Rochester and Olmsted Medical Center, we identified 38 unique patients with first episodes of monomicrobial *Enterobacter* spp. BSI during the study period. Medical records were reviewed by the primary investigator (M.N.A.) to confirm the diagnosis, determine patient residency status, and obtain baseline clinical features and outcome.

Blood cultures were processed using standard microbiology techniques according to the Clinical and Laboratory Standards Institute (CLSI). Both laboratories are certified by the College of American Pathologists. CLSI methods were employed to evaluate *in vitro* antimicrobial susceptibility results of *Enterobacter* spp. bloodstream 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 [17,18,19].

Case definition

Monomicrobial *Enterobacter* spp. BSI was defined as the growth of only *Enterobacter* spp. 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 [20]. The primary source of BSI was defined using the Centers for Disease Control and Prevention criteria [21].

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 Fisher's exact test was used to evaluate associations between categorical variables and Wicoxon rank-sum test was used to test for differences in medians across continuous variables.

The incidence rate, expressed as the number of new cases of *Enterobacter* spp. 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-years denominator with a projected population growth rate after 2000 of 1.9% per year. The 10-year study period was divided into five two-year intervals (1998-1999, 2000-2001, 2002-2003, 2004-2005, and 2006-2007) and age was divided into five groups (0-18, 19-39, 40-59, 60-79, and ≥ 80 years). The incidence rate was directly adjusted to the USA 2000 white population. A 95% confidence interval (CI) for each incidence rate was estimated using a Poisson distribution.

To evaluate the association between seasonal variation and incidence rate of *Enterobacter* spp. BSI, the age- and gender-adjusted incidence rate was calculated for both the four warmest months (June through September) and the eight remaining months; the person-years denominator was multiplied by 1/3 and 2/3, respectively. The incidence rate ratio is the ratio of the incidence rate for the four warmest months relative to the incidence rate for the remaining eight months. A 95% CI for the incidence rate ratio was constructed using bootstrap resampling.

To create an additional measure of seasonal variation, the average monthly temperatures for Rochester, Minnesota, were obtained from historic city records (Weatherbase Historical Weather for Rochester, Minnesota, USA [http://www.weatherbase.com], accessed July 24, 2008). Incidence rates were calculated for each of the 12 months assuming a fixed population within a given year. To test for an association between average monthly temperature and the incidence rate of *Enterobacter* spp. BSI while adjusting for gender, age and calendar year, a multivariable Poisson regression model was used.

The Kaplan-Meier method was used to estimate the 28-day and 1-year all-cause mortality rates. Patients were followed from the date of first episode of *Enterobacter* spp. BSI until death or last healthcare encounter; long-term follow-up was available through the REP. Patients lost to follow-up were censored on the date of their last healthcare encounter. All analyses were carried out using the SAS statistical software package (version 8.2, SAS Institute, Cary, NC). The level of significance for statistical testing was defined as $p<0.05$ (2-sided).

Results

We identified 38 unique patients with *Enterobacter* spp. BSI during the study period; 26 had *E. cloacae*, 10 had *E. aerogenes*, and 2 had *E. sakazakii* BSI. The median age of patients with *Enterobacter* spp. BSI was 58 years (IQR: 45-75); and 20 (53%) were female. Most cases were healthcare-associated (58%) or nosocomial (21%); the remaining 21% of cases were community-acquired. The urinary tract was the most common identified primary source of infection (24%), followed by the gastrointestinal tract (18%), central venous catheter-related (11%), the respiratory tract (5%), skin and soft tissue (5%), bone and joint

(3%), and central nervous system (3%). Twelve patients (32%) had primary BSI of unknown source.

The overall age- and gender-adjusted incidence rate of *Enterobacter* spp. BSI was 3.3 (95% CI: 2.3-4.4) per 100,000 person-years. The age-adjusted incidence rate of *Enterobacter* spp. BSI per 100,000 person-years was 3.9 (95% CI: 2.0-5.8) in males and 3.2 (95% CI: 1.8-4.6) in females. The incidence rate of *Enterobacter* spp. BSI increased linearly with age (p=0.007; Figure 1). After adjusting for gender and age, there was a linear increase in the incidence rate of *Enterobacter* spp. BSI from 1998 to 2007 (p=0.002; Figure 2).

