Epidemiology and outcome of Gram-negative bloodstream infection in children: a population-based study

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SUMMARY

Population-based studies of Gram-negative bloodstream infection (BSI) in children are lacking. Therefore, we performed this population-based investigation in Olmsted County, Minnesota, to determine the incidence rate, site of acquisition, and outcome of Gram-negative BSI in children aged $\leqslant 18$ years. We used Kaplan–Meier method and Cox proportional hazard regression for mortality analysis. We identified 56 unique children with Gram-negative BSI during the past decade. The gender-adjusted incidence rate of Gram-negative BSI per 100 000 person-years was 129·7 [95% confidence interval (CI) 77·8–181·6]) in infants, with a sharp decline to 14·6 (95% CI 6·0–23·2) and 7·6 (95% CI 4·3–10·9) in children aged 1–4 and 5–18 years, respectively. The urinary tract was the most commonly identified source of infection (34%) and *Escherichia coli* was the most common pathogen isolated (38%). Over two-thirds (68%) of children had underlying medical conditions that predisposed to Gram-negative BSI. The overall 28-day and 1-year all-cause mortality rates were 11% (95% CI 3–18) and 18% (95% CI 8–28), respectively. Younger age and number of underlying medical conditions were associated with 28-day and 1-year mortality, respectively. Nosocomial or healthcare-associated acquisition was associated with both 28-day and 1-year mortality.

Key words: Bacteraemia, Gram-negative, incidence, mortality, paediatric.

INTRODUCTION

Gram-negative bloodstream infections (BSI) are common in preterm infants and children with cancer and other immunocompromised states [1–3]. Previous studies of the epidemiology and outcome of Gram-negative BSI in children were mostly derived from referral tertiary-care centres; many were strictly limited to nosocomial Gram-negative BSI [4–7].

Population-based studies that specifically address Gram-negative BSI in children are lacking. Previous population-based studies of Gram-negative BSI were primarily focused on the adult population [8, 9], restricted to a certain paediatric age group [10, 11], or strictly limited to one Gram-negative pathogen [12–16]. To our knowledge, only one previous population-based study has evaluated BSI in all paediatric age groups [17]. Since the main interest of that study was to examine for a change in the incidence rate of BSI

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due to *Streptococcus pneumoniae* and other Gram-positive pathogens, there was no particular emphasis on BSI due to Gram-negative bacilli that accounted for only 27% of BSI in that report. Therefore, we designed this population-based investigation to examine the incidence rate and site of acquisition of BSI due to Gram-negative bacilli in infants, children aged 1–4 and 5–18 years. Additionally, we discuss the underlying medical conditions of the cohort and factors associated with 28-day and 1-year all-cause mortality.

MATERIALS AND METHODS

Setting

Olmsted County is located in southeastern Minnesota and has a population of 124 277 according to the 2000 census [18]. The population characteristics of Olmsted County residents have been described previously [19, 20]. 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 centres are geographically isolated from other urban centres as previously described [16, 19, 21]; 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 paediatric population, aged ≤18 years, from 1 January 1998 to 31 December 2007. Using the microbiology databases at the Mayo Medical Center, Rochester, and Olmsted Medical Center, we identified 56 unique children with first episodes of Gram-negative BSI.

Blood cultures were processed using standard microbiology techniques according to the Clinical and Laboratory Standards Institute (CLSI). The institutional review boards of both institutions approved the study. The detailed case ascertainment and blood culture methods used have been described previously [8, 16, 22].

Case definition

Gram-negative BSI was defined as the growth of any aerobic Gram-negative bacillus in a blood culture.

Monomicrobial Gram-negative BSI was defined as the growth of only one Gram-negative microorganism in a blood culture; and polymicrobial BSI was defined as the growth of more than one microorganism 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 [23]. The primary source of BSI was defined using the Centers for Disease Control and Prevention criteria [24].

Statistical analysis

The incidence rate, expressed as the number of new cases of BSI per 100 000 person-years, was calculated assuming that the entire paediatric population of Olmsted County was at risk of BSI. Gender-adjusted incidence rates were described for the following age groups (<1, 1–4, 5–18 years) and by site of acquisition. The 2000 Olmsted County census figures were used to compute the age, gender and time-specific person-years denominator assuming a projected population growth rate of 1·9% per year after 2000. The incidence rate was directly adjusted to the US 2000 white population [18]. Adjusted incidence rates and confidence intervals (CI) were calculated assuming the individual rates have Poisson error [25].

