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ORIGINAL PAPER

Bloodstream infection due to β-hemolytic streptococci: a population-based comparative analysis

Kevin B. Laupland[1,2,3] · Kelsey Pasquill[4] · Elizabeth C. Parfitt[3] · Lisa Steele[4]

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Abstract

Purpose Although the burden of illness due to *Streptococcus pyogenes* is widely recognized, other β-hemolytic streptococci are also important causes of invasive infections. The objective of this study was to compare the population-based epidemiology of groups A, B, and C/G β-hemolytic streptococcal bloodstream infection (BSI).

Methods Population-based surveillance was conducted in the western interior of British Columbia, Canada, 2011–2018.

Results A total of 210 episodes were identified for an incidence of 14.4 per 100,000; the incidences of groups A, B and C/G streptococcal BSI were 4.2, 4.7, and 5.5 per 100,000, respectively. There was an increasing annual incidence of β-hemolytic streptococcal BSI from 2011 through to a peak incidence in 2016 that decreased thereafter. Fifty-two percent (110) of BSIs were community associated, 43% (91) were healthcare associated, and 4% (9) were hospital onset. Patients with group A were younger, more likely to be female, and have fewer co-morbidities than patients with groups B and C/G streptococcal BSI. The most common focus of infection was soft tissue (109/52%), followed by primary (33; 16%), and bone and joint (20; 10%) and these varied by streptococcal species ($p < 0.001$). The 30-day all-cause case fatality rate was 11% (24/210) and did not significantly vary by group ($p = 0.7$).

Conclusion Although the determinants vary, the overall burden of disease related to BSI is similar amongst groups A, B and C/G β-hemolytic streptococci.

Keywords Incidence · Mortality · Bacteremia · Risk factor

Introduction

The β-hemolytic streptococci including groups A (*Streptococcus pyogenes*), B (*Streptococcus agalactiae*), and C/G (predominantly *Streptococcus dysgalactiae* subsp *equisimilis*) are important agents of invasive infections in humans [1–3]. Population-based studies conducted in high-income jurisdictions globally during the past 2 decades have identified incidence rates of approximately 2–4 per 100,000 population for each of groups A, B and C/G β-hemolytic streptococcal bloodstream infection (BSI) [4–8]. Group A streptococcus re-emerged as a major invasive pathogen during the 1980s, with many cases associated with high severity including necrotizing fasciitis and toxic shock [1, 9]. Group B streptococcal infection has long been recognized as a major cause of neonatal sepsis, but its epidemiology has shifted in recent decades with fewer cases in the young and an increasing burden in adults particularly those with medical co-morbidities [5, 10]. β-hemolytic group C/G streptococcal BSI are less well studied at the population level but appear to be causing an increasing burden of disease [3, 6, 7, 11].

The cumulative body of literature investigating β-hemolytic streptococcal infections involves hundreds of millions of patient-years of observation. However, population-based data on group C/G β-hemolytic streptococcal infections are limited. Few studies have directly compared the epidemiology of invasive disease due to the β-hemolytic

✉ Kevin B. Laupland
Kevin.laupland@qut.edu.au

1 Department of Intensive Care Services, Royal Brisbane and Women's Hospital, Level 3 Ned Hanlon Building, Butterfield Street, Herston, QLD 4029, Australia

2 Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia

3 Department of Medicine, Royal Inland Hospital, Kamloops, BC, Canada

4 Department of Pathology and Laboratory Medicine, Royal Inland Hospital, Kamloops, BC, Canada

streptococci in non-selected cohorts, and to our knowledge none have been conducted for this decade [3, 6, 12, 13]. The objective of this study was to define the contemporary epidemiology of BSI due to groups A, B, and C/G β-hemolytic streptococci in a Canadian population-based cohort.

Materials and methods

This study utilized a population-based surveillance cohort design. The surveillance population, methodology, and definitions have been previously described [14]. In brief, we included all residents of the western interior of British Columbia (2018 population 191,385) during 2011–2018 with incident BSI due to groups A, B, and C/G β-hemolytic streptococci; those belonging to the *Streptococcus anginosus* group were excluded [15]. Cases were identified through a regional laboratory system that performs all of the blood culture testing for the surveillance population. Case-by-case clinical review was conducted to confirm demographic, clinical, and outcome variables. This study was approved by the Interior Health Research Ethics Board and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (201314052-I).

