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ORIGINAL ARTICLE

Incidence, clinical characteristics, and outcomes of *Streptococcus dysgalactiae* subspecies *equisimilis* bacteremia in a tertiary hospital: comparison with *S. agalactiae* bacteremia

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Abstract

The clinical characteristics and outcomes of *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE) bacteremia cases have not been adequately evaluated. We retrospectively enrolled consecutive adult patients with SDSE or *S. agalactiae* (group B streptococci, GBS) bacteremia at a tertiary care hospital (Republic of Korea) from August 2012 to December 2016. We compared the incidence, seasonality, clinical characteristics, and outcomes of 52 SDSE bacteremia cases with 151 GBS bacteremia cases. The incidence of SDSE and GBS bacteremia in these patients was 1.28/100,000 and 4.22/100,000 person-days, respectively. Most SDSE bacteremia cases were of community-onset infection (SDSE 94.2% vs GBS 83.4%; $p = 0.052$). Lancefield group G was the most common bacteria type among SDSE isolates (43/47; 91.5%). Patients with SDSE bacteremia were older (median, 68.0 years vs 61.0 years; $p = 0.03$). In both groups, solid tumor was the most common underlying disease, and more than half of the patients were immunocompromised (51.9% vs 54.3%; $p = 0.77$). Chronic kidney disease was more common in the SDSE group (19.2% vs 5.3%; $p < 0.01$). Cellulitis was the most common clinical syndrome of SDSE bacteremia and was more common in the SDSE group (59.6% vs 29.1%; $p < 0.01$). SDSE bacteremia cases occurred more frequently in the warm season compared with GBS bacteremia cases (65.4% vs 37.1%; $p < 0.01$); in-hospital mortalities were not significantly different between the groups (3.8% vs 10.6%; $p = 0.17$). In conclusion, SDSE bacteremia is commonly associated with cellulitis, especially in older and immunocompromised patients during the warm season.

Keywords *Streptococcus dysgalactiae* · *Streptococcus agalactiae* · Bacteremia · Cellulitis

Introduction

Streptococcus dysgalactiae subspecies *equisimilis* (SDSE) is classified as one of the large colony-forming pyogenic beta-hemolytic streptococci [1]. According to prior studies on phylogenetic analysis, SDSE is closely related to *S. agalactiae* (group B streptococci, GBS) and *S. pyogenes* (group A streptococci, GAS) [2–5]. SDSE is known to be a constituent of the normal flora of the skin, upper respiratory tract, gastrointestinal tract, and female genital tract. In contrast to GBS and GAS, it has not been regarded as a significant pathogen in humans. Recently, SDSE has garnered attention as a possible pathogen involved in invasive infections in humans [6, 7]. Similar to other pyogenic streptococci, SDSE can cause serious or fatal infections, such as necrotizing fasciitis or toxic shock syndrome [6, 8].

To date, several investigators have addressed the characteristics of invasive SDSE infections [6, 8–13] and have reported that existing studies have limitations that include incomplete species identification of isolates [10, 12], inclusion of non-bacteremic cases along with bacteremic cases [6, 9, 10], or absence of a control group [13]. Furthermore, prior investigators did not evaluate the incidence and clinical characteristics of patients with hospital-acquired or immunocompromised conditions. Therefore, we aimed to investigate the incidence,

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clinical characteristics, and outcomes of SDSE bacteremia cases at a tertiary care hospital and to compare them with those of GBS bacteremia; GBS are well characterized and represent the main pathogen of pyogenic beta-hemolytic streptococci.