The age- and gender-adjusted incidence rate of *Enterobacter* spp. BSI per 100,000 person-years was 3.5 (95% CI: 1.6–5.4) during the warmest four months of the year (June through September) compared to 3.3 (95% CI: 2.0–4.5) during the remainder of the year (incidence rate ratio 1.07 [95% CI: 0.47-2.01]). Additionally, there was no association between the incidence rate of *Enterobacter* spp. BSI and average temperature (p=0.83; Figure 3).

Patients with *E. aerogenes* BSI were older than those with *E. cloacae* BSI (median age 74 vs. 52 years, p=0.008; Table 1). Additionally, patients with *E. aerogenes* BSI were more likely than those with *E. cloacae* BSI to have a community-acquired site of infection acquisition (60% vs. 8%, p=0.002) and a urinary tract primary source of infection (50% vs. 15%, p=0.08).

The age- and gender-adjusted incidence rates of *E. cloacae* and *E. aerogenes* BSI per 100,000 person-years were 2.2 (95% CI: 1.4-3.1) and 0.9 (95% CI: 0.4-1.5), respectively. The age-adjusted incidence rates of *E. cloacae* BSI were comparable in males and females (2.2 [95% CI: 0.8-3.5] and 2.4 [95% CI: 1.2-3.7] per 100,000 person-years, respectively). The incidence rates of *E. aerogenes* BSI for males and females were 1.6 [95% CI: 0.3-2.8] and 0.6 [95% CI: 0-1.3] per 100,000 person-years, respectively.

Complete patient follow-up was obtained for most of the cohort; no patient was lost to follow-up within 28 days and only 3 (8%) were lost to follow-up within 1 year of *Enterobacter* spp. BSI. The overall 28-day and 1-year all-cause mortality rates of *Enterobacter* spp. BSI were 21% (95% CI: 8-34%) and 38% (95% CI: 22-53%), respectively. Although the overall 28-day all-cause mortality rate was relatively higher in patients with *E. aerogenes* as compared to those with *E. cloacae* BSI (30% [95% CI: 2-58%] vs. 15% [95% CI: 2-29%], Figure 4a), there was no apparent difference in the long-term survival (Figure 4b).

The *in vitro* antimicrobial susceptibility rates of *Enterobacter* spp. bloodstream isolates to all tested antimicrobial agents are shown in Table 2. Among all tested beta-lactams, ceftazidime and piperacillin-tazobactam had the lowest *in vitro* susceptibility rates (87% and 89%, respectively). No cefepime- or carbapenem-resistant *Enterobacter* spp. bloodstream isolates were detected in our population over the past decade.

Discussion

To our knowledge, this is the first population-based study to describe the epidemiology, outcome, and *in vitro* antimicrobial resistance rates of *Enterobacter* spp. BSI. We demonstrated a linear trend of an increasing incidence rate of *Enterobacter* spp. BSI during the past decade. The age- and gender-adjusted incidence rate of *Enterobacter* spp. BSI increased from 0.8 (95% CI: 0-1.9) to 6.2 (95% CI: 3.0-9.3) per 100,000 person-years between 1998 and 2007. There was no seasonal variation in the incidence rate of *Enterobacter* spp. BSI.

Based on an age- and gender-adjusted incidence rate of 2.2 (95% CI: 1.4-3.1) per 100,000 person-years, *E. cloacae* was the fourth most common gram-negative bacillus to cause BSI in our population; *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (incidence rates of 41.4 [95% CI: 37.6-45.3], 9.7 [95% CI: 7.8-11.6], and 4.7 [95% CI: 3.4-6.1] per 100 000 person-years, respectively) were the three most common causes of BSI due to gram-negative bacilli as previously described [11,17,22]. The incidence rate of BSI due to all four organisms increased with age. The median age of 52 years in patients with *E. cloacae* BSI was notably lower than that in patients with *E. coli*, *K. pneumoniae*, and *P. aeruginosa* BSI (69, 73 and 69 years, respectively). In contrast to *E. coli* BSI that was more common in females [11,23], and *K. pneumoniae* and *P. aeruginosa* BSIs that were more common in males [17,22,24,25], the incidence rate of *E. cloacae* BSI was not influenced by gender. Most cases of *E. cloacae* BSI were healthcare-associated or nosocomial and nearly one-third had no known primary source of infection, which is consistent with previous reports [5,9,10,26].