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 Gram-negative BSI until death or last healthcare encounter. Patients who were lost to follow-up were censored on the date of their last healthcare encounter. Ninety-five percent CIs were computed for the mortality rates using standard errors derived from the Greenwood formula. The log-rank test was used to compare survival rates between sites of acquisition (community-acquired *vs.* nosocomial or healthcare-associated).

Cox proportional hazard regression was used to identify univariate risk factors for 28-day and 1-year all-cause mortality. The following variables were evaluated as potential risk factors: age, number of underlying medical conditions, year of diagnosis, and gender.

The χ^2 or Fisher's exact test, as appropriate, was used to assess for associations between categorical variables. All analyses were performed using JMP (version 8.0, SAS Institute Inc., USA). The level of

Table 1. *Incidence rates of Gram-negative bloodstream infection in children by age group, gender, and site of acquisition, 1998–2007*

Variable	Age group (years)			
	<1	1–4	5–18	Age-adjusted*
Gender				
Female	15 (165·7)	5 (13·6)	10 (7·4)	16·3 (10·5–22·1)
Male	9 (95·5)	6 (15·6)	11 (7·7)	13·5 (8·3–18·7)
Site of acquisition				
Community-acquired†	7 (37·9)	3 (4·0)	12 (4·3)	5·9 (3·4–8·4)
Nosocomial or HCA†	17 (91·8)	8 (10·6)	9 (3·3)	9·0 (6·0–12·0)
Total†	24 (129·7)	11 (14·6)	21 (7·6)	14·9 (11·0–18·8)

HCA, Healthcare-associated.

Data are given as counts (incidence rates per 100 000 person-years) unless indicated otherwise.

* Incidence rates (95% confidence intervals) in this column are age-adjusted to the US white 2000 census.

† Incidence rates in these rows are gender-adjusted to the US white 2000 census.

significance for statistical testing was defined as $P < 0.05$ (two-sided).

RESULTS AND DISCUSSION

We identified 56 unique children aged ≤18 years with Gram-negative BSI during the study period. Infants had the highest incidence rate of Gram-negative BSI in all children with a gender-adjusted incidence rate of 129·7 (95% CI 77·8–181·6) per 100 000 person-years. Following the first year of life, the incidence rate of Gram-negative BSI fell by almost tenfold and 20-fold in children aged 1–4 and 5–18 years to 14·6 (95% CI 6·0–23·2) and 7·6 (95% CI 4·3–10·9) per 100 000 person-years, respectively. This decline was contrary to that in the adult population where the incidence rate of Gram-negative BSI increased with age [8, 22]. In infants, the incidence rate of Gram-negative BSI was higher in females than in males; there was no gender difference in the incidence rate in children aged 1–4 and 5–18 years (Table 1).

The site of acquisition differed in children with Gram-negative BSI by age group. Only 29% and 27% of Gram-negative BSI in infants and children aged 1–4 years were community-acquired, respectively. In contrast, over one-half (57%) of Gram-negative BSI in children aged 5–18 years were community-acquired which is similar to that in the adult population [22].

Most children in this investigation (68%) had underlying medical conditions predisposing to Gram-negative BSI, which is consistent with the results of previous reports [1–3]. Children with nosocomial or healthcare-associated Gram-negative BSI were more likely to have an underlying medical condition compared to those with community-acquired BSI (91% vs. 32%, $P < 0.001$).

In infants, the most common underlying conditions were: preterm delivery (38%), failure to thrive (21%), central nervous system (CNS) disorders such as hydrocephalus, meningomyelocele and seizure disorders (17%), cancer (8%), immunocompromised states including neutropenia, organ transplantation, and receipt of corticosteroids or other immunosuppressive medications (8%), congenital heart disease (4%), liver failure (4%), and necrotizing enterocolitis (4%).

In children aged 1–18 years, immunocompromised states (31%) and cancer (22%) were the most common underlying medical conditions. Other conditions included urological disorders such as kidney stones, vesicoureteral reflux and neurogenic bladder (9%), CNS disorders (9%), end-stage renal disease (3%), and cystic fibrosis (3%).

Forty-seven (84%) of 56 first episodes of Gram-negative BSIs were monomicrobial and nine (16%) were polymicrobial. Of monomicrobial Gram-negative bloodstream isolates, *Escherichia coli* was the most common microorganism (38%), followed by *Pseudomonas aeruginosa* (13%), *Klebsiella* spp. (9%), *Enterobacter* spp. (6%), *Salmonella* spp. (6%), *Acinetobacter* spp. (6%), *Haemophilus* spp. (4%), and others (17%).

