[UCI]I804:48009-200000171237

Master of Medicine

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

Streptococcus dysgalactiae subspecies *equisimilis* 균혈증의 빈도, 임상적 특징 및 예후에 관한 연구: *S. agalactiae* 균혈증과의 비교

The Graduate School of

the University of Ulsan

Department of Medicine

Joung Ha Park

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

Supervisor: Sang-Ho Choi

A Master's Thesis

Submitted to the Graduate School of the University of Ulsan
In Partial Fulfillment of the Requirements
for the Degree of

Master of Medicine
By

Joung Ha Park

Department of Medicine
Ulsan, Korea
December 2018

Incidence, clinical characteristics, and outcomes of

Streptococcus dysgalactiae subspecies *equisimilis* bacteremia in

a tertiary hospital: comparison with *S. agalactiae* bacteremia

This certifies that the master's thesis of Joung Ha Park is approved

---

Committee Chairman Professor Sang-Oh Lee

Committee Member Professor Sang-Ho Choi

Committee Member Professor Heungsup Sung

Department of Medicine

Ulsan, Korea

December 2018

Abstract

Background: Invasive *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE) infections have been reported increasingly. The clinical characteristics and outcomes of patients with SDSE bacteremia have not been adequately evaluated. We reviewed the incidence, clinical characteristics, and outcomes of SDSE bacteremia cases.

Methods: We retrospectively enrolled consecutive adult patients with SDSE or *S. agalactiae* (Group B streptococci, GBS) bacteremia who had been admitted to the Asan Medical Center, a tertiary care hospital in the Republic of Korea, from August 2012 to December 2016. We compared the incidence, seasonality, clinical characteristics, and outcomes of patients with SDSE bacteremia with patients with GBS bacteremia.

Results: The incidence of SDSE and GBS bacteremia in admitted patients was 1.28/100,000 and 4.22/100,000 person-days, respectively. A total of 52 SDSE and 151 GBS bacteremia adult cases were finally included for analysis. Most of SDSE bacteremia series were community-onset (SDSE 94.2% vs GBS 83.4%, p = 0.052). Lancefield group G was the most common type among SDSE isolates (43/47, 91.5%). Patients with SDSE bacteremia

were older (median 68.0 vs 61.0 years old, $p = 0.03$) and SDSE bacteremia occurred more common in men than the GBS group (61.5% vs 41.7%, $p = 0.01$). In both groups, solid tumor (40.4% vs 42.4%, $p = 0.80$) was the most common underlying disease, and more than half of patients had immunocompromised conditions (51.9% vs 54.3%, $p = 0.77$). Chronic kidney disease without dialysis was more common in the SDSE group (19.2% vs 5.3%, $p < 0.01$). The most common clinical syndromes of SDSE bacteremia was cellulitis, which was significantly more common than the GBS group (59.6% vs 29.1%, $p < 0.01$). SDSE bacteremia cases occurred more frequently in the warm season (June-September) than GBS bacteremia ones (65.4% vs 37.1%, $p < 0.01$). In-hospital mortality (3.8% vs 10.6%, $p = 0.17$) and bacteremia-related mortality (3.8% vs 7.9%, $p = 0.53$) of SDSE bacteremia series were not significantly different from the GBS group.

Conclusions: SDSE bacteremia was commonly associated with cellulitis, especially in older and immunocompromised patients during the warm season. However, SDSE bacteremia-related mortality was low even in immunocompromised patients.

Keywords: *Streptococcus dysgalactiae* subsp. *equisimilis*, *Streptococcus agalactiae*, bacteremia, cellulitis

Contents

List of tables and figures

Introduction

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

To date, some investigators have addressed the characteristics of invasive SDSE infection.[6, 8-13)] Those studies have limitations in that incomplete species identification of isolates,[10, 12)] the 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, clinical characteristics and outcomes of SDSE bacteremia series in a tertiary care hospital, with a comparison to GBS bacteremia, which is well-characterized and the main pathogen of pyogenic beta-hemolytic streptococci.