Materials and methods

Study design, population, and setting

This was a retrospective cohort study conducted at the Asan Medical Center, a 2700-bed tertiary care teaching hospital, in Seoul, South Korea. We reviewed the electronic medical records of all consecutive adult patients (aged > 18 years) with SDSE and GBS bacteremia between August 2012 and December 2016. Using a computerized database of clinical microbiology unit, we identified patients whose blood culture samples had yielded SDSE or GBS. We collected data regarding patients' demographic characteristics, underlying diseases or conditions, the portal of entry, antimicrobial susceptibility, clinical manifestations at the time of bacteremia observation, and outcome. SDSE has been identified since August 2012 in our hospital (see section "Blood culture, species identification of streptococci, and antimicrobial susceptibility testing"). The

Table 1 Demographics, underlying disease or condition, and setting of patients with SDSE and GBS bacteremia

Clinical characteristics	SDSE ($n = 52$)	GBS ($n = 151$)	p value
Age, years, median (IQR)	68.0 (58.0–74.8)	61.0 (53.0–72.0)	0.03
15–39	0	11 (7.3)	
40–64	23 (44.2)	78 (51.7)	
≥ 65	29 (55.8)	62 (41.1)	
Male sex	32 (61.5)	63 (41.7)	0.01
Underlying diseases			
Any underlying disease	49 (94.2)	138 (91.4)	0.51
Solid tumor	21 (40.4)	64 (42.4)	0.80
Diabetes mellitus	14 (26.9)	34 0 (22.5)	0.52
Liver cirrhosis	12 (23.1)	31 (20.5)	0.70
Chronic kidney disease without dialysis	10 (19.2)	8 (5.3)	< 0.01
Cardiovascular disease	9 (17.3)	14 (9.3)	0.12
Solid organ transplantation	5 (9.6)	6 (4.0)	0.12
End-stage renal disease	2 (3.8)	3 (2.0)	0.11
Trauma	3 (5.8)	2 (1.3)	0.11
Heavy alcohol consumption	1 (1.9)	7 (4.6)	0.68
Hematologic malignancy	1 (1.9)	8 (5.3)	0.45
Bone marrow transplantation	0	2 (1.3)	1.0
Underlying conditions			
Immunocompromised condition[a]	27 (51.9)	82 (54.3)	0.77
Lymphedema	15 (28.8)	30 (19.9)	0.18
Cytotoxic chemotherapy within 1 month	6 (11.5)	27 (17.9)	0.29
Central venous catheter	6 (11.5)	16 (10.6)	0.85
Impaired skin barrier	5 (9.6)	11 (7.3)	0.56
Immunosuppressant within 1 month	5 (9.6)	12 (7.9)	0.77
Leukopenia (ANC < 500/mm^3)	2 (3.8)	12 (7.9)	0.53
Recent surgery within 1 month	1 (1.9)	5 (3.3)	1.0
Others	3 (5.8)	7 (4.6)	0.72
Setting of infection			0.052
Community onset	49 (94.2)	126 (83.4)	
Community acquired	33 (63.5)	96 (63.6)	
Healthcare associated	16 (30.8)	30 (19.9)	
Hospital acquired	3 (5.8)	25 (16.6)	

SDSE Streptococcus dysgalactiae subspecies *equisimilis*, *GBS* group B streptococci (*Streptococcus agalactiae*), *IQR* interquartile range, *ANC* absolute neutrophil count

[a] Patients who underwent solid organ transplantation, bone marrow transplantation, or cytotoxic chemotherapy within 6 months or received immunosuppressants, including corticosteroids within 1 month

Table 2 Antibiotic resistance in SDSE and GBS bacteremia

Antibiotic resistance	SDSE ($n = 52$)	GBS ($n = 151$)	p value
Beta-lactams			
Penicillin	0	0/149	–
Ampicillin	0	0/136	–
Ceftriaxone	0	0/150	–
Cefotaxime	0	0/135	–
Cefepime	0/51	0/136	–
Meropenem	0/37	1/87 (1.1)	1.0
Macrolides			
Azithromycin	22 (42.3)	38/137 (27.7)	0.06
Clarithromycin	13/36 (36.1)	20/83 (24.1)	0.18
Erythromycin	22 (42.3)	44 (29.1)	0.08
Fluoroquinolones			
Levofloxacin	0	40 (26.5)	< 0.01
Tetracyclines			
Tetracycline	29 (55.8)	56/137 (40.9)	0.07
Minocycline	22/36 (61.1)	36/78 (46.2)	0.14
Others			
Vancomycin	0	0	–
Clindamycin	18 (34.6)	44 (29.1)	0.46
Daptomycin	0/35	0/82	–
Linezolid	0/36	0/81	–
Chloramphenicol	0	0/137	–

SDSE Streptococcus dysgalactiae subspecies *equisimilis*, *GBS* group B streptococci (*Streptococcus agalactiae*)

study protocol was approved by the Institutional Review Board of the Asan Medical Center, Seoul, South Korea (IRB No. 2019-0243).

