European Journal of Clinical Microbiology & Infectious Diseases (2022) 41:1407–1413
https://doi.org/10.1007/s10096-022-04505-5

ORIGINAL ARTICLE

Clinical and molecular epidemiology of invasive group B Streptococcus infections in adults in a referral center in Korea

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Received: 15 June 2022 / Accepted: 30 September 2022 / Published online: 8 October 2022

Abstract

Invasive group B Streptococcus (GBS) infections are increasing among adults with underlying health conditions; however, clinical manifestations and serotype distribution remain unclear. This study investigated the molecular characteristics and antimicrobial resistance of invasive GBS in Korean adults. GBS isolates from patients with invasive diseases during 2006–2015 were investigated for capsular serotype, multilocus sequence type (ST), antimicrobial susceptibility, and resistance genes. Among the 74 isolates analyzed, the most common serotype was Ib (31.1%), followed by III (21.6%), V (20.3%), Ia (12.2%), and VI (12.2%). Thirteen STs were detected, with ST1, ST10, ST19, and ST23 as the most prevalent. The dominant capsular serotype exhibited by ST1 was V, and those expressed by ST10, ST19, and ST23 were Ib, III, and Ia, respectively. Erythromycin and levofloxacin resistance were observed in 33.8% and 31.1% of the isolates, respectively. ST10-Ib ($n = 11/11$, 100%) and ST654-Ib ($n = 3/3$, 100%) were dominant levofloxacin-resistant strains. Serotypes Ib, III, and V were most common among adults, which is inconsistent with recent reports in Korea where III, V, and Ia were predominant in infants. The difference in the serotype distribution between adults and children may be associated with the selective pressure imparted by antibiotics.

Keywords Group B Streptococcus · *Streptococcus agalactiae* · Multilocus sequence typing · Serotype · Antibiotic resistance

Introduction

Invasive group B Streptococcus (GBS) infections have long been a major cause of invasive disease in neonates and young infants and are well characterized in pregnant women [1, 2]. Invasive GBS infections are observed in non-pregnant patients with predisposing medical conditions, such as cardiovascular disease, chronic liver or renal disease, diabetes mellitus, malignancy, and other immunocompromising conditions, or in subjects 65 years of age and older [3]. Recently, infections among non-pregnant adults are increasing in many countries [3–5]. Furthermore, population-based surveillance in six countries showed that, while rates of neonatal disease were stable, the incidence in those over 60 years of age doubled during 2000–2010 [4]. According to a recent report in the USA, the incidence of GBS among non-pregnant adults increased from 3.6% per 100,000 individuals in 1990 to 10.9% in 2016, which currently exceeds the rate for invasive pneumococcal disease in this population [5, 6]. The reason for this increase could be the increasing prevalence of underlying health conditions and an aging population [7, 8]. However, this increase may also be associated with certain serotypes of GBS [6].

The clinical manifestations and serotype distribution in adults differ from those observed in neonatal infections; moreover, the molecular characteristics of the bacteria causing these infections are not well described. This study aimed to investigate the molecular characteristics and antimicrobial resistance of GBS isolated from adults with invasive bacterial infections in a referral center in Korea over a period of 10 years.

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Materials and methods

Study design

GBS isolates previously obtained from adults with invasive GBS disease at Seoul National University Bundang Hospital (2006–2015) were analyzed for capsular serotype, multilocus sequence type (ST), antimicrobial susceptibility, and resistance genes. A case was defined as invasive GBS disease when GBS was isolated from a normally sterile site, including the blood, cerebrospinal fluid, and synovial fluid. In our hospital, automatic consultation to infectious disease physicians is done for blood culture results indicating bacteremia, and consultation for infections of other sterile sites is performed for proper antibiotic choice, route, and duration. The study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (B-2110–716-301). A written consent was waived in this study.