Methods

Study design, population, and setting

This study is a retrospective cohort study in 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 (more than 15 years old) with SDSE and GBS bacteremia from Agust 2012 to December 2016. Using a computerized database of clinical microbiology unit, patients whose blood cultures had yielded SDSE or GBS were identified. Then, we collected data regarding patients' demographic characteristics, underlying diseases or conditions, portal of entry, antimicrobial susceptibility, clinical manifestations at the time of bacteremia, and outcome. SDSE has been identified since August 2012 in our hospital (See below, *Blood culture, species identification, and antimicrobial susceptibility testing* section).

Definitions

The date of onset of bacteremia was defined as the date on which the blood sample was obtained for the first positive culture result. Bacteremia was considered to be a hospital-

acquired infection if the sample in the positive blood culture was obtained > 48 hours after admission and if there was no evidence of infection at the time of admission; otherwise, bacteremia was considered to be a community-onset infection. Community-onset infection cases were subcategorized as community-acquired or healthcare-associated infection. Healthcare-associated bacteremia was defined as cases in patients receiving home and/or ambulatory intravenous therapy, chemotherapy, hemodialysis, wound care, specialized nursing care, or who had hospitalized in other hospitals for ≥ 2 days within the last 90 days and those residing in a nursing home or long-term care facility.[14] The immunocompromised condition was defined as patients who underwent solid organ transplantation, bone marrow transplantation, or cytotoxic chemotherapy within 6 months or took immunosuppressants, including corticosteroids within 1 month.[15] Warm seasons were from June to September, of which monthly mean temperature was above 20℃ when compared the seasonality of SDSE and GBS bacteremia. Monthly mean temperature was collected based on data of the Korea Meteorological Administration. Clinical syndromes were assessed based on clinicians' diagnoses. Primary bacteremia was defined as

bacteremia that did not have the obvious infectious sources. Septic shock as the initial clinical manifestation was defined as described in the most recent international consensus (Sepsis-3).[16] Clinical outcomes were evaluated based on length of hospital stay, intensive care unit (ICU) admission duration, and mortality. Death was considered to have been related to bacteremia if the patient died ≤14 days after the onset of bacteremia and if other cause of death than bacteremia was not identified.

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

All blood cultures were processed by the hospital microbiology laboratory using a standard blood culturing system (BACTEC 9240 or BACTEC FX; Becton Dickinson, NJ, USA). Species identification and antimicrobial susceptibilities were determined using the Vitek (bioMérieux-Vitek, France) or MicroScan (Beckman Coulter, Inc., CA, USA), based on the standard criteria of the Clinical and Laboratory Standards Institute (CLSI).[17] Intermediate susceptibility to each antimicrobial agent was considered to indicate resistance. Then, SDSE

was classified by Lancefield grouping serological analysis.

Statistical analysis

Categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate, and continuous variables using Student *t*-test and the Mann-Whitney U test, as appropriate. Continuous data were expressed as the median and interquartile range. All tests of significance were two-tailed and a *P* value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

The incidence of SDSE and GBS bacteremia

During the study period, a total of 23,457 blood culture sets revealed bacterial growth. Streptococcal species contributed to 6.0% (n = 1,402) of all these cultures. Of 1,402 blood isolates which yielded streptococci, SDSE and GBS contributed to 3.8% (n = 52) and 12.4% (n = 171), respectively. The incidence rate of SDSE and GBS bacteremia in admitted patients was 1.28/100,000 and 4.22/100,000 person-days. All of 52 SDSE bacteremias occurred in adults, whereas 20 GBS bacteremia occurred in pediatric patients. Finally, 52 SDSE bacteremia and 151 GBS bacteremia adult cases were included and compared.

Demographics, underlying disease or condition, and setting of bacteremia

Epidemiological characteristics of the study population are shown in Table 1. Patients with SDSE bacteremia were older (median 68.0 vs 61.0 years, p = 0.03) and SDSE bacteremia occurred more common in men (61.5% vs 41.7%, p = 0.01) than the GBS group. All of the