Definitions

The date of bacteremia onset was defined as the date on which the blood sample was obtained for the first positive culture result. Bacteremia was considered a hospital-acquired infection if the sample in the positive blood culture was obtained > 48 h after admission to the hospital and if there was no evidence of infection at the time of hospital admission; otherwise, bacteremia was considered a community-onset infection. Community-onset infection cases were subcategorized as community-acquired or healthcare-associated infection. Healthcare-associated bacteremia was defined in patients receiving home and/or ambulatory intravenous therapy, chemotherapy, hemodialysis, wound care, and specialized nursing care, in patients who had been hospitalized in other hospitals for ≥ 2 days within the last 90 days and in patients who had been residing in a nursing home or long-term care facility [14]. Immunocompromised patients were defined as those who had undergone solid organ transplantation, bone marrow transplantation, or cytotoxic chemotherapy within 6 months or those who had received immunosuppressants, including corticosteroids, within 1 month [15]. Clinical syndromes were assessed based on the clinicians' diagnoses. Primary bacteremia was defined as bacteremia that did not have obvious infectious sources. Septic shock as the initial clinical manifestation was defined as described by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [16]. Clinical outcomes were evaluated based on the length of hospital stay, duration of stay in the intensive care unit (ICU), and mortality. Death was considered to be related to bacteremia if the patient died ≤ 14 days after the bacteremia onset and if the cause of death other than bacteremia was not identified.

Blood culture, species identification of streptococci, and antimicrobial susceptibility testing

All blood culture samples were processed by the hospital microbiology laboratory using the standard blood culture system (BACTEC 9240 or BACTEC FX; Becton Dickinson, NJ, USA). Species identification and antimicrobial susceptibilities were determined using VITEK (bioMérieux, France) or MicroScan (Beckman Coulter, Inc., CA, USA) in accordance with the standard criteria of the Clinical and Laboratory Standards Institute [17]. Intermediate susceptibility to each antimicrobial agent was considered to indicate resistance. Lancefield grouping serological analysis was performed to classify SDSE.

Statistical analysis

Categorical variables were compared using the χ^2 or Fisher's exact test and continuous variables using Student's t test and Mann–Whitney U test as appropriate. Continuous data were expressed as the median values and interquartile range. All significance tests were two-tailed, and $p < 0.05$ was considered to be statistically significant. All of the analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results and discussion

Incidence, demographics, underlying disease or condition, and setting of SDSE and GBS bacteremia

During the study period, the incidence of SDSE and GBS bacteremia in admitted patients was 1.28/100,000 and 4.22/100,000 person-days, respectively. Finally, 52 SDSE

Table 3 Clinical manifestation of SDSE and GBS bacteremia

	SDSE ($n = 52$)	GBS ($n = 151$)	p value
Initial manifestations			
Septic shock	10 (19.2)	27 (17.9)	0.83
Altered mental status	7 (13.5)	25 (16.6)	0.60
Acute respiratory failure	5 (9.6)	13 (8.6)	0.78
Laboratory findings			
WBC ($\times 10^3/\mu L$)	10.2 (6.6–14.1)	9.8 (5.8–15.5)	0.90
Platelet ($\times 10^3/\mu L$)	163.5 (89.5–248.3)	158.0 (88.0–228.0)	1.0
CRP (mg/dL)	2.7 (0.6–12.1)	6.4 (1.0–15.8)	0.13
Procalcitonin (ng/mL)	0.6 (0.1–10.2)	0.7 (0.2–7.5)	0.98
Clinical syndrome			
Cellulitis	31 (59.6)	44 (29.1)	< 0.01
Primary bacteremia	9 (17.3)	40 (26.5)	0.18
Pneumonia	2 (3.8)	9 (6.0)	0.73
Osteomyelitis	3 (5.8)	13 (8.6)	0.77
Septic arthritis	2 (3.8)	5 (3.3)	1.0
Abscess (except for skin)	2 (3.8)	9 (6.0)	0.73
Intra-abdominal infection	2 (3.8)	18 (11.9)	0.09
Necrotizing fasciitis	1 (1.9)	0 (0)	0.26
Urinary tract infection	1 (1.9)	11 (7.3)	0.30
Infective endocarditis	0	9 (6.0)	0.12
Meningitis	0	3 (2.0)	0.57
Surgical site infection	0	2 (1.3)	1.0
Toxic shock syndrome	1 (1.9)	1 (0.7)	0.45
Others	2 (3.8)	6 (4.0)	1.0