E. aerogenes is an uncommon cause of gram-negative BSI with an age- and gender-adjusted incidence rate of 0.9 (95% CI: 0.4-1.5) per 100,000 person-years. Although the incidence rate of *E. aerogenes* BSI in males was nearly three times that in females, the difference was not statistically significant due to the small number of patients with *E. aerogenes* BSI in our population. Patients with *E. aerogenes* were older and more likely to have a urinary tract primary source of infection than those with *E. cloacae* BSI, which is consistent with the results of a recent investigation [27].

Our finding of an increasing incidence rate of *Enterobacter* spp. BSI over the past decade is consistent with the results of a recent investigation that demonstrated increasing frequency of *Enterobacter* spp. as a cause of BSI in a tertiary care center in Spain from 1991 to 2006 [7]. It is also consistent with observations of earlier pediatric studies that suggested the emergence of *Enterobacter* spp. as an important cause of BSI in children [28,29]. The increase in incidence rate of *Enterobacter* spp. BSI in our population is unlikely due to changes in physicians' practices in obtaining blood cultures in febrile patients, because the incidence rates of BSI due to *E. coli*, *Klebsiella* spp., and other gram-negative bacilli have remained stable over the same time period [11,19,22]. Because most cases of *Enterobacter* spp. BSI were healthcare-associated or nosocomial, it is likely that changes within the local hospitals' environment have resulted in this increase in incidence rate. It is conceivable that an increasing number of patients are colonized with *Enterobacter* spp. following hospital admission or contact with the healthcare setting for an outpatient procedure such as urinary tract instrumentation, hemodialysis, or outpatient chemotherapy [30]. In addition, some studies have identified previous exposure to broad-spectrum antimicrobial agents, particularly third-generation cephalosporins, as a risk factor for *Enterobacter* spp. BSI [4,9,31]. It is possible that the increasing use of these antimicrobial agents in our local population is temporally associated with the increase in the incidence rate of *Enterobacter* spp. BSI, but these data were not collected to permit that determination.

Our observation of an increasing incidence rate of *Enterobacter* spp. BSI deserves additional study. Subsequent work should determine whether the increase in incidence rate of *Enterobacter* spp. BSI that was seen locally is also present in other locales. The development of a multi-national population-based study to examine temporal trends in *Enterobacter* spp. BSI with molecular testing of bloodstream isolates would provide vital clinical and microbiological information to advance this field.

Enterobacter spp. is more likely than other commonly isolated gram-negative bacilli, such as *E. coli* and *Klebsiella* spp., to be resistant to antimicrobial agents. For example, 13% of *Enterobacter* spp. bloodstream isolates in our local area were not susceptible to third-

generation cephalosporins as compared to only 1% of both *E. coli* [32] and *Klebsiella* spp. bloodstream isolates [22]. The increased resistance is likely due to the inherent capability of *Enterobacter* spp. isolates to produce inducible chromosomal beta-lactamases, including Amp C. Even when the isolates demonstrate *in vitro* antimicrobial susceptibility, exposure to certain types of beta-lactam antibiotics, including cephalosporins and extended-spectrum penicillins, can cause a transient increase or induction of Amp C production, resulting in antimicrobial resistance and possibly a predisposition to treatment failures [31,33,34]. It has been demonstrated that 15-19% of *Enterobacter* spp. isolates develop resistance to third-generation cephalosporins during treatment [4,35]. Therefore, this increase in the incidence rate of *Enterobacter* spp. BSI makes the choice of an empiric antimicrobial regimen in patients with gram-negative BSI, while awaiting identification of the gram-negative bacillus, much more difficult, especially in patients with recent contact with the healthcare system and other identifiable risk factors for *Enterobacter* spp. BSI.