Bacterial strains and antimicrobial susceptibility tests

Isolates from invasive GBS cases were collected through a hospital-wide surveillance system at Seoul National University Bundang Hospital and stored at − 70 °C. GBS isolates were identified using the automated microbiology system MicroScan Walk-Away (Siemens Healthcare Diagnostics; Deerfield, IL, USA). Gram-positive isolates that showed β-hemolysis on sheep blood agar and positive CAMP test results were identified as GBS [9]. The gradient diffusion E-test was used to determine the minimal inhibitory concentrations (MICs) of penicillin, erythromycin, clindamycin, and levofloxacin. The double-disk synergy test (D-test) was performed to determine the inducible resistance of erythromycin and clindamycin. Isolates were regarded as susceptible, intermediate, or resistant according to the interpretative criteria published by the Clinical and Laboratory Standards Institute Guidelines in 2017 [10]. An MIC ≤ 0.12 μg/mL was used to define susceptibility for penicillin. For erythromycin and clindamycin, an MIC ≤ 0.25 μg/mL indicated susceptibility, and an MIC ≥ 1 μg/mL indicated resistance. GBS showing an MIC ≤ 2 μg/mL for levofloxacin was determined to be susceptible, and that showing an MIC ≥ 8 μg/mL was considered resistant. Macrolide resistance phenotypes obtained using MICs were classified as $cMLS_B$ (constitutive macrolide, lincosamide, and streptogramin B) for those with erythromycin and clindamycin resistance; $iMLS_B$ (inducible) for isolates that were erythromycin resistant, clindamycin susceptible, and D-test positive; and M phenotype for isolates resistant to erythromycin, susceptible to clindamycin, and D-test negative. All macrolide-resistant isolates were screened for molecular resistance mechanisms. The *erm*A, *erm*B, and *mef*A genes were detected using PCR amplification with primers as described previously [11, 12].

Serotyping and multilocus sequence typing (MLST)

The capsular polysaccharide (CPS) types were determined using PCR amplification and sequencing of the CPS type–specific regions of the cps locus in serotypes Ia, Ib, and II through VII [13]. Low-frequency serotypes VIII and IX are not included in the protocol. The DNA sequences of the internal fragments of the seven housekeeping genes (*adhP*, *atr*, *glck*, *glnA*, *pheS*, *sdhA*, and *tkt*) were amplified through PCR using oligonucleotide primers previously described by Jones et al. [14]. The amplicons were then sequenced and submitted to the GBS MLST database (https://pubmlst.org/organisms/streptococcus-agalactiae) to designate each locus and assign the ST. STs that shared six identical alleles of the seven loci were clustered into a clonal complex (CC) using goeBURST (https://www.phyloviz.net/goeburst/) [15].

Statistical analyses

Descriptive data of the data was provided for the clinical information, serotype and MLST distribution, and antibiotic resistance rate. All data were analyzed using SPSS version 22.0, and a P value < 0.05 was considered statistically significant.

Results

Demographics and clinical characteristics

During 2006–2015, among the 107 invasive GBS cases, 74 patients (69.2%) were aged 19 years and older. The demographics and clinical characteristics of the subjects included in this study are shown in Table 1. The median age of the 74 subjects was 68 years (interquartile range, 61–76 years), and 75.7% (56/74) aged 60 years or older. There were 41 male subjects (55.4%). Moreover, 69 patients (93.2%) had underlying diseases, including cardiovascular disease (n = 38, 51.4%), malignancy (n = 35, 47.3%), diabetes mellitus (n = 26, 35.1%), neurological disease (n = 19, 25.7%), liver disease (n = 11, 14.9%), renal disease (n = 8, 10.8%), gastrointestinal disease (n = 5, 6.8%), and pulmonary disease (n = 2, 2.7%).

According to clinical diagnosis, bacteremia without primary focus was most common and observed in 14 patients (18.9%), followed by intra-abdominal infection (n = 12,

Table 1 Demographics and characteristics of patients included in this study

	Number ($n=74$)	Percentage (%)
Age, years, median (IQR)	68 (61–76)	
20–29 years	1	1.4
30–39 years	4	5.4
40–49 years	5	6.8
50–59 years	8	10.8
60–69 years	23	31.1
70–79 years	21	28.4
≥ 80 years	12	16.2
Male	41	55.4
Underlying disease	69	93.2
Cardiovascular disease	38	51.4
Malignancy	35	47.3
Diabetes mellitus	26	35.1
Neurologic disease	19	25.7
Liver disease	11	14.9
Renal disease	8	10.8
Gastrointestinal disease	5	6.8
Pulmonary disease	2	2.7
Clinical diagnosis		
Bacteremia without primary focus	14	18.9
Intra-abdominal infection	12	16.2
Skin and soft tissue infection	11	14.9
Osteoarticular infection	11	14.9
Pneumonia	9	12.2
Genitourinary tract infection	8	10.8
Infective endocarditis	6	8.1
Central nervous system infection	3	4.1
Pregnancy-associated infections	0	0.0
30-day mortality	12	16.2
Age of subjects with 30-day mortality, years, median (IQR)	74 (65.5–77.3)	
Mortality according to diagnosis		
Bacteremia without primary focus	2/14	14.3
Intra-abdominal infection	2/12	16.7
Skin and soft tissue infection	0/11	0.0
Osteoarticular infection	0/11	0.0
Pneumonia	5/9	55.6
Genitourinary tract infection	0/11	0.0
Infective endocarditis	2/6	33.3
Central nervous system infection	1/3	33.3