We defined an incident BSI by the first isolate per patient per clinical infection episode; repeat isolation of the same group within 30 days was considered the same episode. Infections were classified as community associated, healthcare associated, and hospital onset per the definitions of Friedman et al. [16]. Co-morbid medical illnesses were classified as per Charlson et al. [17]. A clinical focus of infection was assigned by case-by-case chart review by a senior infectious diseases consultant. Blood culturing rate was defined by the number of blood culture sets (i.e., one aerobic and one aerobic bottle pair from a single blood draw) submitted for culture at the regional laboratory per 100,000 population.

All analyses were conducted using Stata 15.1 (StataCorp, College Station, USA). Incidence rates were calculated using denominator data available from the provincial registry [18]. Group categorical comparisons were made using Fisher's exact test and medians were compared using the Kruskal–Wallis test. A p value less than 0.05 was deemed to represent statistical significance for all comparisons.

Results

During 2011–2018, a total of 210 episodes of β-hemolytic streptococcal BSI occurred among 199 residents of the western interior for an overall incidence of 14.4 per 100,000. There were 61, 69, and 80 episodes of groups A, B and C/G streptococcal BSI for annual incidence rates of 4.2, 4.7, and 5.5, respectively. Second and third incident episodes occurred in nine and two patients, respectively; the time to subsequent incident episodes was a median of 353 (interquartile range, IQR, 213–952) days. Among the seven patients who had two episodes, in three cases the same group was responsible for the second BSI episode (two with group B, one with group A) with the other four being different (group C then A in two cases, one each of group A then C and group C then B). In the two patients that had three incident episodes, one had group A, B then C and the other was group G twice followed by group C BSI.

There was an increasing annual incidence of β-hemolytic streptococcal BSI from the start of surveillance through to a peak incidence in 2016 that decreased thereafter as shown in Fig. 1. While in the first 4 years of the study the increase in incidence was associated with an increase in culturing rate, this relationship was not evident in the latter half of the study (Fig. 1). There was no association between proportional changes in annual incidence by year related to streptococcal group ($p=0.4$), onset type ($p=0.3$), or gender ($p=0.3$).

There was moderate variation in the distribution of β-hemolytic streptococcal BSI during the months of the year as shown in Fig. 2. While only rare cases of group A streptococcal BSI occurred in May (2; 3%) and June (1; 2%), there was a notable peak of 13 (21%) cases that occurred in November (Fig. 2) of which 7 of these were in 2016. On the other hand, group B cases, with the exception of July tended toward higher occurrences from April through October and being low in the winter months (Fig. 2). There was no evident pattern to the occurrence with group C/G BSI during the months of the year.

A number of demographic and clinical variables were different among groups A, B, and C/G streptococcal BSI as shown in Table 1. Among those aged less than 20 years, β-hemolytic streptococcal BSI was infrequent (12 cases; 7, 4, and 1 groups A, B and C/G, respectively). Three late-onset neonatal group B streptococcal BSI occurred

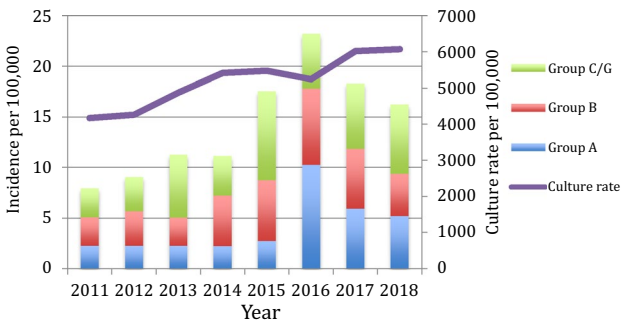

Fig. 1 Annual incidence of β-hemolytic streptococcal bloodstream infection by culturing rate