The lack of seasonal variation in the incidence rate of *Enterobacter* spp. BSI in this investigation is consistent with the results of a large study from four continents [12]. However, this is in contrast to our previous work that demonstrated a higher incidence rate of *E. coli* BSI during the warmest four months than in the reminder of the year [11]. The factors involved in the presence or absence of seasonal variation in BSI have yet to be identified.

Patients with *E. cloacae* BSI were younger than those with *E. aerogenes* BSI in our investigation and it is conceivable that the younger age accounted for the lower mortality rate in the former group. The relatively small sample size did not permit an examination of predictors of mortality in a multivariable model to confirm this notion. The 28-day all-cause mortality rate of 15% in patients with *E. cloacae* BSI was notably lower than the short-term mortality rates (21-69%) reported in investigations extending back to the 1980s [6,8-10,26,36,37]. In more recent investigations, mortality rates of 13-15% have been described and are consistent with our results [7,27]. We speculate that this decline in mortality could be due to advancements in critical care and antimicrobial management.

The unique availability of long-term patient follow-up through the REP resources in our population permitted an estimation of 1-year all-cause mortality rate following *Enterobacter* spp. BSI that has not been previously described. Over one-third of patients did not survive beyond one year following *Enterobacter* spp. BSI, and was most likely due to multiple comorbid conditions that characterized these patients. This observation was similar to what we previously observed in patients with *Klebsiella* spp. BSI [22].

The *in vitro* antimicrobial resistance rates of *Enterobacter* spp. bloodstream isolates in our population-based study were notably lower than those reported previously from tertiary care centers. Resistance rate to third-generation cephalosporins was 13% in our study as compared to 17-51% in hospital-based investigations [2,27,38-40]. Similarly, the 5% resistance rate to fluoroquinolones was also lower than previously reported rates of 8-14% from tertiary care centers [2,27,38-41]. Carbapenem-resistance rates among *Enterobacter* spp. isolates were under 1% in both population- and hospital-based studies [27,38,40]. The lower antimicrobial resistance rates reported from population-based studies as compared to investigations from tertiary care centers were likely due to referral bias that can adversely affect isolate susceptibility data in tertiary care centers [17]. It is conceivable that referral patients underwent more procedures, antimicrobial exposure and complications that prompted transfer to tertiary care centers and predisposed to colonization or infection with bacteria that harbored antimicrobial resistance.

The strength of this study is the population-based design and, therefore, lack of referral bias. Contrary to previous hospital-based studies that have estimated the incidence rate of *Enterobacter* spp. BSI per the number of admissions to a particular hospital, we determined the incidence rate by 100,000 person-years in a well-defined population.

Our study has limitations. First, our data is derived from one geographic area. Studies from multiple geographic locations may provide a more comprehensive view. Second, we did not perform pulse-field gel electrophoresis to investigate whether the increasing incidence rate of *Enterobacter* spp. BSI was a result of clonal spread of a single strain in the medical facilities in our region or due to patient-unique strains. For example, the peak in incidence rate of *Enterobacter* spp. BSI that was observed in the 2006-2007 interval might have been related to a nosocomial outbreak rather than a reflection of a true increase in incidence rate of *Enterobacter* spp. BSI among the general population. Third, the lack of seasonal variation in *Enterobacter* spp. BSI might have been due to lack of power due to the relatively small sample size. 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, *Enterobacter* spp. has emerged as an important cause of gram-negative BSI. The increase in incidence rate of *Enterobacter* spp. BSI over the past 10 years should prompt physicians to have a higher suspicion for *Enterobacter* spp. in patients with suspect or proven BSI. Empiric antimicrobial coverage should include coverage for these microorganisms, particularly in patients with frequent contact with the healthcare setting. For as yet unexplained reasons, the more recent mortality rate in patients with *Enterobacter* spp. BSI has declined.