IQR, interquartile range

16.2%), osteoarticular infection ($n=11$, 14.9%), and skin and soft tissue infection (SSTI; $n=11$, 14.9%). Pneumonia was observed in 9 patients (12.2%), genitourinary tract infection in 8 patients (10.8%), infectious endocarditis in 6 patients (8.1%), and central nervous system (CNS) infection in 3 patients (4.1%). Pregnancy-associated infections were not observed in this study. The overall 30-day mortality was 16.2%, among which 41.7% (5/12) were diagnosed with pneumonia. Mortality according to diagnosis was the highest for pneumonia (5/9, 55.6%), followed by CNS infection (1/3, 33.3%), infectious endocarditis (2/6, 33.3%), intra-abdominal infection (2/12, 16.7%), and bacteremia (2/14, 14.3%).

Serotype distribution

Six capsular serotypes were identified in 74 GBS isolates. Serotype Ib was the most prevalent ($n=23$, 31.1%), followed by serotype III ($n=16$, 21.6%), serotype V ($n=15$, 20.3%), serotype Ia ($n=9$, 12.2%), serotype VI ($n=9$, 12.2%), and serotype II ($n=2$, 2.7%) (Table 2).

There was no correlation between serotype and disease, and the most prevalent serotypes Ib, III, and V were associated with almost all disease presentations (Table 2). Serotype Ib was the most prevalent among cases of SSTI ($n=5$, 45.5%) and genitourinary tract infections ($n=6$, 75.0%). There were only three cases of CNS infection, each due to serotypes Ia, Ib, and III.

When analyzing the serotype distribution of the invasive GBS isolates during the study period, there was no significant difference in the distribution or increased prevalence of a single serotype during the study period (data not shown).

Multilocus ST

In the MLST analysis, 13 prevalent STs were identified, wherein ST1 ($n=14$, 32.4%), ST10 ($n=11$, 14.9%), ST19 ($n=9$, 12.2%), and ST23 ($n=6$, 8.1%) were prevalent (Table 3). The dominant capsular serotype expressed by ST1 was serotype V, while ST 10 expressed serotype Ib. Meanwhile, the dominant capsular serotype expressed by ST19 was serotype III, and that expressed by ST23 was serotype Ia. Through goeBURST analysis, four CCs, namely CC1 ($n=26$, 35.1%), CC10 ($n=24$, 32.4%), CC19 ($n=14$, 18.9%), and CC23 ($n=9$, 12.2%), and one singleton (ST17) were identified.

Antimicrobial susceptibility

All isolates were susceptible to penicillin. Erythromycin, clindamycin, and levofloxacin resistance were observed in 33.8%, 37.8%, and 31.1% of the isolates, respectively (Fig. 1). All isolates carrying *erm*B were highly resistant to erythromycin and clindamycin, with an MIC > 256 μg/mL, and the dominant strain was ST1 serotype V ($n=13/15$, 86.7%). The *erm*A-positive isolates were only detected in ST335 serotype III isolates ($n=4/4$, 100%). Meanwhile, ST10 serotype Ib ($n=11/11$,

Table 2 Distribution of capsular serotypes of group B Streptococcus (GBS) from invasive GBS infections in adults according to clinical manifestations

Diagnosis	Serotype (*n*, %)						Total (*n*, %)
	Ia	Ib	II	III	V	VI	
Bacteremia without primary focus	1 (7.1)	3 (21.4)	0 (0)	4 (28.6)	3 (21.4)	3 (21.4)	14 (18.9)
Intra-abdominal infection	2 (16.7)	2 (16.7)	2 (16.7)	3 (25.0)	2 (16.7)	1 (8.3)	12 (16.2)
Skin and soft tissue infection	0 (0)	5 (45.5)	0 (0)	3 (27.3)	2 (18.2)	1 (9.1)	11 (14.9)
Osteoarticular infection	2 (18.2)	2 (18.2)	0 (0)	4 (36.4)	3 (27.3)	0 (0)	11 (14.9)
Genitourinary tract infection	0 (0)	6 (75.0)	0 (0)	0 (0)	2 (25.0)	0 (0)	8 (10.8)
Pneumonia	2 (22.2)	3 (33.3)	0 (0)	0 (0)	1 (11.1)	3 (33.3)	9 (12.2)
Infective endocarditis	1 (16.7)	1 (16.7)	0 (0)	1 (16.7)	2 (33.3)	1 (16.7)	6 (8.1)
Central nervous system infection	1 (33.3)	1 (33.3)	0 (0)	1 (33.3)	0 (0)	0 (0)	3 (4.1)
Total (*n*, %)	9 (12.2)	23 (31.1)	2 (2.7)	16 (21.6)	15 (20.3)	9 (12.2)	74 (100)