SDSE Streptococcus dysgalactiae subspecies *equisimilis*, *GBS* group B streptococci (*Streptococcus agalactiae*), *WBC* white blood cell, *CRP* C-reative protein

bacteremia and 151 GBS bacteremia adult cases were included and compared in the study.

The epidemiological characteristics of the study population are shown in Table 1. In both groups, the most common underlying disease was solid tumor, followed by diabetes mellitus and liver cirrhosis. Chronic kidney disease without dialysis was more common in the SDSE group than in the GBS group (19.2% vs 5.3%, $p < 0.01$). More than 50% of the patients had immunocompromised conditions. Fifteen and 30 patients of the SDSE group and GBS group had underlying lymphedema, respectively. Community-onset infection tended to be more common in the SDSE group than in the GBS group (94.2% vs 83.4%; $p = 0.052$).

Seasonality of SDSE and GBS bacteremia

Figure 1 shows the monthly distribution of SDSE and GBS bacteremia cases from January 2013 to December 2016. GBS bacteremia sporadically occurred throughout the year, whereas SDSE bacteremia predominantly occurred during the warm season (June to September) (65.4% vs 37.1%; $p < 0.01$).

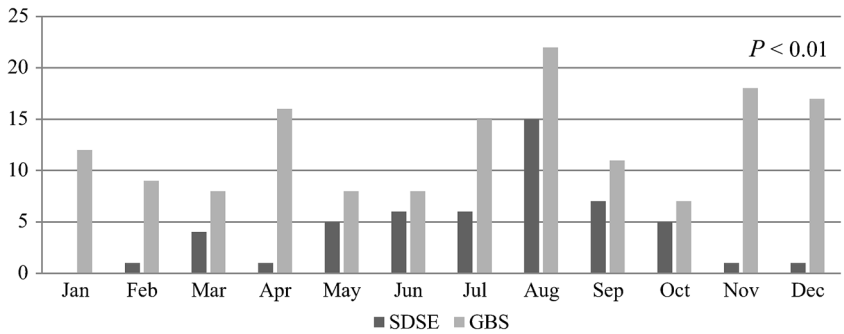

Fig. 1 Seasonality of SDSE and GBS bacteremia. SDSE, *Streptococcus dysgalactiae* subspecies *equisimilis*; GBS, group B streptococci (*Streptococcus agalactiae*). *P* value was calculated by comparing seasonal distribution between the SDSE and GBS groups ($P < 0.01$)

Table 4 Outcome of SDSE and GBS bacteremia

	SDSE ($n = 52$)	GBS ($n = 151$)	p value
Length of hospital stay, median (IQR)	11.0 (6.0–16.0)	15.0 (6.0–25.0)	0.08
ICU care	8 (15.4)	22 (14.6)	0.89
30-day mortality	4 (7.7)	12 (7.9)	1.0
90-day mortality	4 (7.7)	20 (13.2)	0.33
In-hospital mortality	2 (3.8)	16 (10.6)	0.17
Bacteremia-related mortality	2 (3.8)	12 (7.9)	0.53

SDSE Streptococcus dysgalactiae subspecies *equisimilis*, *GBS* group B streptococci (*Streptococcus agalactiae*), *ICU* intensive care unit

Microbiology and antimicrobial susceptibility of SDSE and GBS isolates

Lancefield grouping classification data were available for 47 SDSE isolates. The most common antigen type was group G (43/47; 91.5%), followed by group A (2/47; 4.2%), group C (1/47; 2.1%), and group F (1/47; 2.1%).