The most common nosocomial or healthcare-associated Gram-negative bloodstream isolate was *E. coli* (30%), followed by *P. aeruginosa* (22%), *Klebsiella* spp. (15%), *Enterobacter* spp. (11%), and
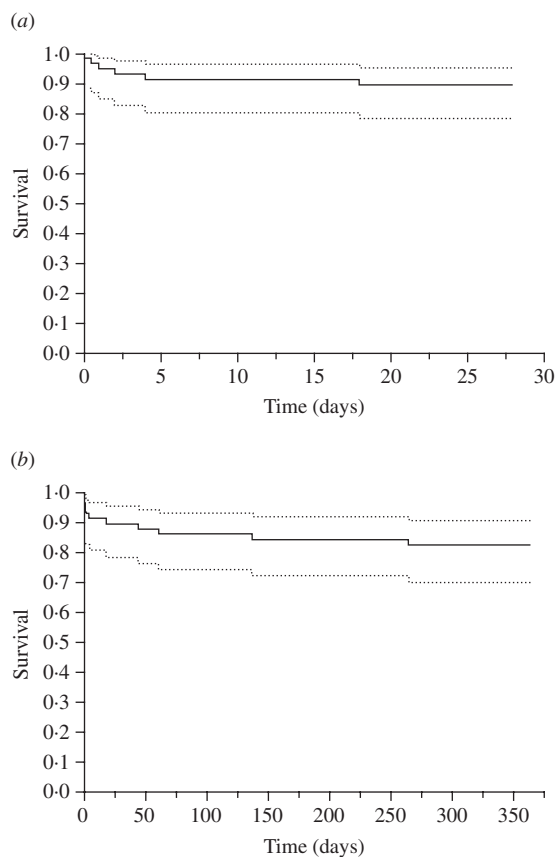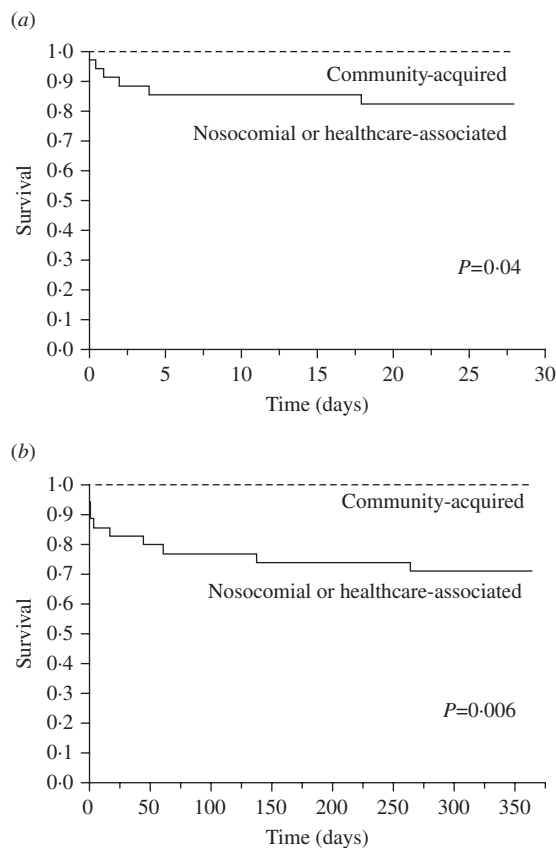
Fig. 1. Kaplan–Meier plot of (*a*) 28-day and (*b*) 1-year overall survival curves of children with Gram-negative bloodstream infection. Dotted lines indicate 95% confidence intervals.

Fig. 2. Kaplan–Meier plot of (*a*) 28-day and (*b*) 1-year survival of children with Gram-negative bloodstream infection by site of infection acquisition. *P* value denotes a difference in survival using log-rank test.

others (22%). *E. coli* was the isolate in half the cases of community-acquired Gram-negative BSI, followed by *Salmonella* spp. (15%), and others (35%).