Table 3 Relationship between serotype and sequence types of the invasive group B Streptococcus isolates

CC/ST	*n* (%)	Serotype					
		Ia	Ib	II	III	V	VI
CC1	26 (35.1)	0	1	0	1	15	9
ST1	24	0	1	0	0	14	9
ST2	2	0	0	0	1	1	0
CC10	24 (32.4)	0	22	2	0	0	0
ST8	6	0	6	0	0	0	0
ST10	11	0	11	0	0	0	0
ST12	4	0	2	2	0	0	0
ST654	3	0	3	0	0	0	0
CC19	14 (18.9)	0	0	0	14	0	0
ST19	9	0	0	0	9	0	0
ST28	1	0	0	0	1	0	0
ST335	4	0	0	0	4	0	0
CC23	9 (12.2)	9	0	0	0	0	0
ST23	6	6	0	0	0	0	0
ST88	2	2	0	0	0	0	0
ST144	1	1	0	0	0	0	0
ST17	1 (1.4)	0	0	0	1	0	0
Total	74 (100)	9	23	2	16	15	9

CC, clonal complex; *ST*, sequence type; *n*, number

100%) and ST654 serotype Ib ($n=3/3$, 100%) were levofloxacin-resistant. In contrast, none of the serotype Ia isolates was resistant to erythromycin or clindamycin.

Discussion

In this study, we analyzed the clinical characteristics and serotype distribution of GBS strains in adults with invasive GBS infection during 2006–2015. Among the cases, the clinical presentation of bacteremia without primary focus was the most common, followed by SSTI, osteoarticular infections, and genitourinary tract infection. There were no pregnancy-related cases during the study period. Among adults with invasive GBS infection, 93.2% had underlying diseases, the 30-day mortality rate was 16.2%, and the mortality was the highest in patients with pneumonia (55.6%).

Among the serotypes isolated from adults with invasive GBS infection, serotypes Ib (31.1%), III (21.6%), and V (20.3%) were the most common. This distribution is inconsistent with the recent reports on serotype distribution among young infants in Korea, in which serotypes III (44.6%), V (28.6%), and Ia (14.3%) predominated, and serotype Ib was found in only 10.7% of all cases [16]. The predominance of serotype Ib in invasive GBS infection among adults also differed from the result of a recent study