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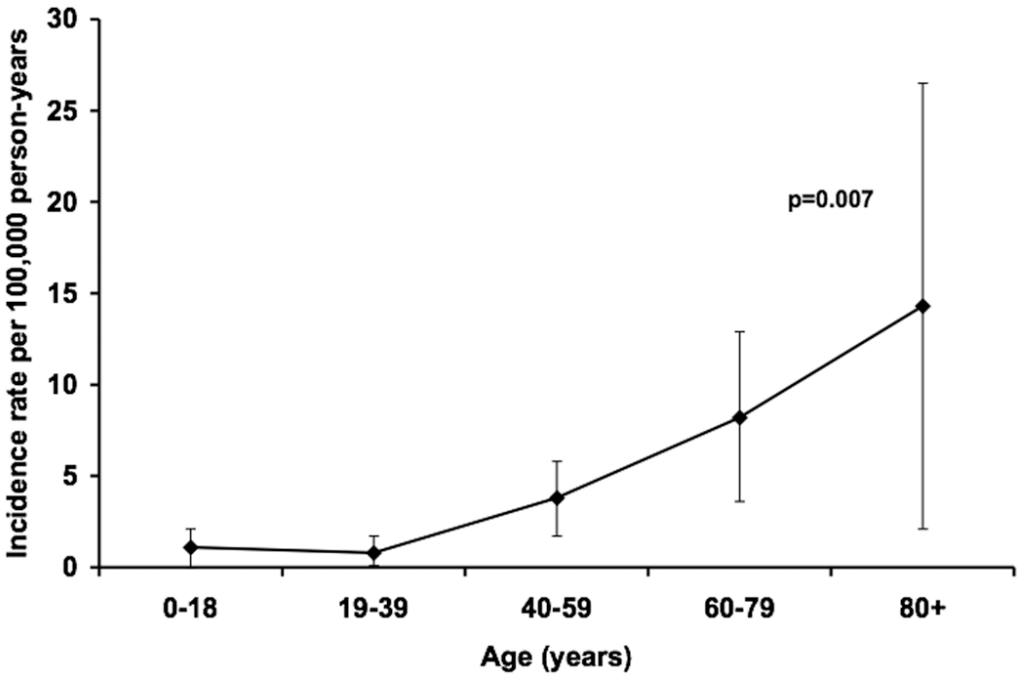

Figure 1.
Gender-adjusted incidence rates of *Enterobacter* species bloodstream infection by age group, 1998-2007.
NOTE. Error bars indicate 95% confidence intervals. P-value denotes a linear change in incidence rate using Poisson regression.

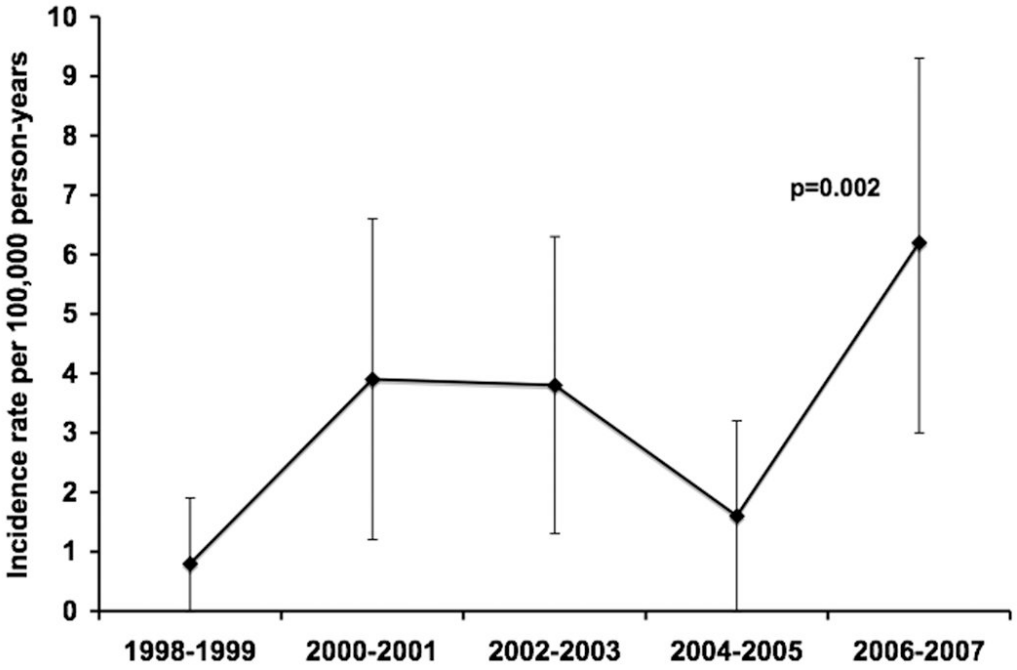

Figure 2.