SDSE patients were older than 40 years. Most of the patients had underlying comorbid illnesses. In both groups, the most common underlying disease was a solid tumor (40.4% vs 42.4%, $p = 0.80$), followed by diabetes mellitus (26.9% vs 22.5%, $p = 0.52$) and liver cirrhosis (23.1% vs 20.5%, $p = 0.70$). Chronic kidney disease without dialysis was more common in the SDSE group than the GBS group (19.2% vs 5.3%, $p < 0.01$). More than half of patients had immunocompromised conditions (51.9% vs 54.3%, $p = 0.77$). Fifteen and 30 patients of both groups had underlying lymphedema (28.8% vs 19.9%, $p = 0.18$). When I analyzed patients with cellulitis in both groups, 12 of 31 patients (38.7%) in the SDSE group had underlying lymphedema. This was not significantly different from the GBS group (22/44, 50%, $p = 0.33$). Community-onset infection tended to be more common in the SDSE group than the GBS group (94.2% vs 83.4%, $p = 0.052$). Most of SDSE bacteremia occurred in a community setting (94.2%; community-acquired 63.5%, and healthcare-associated 30.8%). Hospital-acquired infection tended to be less common in the SDSE group than the GBS group (5.8% vs 16.6%, $p = 0.052$).

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 alcoholics	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)	

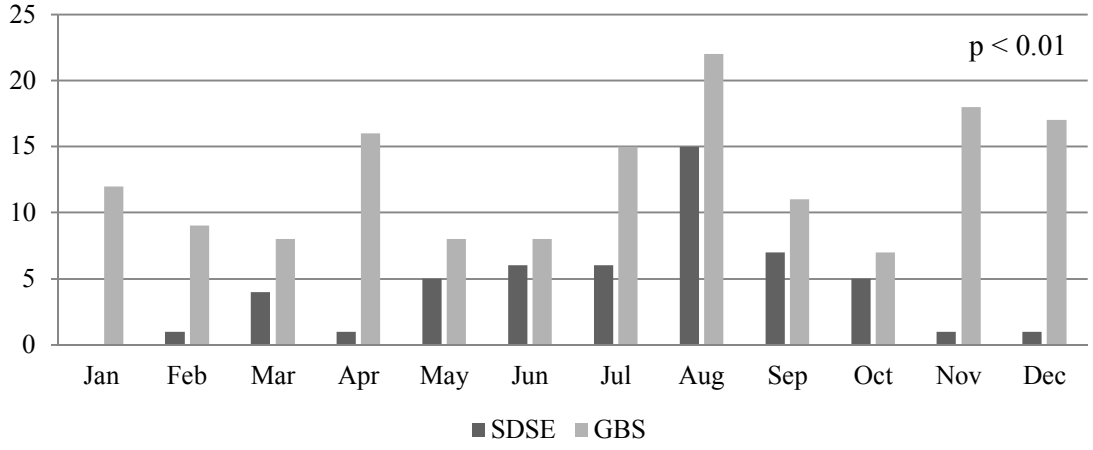
SDSE, *Streptococcus dysgalactiae* subspecies *equisimilis*; GBS, group B streptococci (*Streptococcus agalactiae*); IQR, interquartile range; ANC, absolute neutrophil count

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

Seasonality of SDSE and GBS bacteremia

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

Figure 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 group. ($p < 0.01$)

Clinical manifestations of SDSE and GBS bacteremia

Clinical manifestations at the time of bacteremia are shown in Table 2. Septic shock as the initial manifestation occurred 19.2% and 17.9% of SDSE and GBS bacteremia series, respectively ($p = 0.83$). The most common clinical syndrome of SDSE bacteremia was cellulitis (59.6%) and primary bacteremia (17.3%). In the GBS bacteremia group, the most common clinical syndrome was also cellulitis (29.1%) and primary bacteremia (26.5%). The proportion of cellulitis was significantly higher in the SDSE group ($p < 0.01$). There was one case of toxic shock syndrome in each group.

Table 2. 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 ($x10^3$/uL)	10.2 (6.6-14.1)	9.8 (5.8-15.5)	0.90
Platelet ($x10^3$/uL)	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
Intraabdominal 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

Microbiology and antimicrobial susceptibility of SDSE and GBS isolates

Lancefield classification data was 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%).