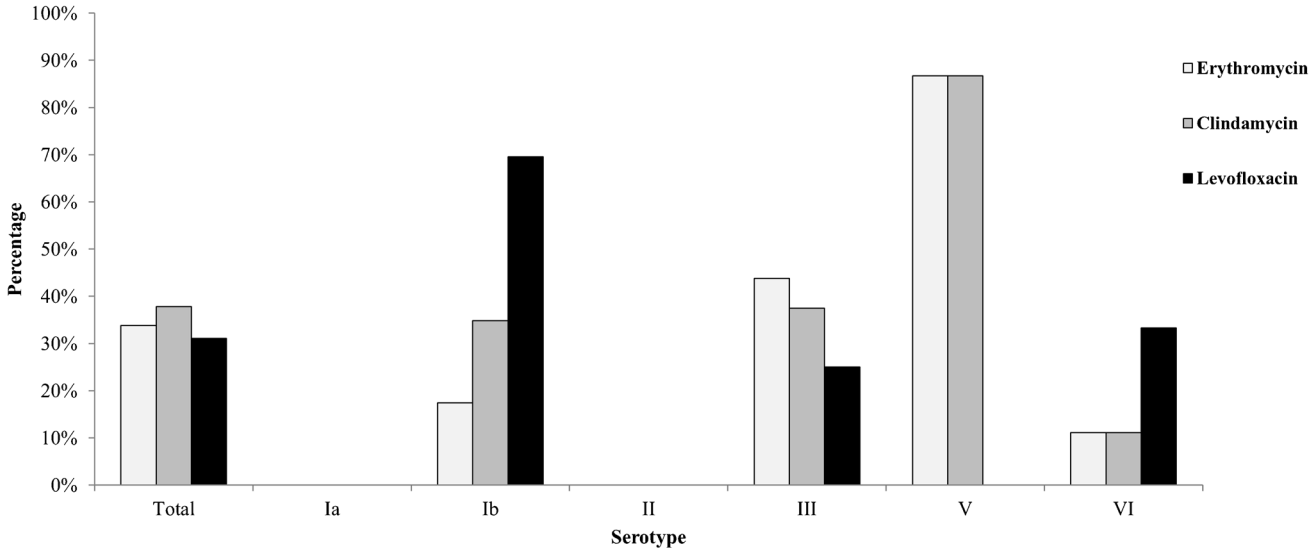

Fig. 1 Antibiotic resistance of group B Streptococcus (GBS) serotypes isolated from adults with invasive GBS infections

on the vaginal-rectal colonization of GBS among pregnant women in Korea, in which serotype III was the most common (42.1%), followed by serotypes Ib (21.1%), V (15.8%), II (10.5%), and VI (5.3%) [17]. Based on the results of the studies involving adult patients in other countries, serotype V is among the commonly reported serotypes since the 1990s [5, 18]. Nonetheless, changes in serotype distribution have been observed in various countries [7]. Serotype III is the most frequently recovered strain from adults in France [19], Norway [20], and Denmark [21]; serotype Ia from adults in the USA [6], Iceland [7], and the UK [8]; serotype Ib from adults in Portugal [22]; and serotype II from adults in Ireland [23]. A study in Japan, which included isolates from 30 adults during 2007–2016, reported that serotype Ib (17%) was the most prevalent, followed by serotypes VI (13%) and V (13%) [24].

Based on the results of this study, the difference in the serotype distribution between children and adults may be associated with the selective pressure induced by the widespread quinolone use in adults and the subsequent development of antibiotic-resistant clones. Fluoroquinolone use has increased significantly in Korea from 1.445/1000 inhabitants/days in 2002 to 2.565/1000 inhabitants/days in 2013 [25]. Among the predominant serotype Ib strains, 69.6% were levofloxacin-resistant, and among STs, all ST10 serotype Ib and ST654 serotype Ib strains showed levofloxacin resistance. This association between serotype Ib and levofloxacin resistance has also been reported in other studies [24, 26]. In contrast, only 25% of the serotype III strains and none of the serotype V or Ia strains showed levofloxacin resistance, which are prevalent serotypes in neonates and children in Korea. These serotypes are associated with macrolide resistance, which are correlated with the ST1 serotype V–associated *erm*B and ST335 serotype III–associated *erm*A as reported previously in Korean infants [15, 27].

Mortality was reported in 16.2% ($n=12$) of the cases, and pneumonia accounted for 41.7% ($n=5$). Among the mortality cases, serotype VI was the most common (41.7%; $n=5$). Mortality with serotype VI infection has also been reported in Japan [26].

This study has several limitations. First, this was a single-center study; therefore, the results may not be indicative of the epidemiological situation at a nationwide level. Second, low-frequency serotypes VIII and IX are not included in the protocol; however, there were no unclassified serotypes in this analysis. Third, although isolates were collected using a hospital-wide surveillance system, some isolates could not be collected or were not viable; thus, they were not included in the analysis. However, the strains included were well characterized, and the results of this study provide important data on the serotype distribution, genotype diversity, and antibiotic susceptibility patterns among the isolates of invasive GBS diseases in adults. In addition, this study is the first to report the molecular characteristics and antibiotic resistance of invasive GBS infections in adults in Korea.

Until recently, invasive GBS infections in adults have been less acknowledged than those in neonates. However, invasive GBS infection is a burden in adults with underlying diseases and shows a relatively high mortality rate. In this study, we found that the serotype distribution of GBS strains in adults differed between neonates and infants, which may be related to differences in antibiotic pressure, such as that induced by fluoroquinolones. With the increase in life expectancy and advancements in the treatments for complex underlying diseases in adults, continuous monitoring of invasive GBS infections in adults is important. The

potential advances in vaccine development also serve as a reason for the surveillance of the serotype distribution of GBS strains in this population.

Acknowledgements The authors thank Eun Sung Lee for her excellent technical assistance with the analysis.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Hyunju Lee, Jeong Su Park, and Kyoung Un Park. The first draft of the manuscript was written by Hyunju Lee, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This study was supported by the Seoul National University Bundang Hospital Research Fund (Grant No. 2016–00019).

Data availability The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on a reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (B-2110–716-301). Written consent was waived in this study.

Competing interests The authors declare no competing interests.

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