Age- and gender-adjusted incidence rates of *Enterobacter* species bloodstream infection by calendar year.

NOTE. Error bars indicate 95% confidence intervals. P-value denotes a linear change in incidence rate using Poisson regression.

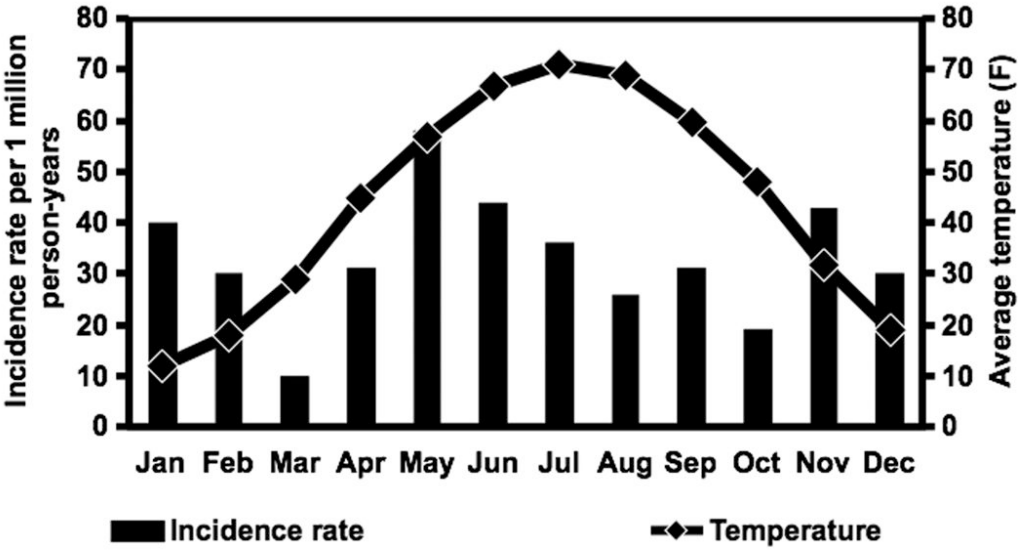

Figure 3.
Monthly age- and gender-adjusted incidence rates of *Enterobacter* species bloodstream infection and average monthly temperatures, 1998-2007.