The results of the antimicrobial susceptibility testing of SDSE and GBS isolates are shown in Table 2. None of the SDSE isolates was resistant to penicillin, cephalosporin, levofloxacin, and carbapenem. The resistance rates to macrolides, clindamycin, and tetracyclines were 36.1–42.3%, 34.6%, and 55.8–61.1%, respectively.

Clinical manifestations and outcomes of SDSE and GBS bacteremia

Clinical manifestations at the time of bacteremia onset are shown in Table 3. In the SDSE bacteremia group, the most common clinical syndromes were cellulitis and primary bacteremia. The proportion of cellulitis was significantly higher in the SDSE group ($p < 0.01$) than in the GBS group.

The outcomes of SDSE and GBS bacteremia are shown in Table 4. Bacteremia-related mortality in the SDSE group was not significantly different from the GBS group.

We determined the clinical characteristics and outcomes of SDSE bacteremia cases by comparing with GBS bacteremia cases at a single tertiary care hospital. The majority of SDSE bacteremia cases were defined as community-onset infections. Cellulitis occurred more frequently in the SDSE group than in the GBS group. Although the study population included a significant number of patients with underlying diseases or immunocompromised conditions, in-hospital mortality and bacteremia-related mortality of SDSE bacteremia cases were low.

We found that chronic kidney disease without dialysis was significantly more common in the SDSE group than in the GBS group. It is difficult to explain the increased risk of SDSE bacteremia in patients with chronic kidney disease who are not undergoing dialysis. It can be a bias associated with the small number of SDSE bacteremia cases or the characteristics of admitted patients in our tertiary care hospital. Additional studies are warranted to identify whether chronic kidney disease without dialysis can be a risk factor of bacteremia by SDSE.

In our results, SDSE bacteremia predominantly occurred from June to September. This finding can be explained by the predominance of cellulitis as a clinical manifestation of SDSE bacteremia. According to a recent report of a population-based investigation in the USA, the average monthly temperature is closely related to cellulitis [18].

All the SDSE isolates were susceptible to beta-lactam agents, including penicillin. However, the resistance rates to macrolides, clindamycin, and tetracyclines were substantial,whereas all of the SDSE isolates were susceptible to levofloxacin. Because there was no resistance to levofloxacin in this study, levofloxacin can be considered a treatment for SDSE bacteremia.

Although immunocompromised conditions were common in our SDSE patients, their mortality rate was lower than expected. Some of the SDSE bacteremia studies showed considerable mortalities (12.0–15.0%) [8, 13]. This finding could be explained by the relatively high proportion of patients with cellulitis, which can be easily detected and treated early, and possible difference of the virulence factors of SDSE strains depending on the regions.

There are several limitations to this study. First, this study was performed at a single tertiary care hospital and the sample size was relatively small. Second, we could not evaluate the risk factors associated with bacteremia-related mortality because only two patients died of SDSE bacteremia. Third, we did not analyze the pathogenic virulence factors and genes associated with resistance to antimicrobial agents of isolated bacteria.

In conclusion, SDSE bacteremia is commonly associated with cellulitis, especially in elderly patients with comorbid illnesses, during the warm season. However, the incidence of SDSE bacteremia-related mortality is low. Thus, additional studies are warranted to reveal the risk and virulence factors associated with invasive SDSE infections.