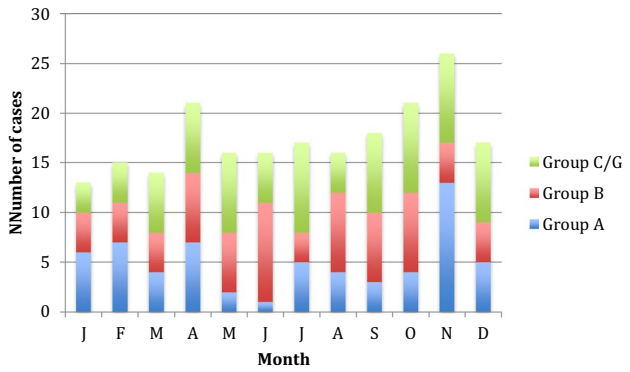

Fig. 2 Seasonal occurrence of β-hemolytic streptococcal bloodstream infection

(29, 62, and 74 days after birth). Among all ages, most of the cases were community onset with hospital-onset cases uncommon (Table 1). Group B BSI was more likely to be healthcare associated or of hospital onset, whereas patients with group A streptococcal BSI were younger with less co-morbid illness as compared to other groups (Table 1). While the Charlson index varied by group (Table 1), none of the individual co-morbidities were significantly different among the three groups (not shown). Most BSI were of soft tissue focus, although there was a range of clinical foci observed that varied by streptococcal group as shown in Table 1.

Overall 193 (92%) episodes were managed by admission to hospital for a median length of stay of 9 (IQR, 5–19) days. The 30-day all-cause case fatality rate was 11% (24/210). Patients who died had higher median age (73.6; IQR, 64.0–82.9 vs. 63.6; IQR 50.8–73.3 years; $p=0.0012$) and Charlson index scores (1; IQR, 0–3 vs. 3; IQR, 2–4; $p=0.0004$) than survivors of the 30-day post-index culture. A number of other variables were found to be associated with death in univariate analysis as shown in Table 2.

Discussion

This study describes the contemporary epidemiology of β-hemolytic streptococcal BSI in a general Canadian population. Although much attention and study has been afforded to groups A and B streptococci over the past 3 decades [1, 2, 5, 19, 20], it is of particular note that this study demonstrates that the contemporary burden of illness related to groups C/G is of a similar or higher magnitude to the other β-hemolytic streptococcal groups.

Our observed incidence rates for groups A and B streptococcal BSI are comparable to those observed with other large population-based studies conducted elsewhere in

Table 1 Demographic and clinical features of groups A, B, and C/G β-hemolytic streptococcal bloodstream infection

Variable	Group A ($n=61$)	Group B ($n=69$)	Group C/G ($n=80$)	Overall ($n=210$)	p value
Onset type					0.027
Community associated	36 (59%)	28 (41%)	46 (58%)	110 (52%)	
Healthcare associated	24 (39%)	34 (49%)	33 (41%)	91 (43%)	
Hospital onset	1 (2%)	7 (10%)	1 (1%)	9 (4%)	
Median age (IQR)	53.6 (31.3–64.9)	67.3 (56.0–78.3)	67.7 (58.5–77.4)	65.1 (51.6–74.8)	< 0.001
Male	28 (46%)	39 (57%)	54 (68%)	121 (58%)	0.038
Median Charlson index score (IQR)	1 (0–2)	2 (1–3)	2 (0–3)	2 (0–3)	0.039
Charlson index score					0.038
0	24 (39%)	13 (19%)	22 (28%)	22 (28%)	
1	12 (20%)	13 (19%)	15 (19%)	15 (19%)	
2	14 (23%)	22 (32%)	13 (16%)	13 (16%)	
≥ 3	11 (18%)	21 (30%)	30 (38%)	30 (38%)	
Focus					< 0.001
Primary/no focus	5 (8%)	11 (16%)	17 (21%)	33 (16%)	
Bone and joint	2 (3%)	10 (14%)	8 (10%)	20 (10%)	
Soft tissue	38 (62%)	26 (38%)	45 (56%)	109 (52%)	
Respiratory	10 (16%)	5 (7%)	1 (1%)	16 (8%)	
Cardiovascular	4 (7%)	1 (1%)	3 (4%)	8 (4%)	
Abdominal/pelvic	0	4 (6%)	4 (5%)	8 (4%)	
Central nervous	0	2 (3%)	0	2 (1%)	
Urinary tract	2 (3%)	10 (14%)	2 (3%)	14 (7%)	