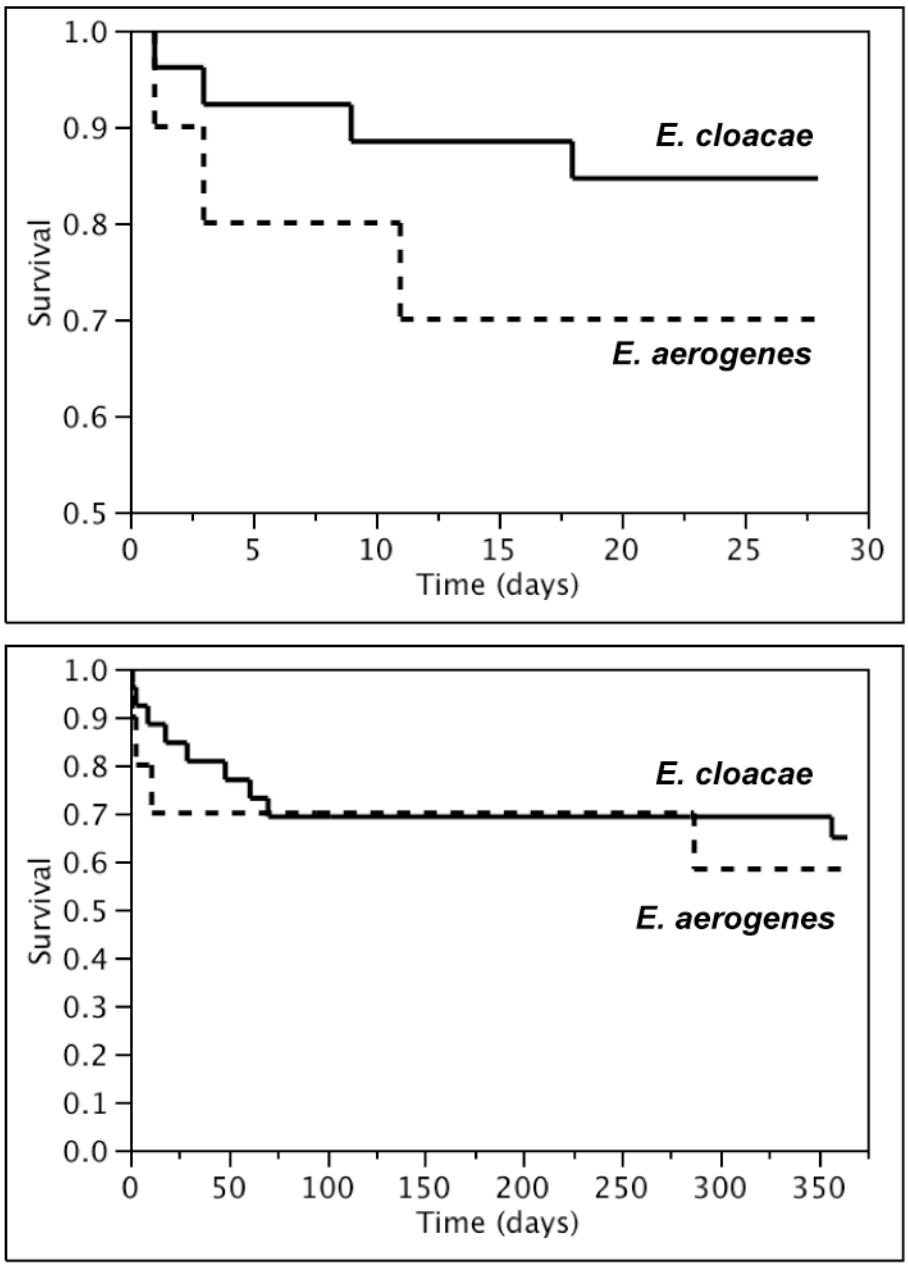

Figure 4.
Kaplan-Meier 28-day (a) and 1-year (b) survival curves of patients with *Enterobacter cloacae* and *Enterobacter aerogenes* bloodstream infection, 1998-2007.

Table 1

Clinical characteristics of patients with *Enterobacter* species bloodstream infection.*

Variable	*E. cloacae* n=26	*E. aerogenes* n=10
Age: median (IQR)	52 (39-71)	74 (61-82)
Female sex, n (%)	15 (58)	4 (40)
Site of acquisition, n (%)		
Community-acquired	2 (8)	6 (60)
Healthcare-associated	17 (65)	3 (30)
Nosocomial	7 (27)	1 (10)
Primary source, n (%)		
Urinary tract	4 (15)	5 (50)
Gastrointestinal tract	5 (19)	1 (10)
Central venous catheter-related	4 (15)	1 (10)
Other	3 (12)	1 (10)
Unknown	10 (38)	2 (20)

IQR: interquartile range

*A 51-year old male and a newborn female with healthcare-associated *E. sakazakii* bloodstream infection secondary to a gastrointestinal tract source and meningitis, respectively, are not shown.

Table 2

In vitro antimicrobial susceptibility rates of *Enterobacter* species bloodstream isolates, 1998-2007.

Antimicrobial	Number of susceptible isolates/number of isolates tested	Susceptibility %
Ceftazidime	33/38	87
Piperacillin-tazobactam	33/37	89
Ciprofloxacin	36/38	95
Levofloxacin	35/37	95
Trimethoprim-sulfamethoxazole	37/38	97
Gentamicin	38/38	100
Cefepime	37/37	100
Imipenem	37/37	100
Meropenem	37/37	100