The observation that *E. coli* was the most common cause of Gram-negative BSI in children in our survey was consistent with findings of the majority of hospital-based paediatric studies [6, 7] and population-based studies in children and adults [8, 9, 17, 22]. Comparing our results to those of a recent investigation of BSI in children in Calgary, Canada [17], the distribution of Gram-negative bacilli causing BSI was relatively similar in the two paediatric populations. One notable exception was that *P. aeruginosa* was the second most common microorganism and accounted for 13% of monomicrobial Gram-negative BSI in children in our population, compared to only 7% of cases in Calgary, where it ranked sixth among Gram-negative bacilli.

The urinary tract was the most common known primary source of infection (34%), followed by the gastrointestinal tract (7%), the respiratory tract (7%),

skin and soft tissue (5%), central venous catheter-related (4%), bone and joint (2%), and central nervous system (2%). Twenty-two children (39%) had Gram-negative BSI with unknown primary site of infection.

Community-acquired Gram-negative BSI were more likely to be of urinary source than nosocomial or healthcare-associated BSI (55% *vs.* 21%, $P = 0.009$). On the other hand, children with nosocomial or healthcare-associated Gram-negative BSI were more likely to have BSI of unknown primary source compared to those with community-acquired BSI (50% *vs.* 23%, $P = 0.04$).

The overall 28-day and 1-year all-cause mortality rates following Gram-negative BSI in this cohort were 11% (95% CI 3–18%) and 18% (95% CI 8–28%), respectively (Fig. 1). The 28-day mortality rate in our study was comparable to that of previous reports of Gram-negative BSI in children [4, 5]. This was also consistent with recently reported 28-day mortality rates following Gram-negative BSI in adults [22, 26].

Table 2. *Factors associated with 28-day all-cause mortality in children with Gram-negative bloodstream infection*

Variable	HR (95% CI)	P value
Age (per year)	0·77 (0·37–0·98)	0·03
Male gender	0·54 (0·08–2·77)	0·47
Number of underlying medical conditions (per condition)	2·51 (0·72–8·72)	0·15
Site of acquisition*		
CA *vs.* HCA or nosocomial	—	0·04
Year of diagnosis (per year)	1·01 (0·77–1·35)	0·93

HR, Hazard ratio; CI, confidence interval; CA, community-acquired; HCA, healthcare-associated.
* Hazard ratio was not calculated for site of acquisition because there were no deaths in community-acquired bloodstream infections. Log-rank test was used to calculate P value for this variable.

Table 3. *Factors associated with 1-year all-cause mortality in children with Gram-negative bloodstream infection*

Variable	HR (95% CI)	P value
Age (per year)	0·96 (0·85–1·05)	0·39
Male gender	0·72 (0·18–2·52)	0·61
Number of underlying medical conditions (per condition)	2·61 (1·00–6·80)	0·05
Site of acquisition*		
CA *vs.* HCA or nosocomial	—	0·006
Year of diagnosis (per year)	1·09 (0·88–1·38)	0·41

HR, Hazard ratio; CI, confidence interval; CA, community-acquired; HCA, healthcare-associated.
* Hazard ratio was not calculated for site of acquisition because there were no deaths in community-acquired bloodstream infections. Log-rank test was used to calculate P value for this variable.

The 28-day and 1-year all-cause mortality rates were lower in children with community-acquired compared to those with nosocomial or healthcare-associated Gram-negative BSI [0% vs. 18% (P = 0·04), and 0% vs. 29% (P = 0·006), respectively; Fig. 2]. Younger age was associated with 28-day all-cause mortality (Table 2) and number of underlying medical conditions was associated with 1-year all-cause mortality (Table 3).

The strength of this study is its population-based design and, therefore, lack of referral bias. Contrary to previous hospital-based studies that have estimated the incidence rate of Gram-negative 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 are derived from one geographic area. Studies from multiple geographic locations may provide a more comprehensive view. Second, since the population of Olmsted County is fairly small, the number of children with Gram-negative BSI during the study period was also small. This limited the ability to perform a multivariable model to determine independent risk factors for mortality. 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, this is the first population-based study to describe the incidence rate, site of acquisition, and short-, and long-term outcomes of Gram-negative BSI in infants and older children in the USA. We demonstrated that Gram-negative BSI is relatively common in infants and occurs much less frequently after the first year of life. Although children with community-acquired Gram-negative BSI had an excellent prognosis, nearly one-third of children with nosocomial or healthcare-associated Gram-negative BSI did not survive beyond 1 year, most likely due to underlying medical conditions that predisposed them to develop BSI.

NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov.

DECLARATION OF INTEREST

None.

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