IQR interquartile range

Table 2 Factors associated with 30-day all-cause case fatality rate among first episodes of β-hemolytic bloodstream infection

Variable	Case fatality rate	*p* value
Group		0.7
A	7/58 (12%)	
B	6/65 (9%)	
C/G	11/76 (14%)	
Onset type		0.012
Community associated	9/107 (8%)	
Healthcare associated	11/83 (13%)	
Hospital onset	4/9 (44%)	
Charlson score		< 0.001
0	0/56	
1	4/39 (10%)	
2	7/47 (15%)	
≥ 3	13/57 (23%)	
Focus		0.002
Primary/no focus	6/32 (19%)	
Bone and joint	0/20	
Soft tissue	6/101 (6%)	
Respiratory	4/15 (27%)	
Cardiovascular	2/8 (25%)	
Abdominal/pelvic	3/8 (38%)	
Central nervous	1/2 (50%)	
Urinary tract	2/13 (16%)	

high-income countries [1, 2, 5, 8, 19, 20]. While there has been regional variability, generally speaking the overall incidence of invasive group A streptococcus infection has increased since the 1990s, the rate of neonatal group B sepsis has decreased, and there has been an increase in group B invasive disease/BSI in adults. Concurrent with these changes in incidence, there has also been a significant decrease in the case fatality rates associated with these infections [12, 21]. As we have observed (Figs. 1, 2), year-to-year and even seasonal variability in the incidence of β-hemolytic streptococcal BSI is significant. These changes in incidence and outcome are likely due to multifactorial reasons which are not limited to increased awareness, higher rates of culture sampling, demographic and risk factor changes in populations, and the circulating strains of infecting organisms [22, 23]. While we do not have direct evidence per se, we suspect that the peak incidence of group A streptococcal cases in 2016 may have been associated with a community outbreak occurring among under-housed people who inject drugs [24, 25].

There are only a small number of studies with which we can compare our observations surrounding the epidemiology of groups C/G streptococcal BSI. Kristensen and Schonheyder reviewed β-hemolytic streptococcal BSI in North Jutland, Denmark during 1981–1993 and observed a rate of approximately 1 per 100,000 population for group C/G with a 7-day case fatality rate of 18% [3]. Ekelund et al. subsequently examined invasive β-hemolytic streptococcal infections in Denmark during 1999–2002 and found an incidence in blood of 2.1 per 100,000 with a 30-day case fatality rate of approximately 19% [12]. Laupland et al. conducted a population-based laboratory study in the Calgary area of Canada during 1999–2004 and identified a rate of 2.2 per 100,000 for group C/G β-hemolytic streptococci; death outcome was not available [6]. Kittang et al. identified 50 invasive group C/G infections in western Norway between 2006 and 2009 for an incidence of 4.1 per 100,000 and a 30-day case fatality rate of 2% [11]. Rantala et al. reported on *Streptococcus dysgalactiae* subsp *equisimilis* bacteremia in adults in Pirkanmaa, Finland during 1995–2004 for an incidence of approximately 3 per 100,000 and 30-day case fatality rate of 17% [7].

There are a number of important strengths and weaknesses of this study that merit discussion. We utilized a population-based surveillance cohort design that minimizes selection bias and facilitates generalization to other similar populations [26]. However, as a result of the relatively small size of our surveillance population we had limited power to detect small but potentially significant differences between the different groups. In addition, the small study size precluded a meaningful logistic regression analysis of factors associated with death. Furthermore, while we collected information on co-morbidities using the widely adopted method of Charlson [17], we did not collect potentially other important variables such as alcohol and illicit drug use histories, socioeconomic determinants such as homelessness, and ethnicity [20, 21, 27]. Although we included an 8-year time span, it is evident that the epidemiology of β-hemolytic streptococcal BSI varies over time and ideally a period of several decades would be preferred. Finally, we did not have details on the serotypes of the isolates that could provide further insight into the changing epidemiology of these infections [24].

In conclusion, this study documents the contemporary epidemiology of β-hemolytic streptococcal BSI in a non-selected Canadian population. These data confirm the burden of disease caused by groups A and B and emphasize the importance of group C/G streptococci as major causes of human suffering and death.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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