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Bennett JE, Dolin R, Blaser MJ, (2015) Mandell, Douglas, and Bennett's principles and practice of infectious diseases
2. Facklam R (2002) What happened to the streptococci: overview of taxonomic and nomenclature changes. Clin Microbiol Rev 15:613–630. https://doi.org/10.1128/CMR.15.4.613-630.2002
3. Rato MG, Nerlich A, Bergmann R et al (2011) Virulence gene pool detected in bovine group C streptococcus dysgalactiae subsp. dysgalactiae isolates by use of a group a S. pyogenes virulence microarray. J Clin Microbiol 49:2470–2479. https://doi.org/10.1128/jcm.00008-11
4. Suzuki H, Lefebure T, Hubisz MJ et al (2011) Comparative genomic analysis of the streptococcus dysgalactiae species group: gene content, molecular adaptation, and promoter evolution. Genome Biol Evol 3:168–185. https://doi.org/10.1093/gbe/evr006
5. Jensen A, Kilian M (2012) Delineation of streptococcus dysgalactiae, its subspecies, and its clinical and phylogenetic relationship to streptococcus pyogenes. J Clin Microbiol 50:113–126. https://doi.org/10.1128/jcm.05900-11
6. Takahashi T, Ubukata K, Watanabe H (2011) Invasive infection caused by streptococcus dysgalactiae subsp. equisimilis: characteristics of strains and clinical features. J Infect Chemother 17:1–10. https://doi.org/10.1007/s10156-010-0084-2
7. Watanabe S, Takemoto N, Ogura K et al (2016) Severe invasive streptococcal infection by streptococcus pyogenes and streptococcus dysgalactiae subsp. equisimilis. Microbiol Immunol 60:1–9. https://doi.org/10.1111/1348-0421.12334
8. Rantala S (2014) Streptococcus dysgalactiae subsp. equisimilis bacteremia: an emerging infection. Eur J Clin Microbiol Infect Dis 33:1303–1310. https://doi.org/10.1007/s10096-014-2092-0
9. Broyles LN, Van Beneden C, Beall B et al (2009) Population-based study of invasive disease due to beta-hemolytic streptococci of groups other than a and B. Clin Infect Dis 48:706–712. https://doi.org/10.1086/597035
10. Ekelund K, Skinhoj P, Madsen J et al (2005) Invasive group a, B, C and G streptococcal infections in Denmark 1999-2002: epidemiological and clinical aspects. Clin Microbiol Infect 11:569–576. https://doi.org/10.1111/j.1469-0691.2005.01169.x
11. Kittang BR, Bruun T, Langeland N et al (2011) Invasive group a, C and G streptococcal disease in western Norway: virulence gene profiles, clinical features and outcomes. Clin Microbiol Infect 17:358–364. https://doi.org/10.1111/j.1469-0691.2010.03253.x
12. Liao CH, Liu LC, Huang YT et al (2008) Bacteremia caused by group G streptococci, Taiwan. Emerg Infect Dis 14:837–840. https://doi.org/10.3201/eid1405.070130
13. Tsai CT, Chi CY, Ho CM et al (2014) Correlation of virulence genes to clinical manifestations and outcome in patients with streptococcus dysgalactiae subspecies equisimilis bacteremia. J Microbiol Immunol Infect 47:462–468. https://doi.org/10.1016/j.jmii.2013.08.019
14. Friedman ND, Kaye KS, Stout JE et al (2002) Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 137:791–797. https://doi.org/10.7326/0003-4819-137-10-200211190-00007
15. Lim YJ, Park HY, Lee JY et al (2018) Clearance of carbapenemase-producing Enterobacteriaceae (CPE) carriage: a comparative study of NDM-1 and KPC CPE. Clin Microbiol Infect 24:1104.e1105–1104.e1108. https://doi.org/10.1016/j.cmi.2018.05.013
16. Shankar-Hari M, Phillips GS, Levy ML et al (2016) Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for Sepsis and septic shock (Sepsis-3). Jama 315:775–787. https://doi.org/10.1001/jama.2016.0289
17. CLSI (ed) (2016) Performance standards for antimicrobial susceptibility testing. 26th ed. CLSI supplement M100. Clinical and Laboratory Standards Institute, Wayne
18. Peterson RA, Polgreen LA, Sewell DK et al (2017) Warmer weather as a risk factor for cellulitis: a population-based investigation. Clin Infect Dis 65:1167–1173. https://doi.org/10.1093/cid/cix487