Results of antimicrobial susceptibility testing of SDSE and GBS isolates are shown in Table 3. I found that none of SDSE isolates was resistant to penicillin, cephalosporin, and carbapenem. On the other hand, the resistance rates to macrolides, clindamycin, and tetracyclines were 36.1-42.3%, 34.6%, and 55.8-61.1%, respectively. Fluoroquinolone resistance was identified only in GBS isolates (SDSE vs GBS, 0% vs 26.5%, $p < 0.001$).

Table 3. Antibiotics resistance of SDSE and GBS bacteremia

Antibiotics 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*)

Outcomes of SDSE and GBS bacteremia

Outcomes of SDSE and GBS bacteremia are shown in Table 4. There was no significant difference in clinical outcomes, such as length of hospital stay, or the incidence of ICU care between both groups. Bacteremia-related mortality of the SDSE group was not significantly different from the GBS group (3.8% vs 7.9%, $p = 0.53$). Of two patients with toxic shock syndrome, one patient with SDSE bacteremia died due to toxic shock syndrome. In-hospital mortality was also not significantly different from the GBS group (3.8% vs 10.6%, $p = 0.17$).

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
ICU admission duration, median (IQR)	5.0 (4.0-9.0)	5.0 (3.0-10.0)	0.76
30 days mortality	4 (7.7)	12 (7.9)	1.0
90 days 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

Discussion

I have determined the clinical characteristics and outcomes of SDSE bacteremia cases by comparing with GBS bacteremia, which is one of the predominant pathogens of pyogenic beta-hemolytic streptococci, in a single tertiary care hospital. Most of SDSE bacteremia cases were a community-onset infection. The most common clinical syndrome of SDSE bacteremia was cellulitis, especially in the warm season (June to September). Cellulitis occurred more frequently in the SDSE group than the GBS group (56.9% vs 29.1%). Although the study population included a significant number of patients with underlying diseases or immunocompromised conditions, in-hospital mortality (3.8%) and bacteremia-related mortality (3.8%) of SDSE bacteremia series were low.

Of pyogenic beta-hemolytic streptococci, main pathogens of invasive infections were known to be GBS and GAS. Although SDSE had not been regarded as a significant pathogen in human, cases of severe invasive SDSE infection have been reported recently in several studies.[6, 7] In our hospital, SDSE bacteremia occurred more commonly than GAS bacteremia during the study period (52 vs 36 cases). The incidence rate of SDSE

bacteremia (1.28/100,000 person-days) was 1.4 times higher than that of GAS bacteremia (0.89/100,000 person-days) and about a third of GBS bacteremia (4.22/100,000 person-days). I used GBS bacteremia group as a control, not GAS, because it was difficult to draw statistically significant results when compared to GAS due to a small number of GAS bacteremia patients. GBS is the leading cause of invasive pyogenic beta-hemolytic streptococci infection,[18] and clinical characteristics and outcomes of GBS bacteremia are well-documented .[19-21]

The SDSE group of this study population had a solid tumor, diabetes mellitus, and liver cirrhosis commonly. Most of the patients had underlying comorbid illnesses, of which solid tumor and diabetes mellitus were most common. Interestingly, chronic kidney disease without dialysis was significantly more common in the SDSE group than the GBS group. Patients with renal impairment have a high incidence of bloodstream infection, especially if the patients undergo hemodialysis.[22] Vascular access, such as arteriovenous fistula, or central catheter for dialysis, could be a risk factor of bloodstream infection by gram-positive microorganisms.[23, 24] However, it is difficult to explain increased risk of

SDSE bacteremia in patients with chronic kidney disease who are not undergoing dialysis. It could be a bias associated with the small number of SDSE bacteremia cases or the characteristics of admitted patients in our tertiary care hospital. Further studies are needed to identify whether chronic kidney disease without dialysis could be a risk factor of bacteremia by SDSE.

In our results, SDSE bacteremia occurred predominantly during the warm season (June to September). This finding could be explained by the predominance of cellulitis as a clinical manifestation of SDSE bacteremia. In a recent report of population-based investigation in the United States, average monthly temperature was closely related with cellulitis.[25] Since cellulitis was the main clinical syndrome of the SDSE group, SDSE bacteremia seemed to occur more frequently in the warm season when compared to GBS bacteremia cases.

I found that all of SDSE isolates were susceptible to beta-lactam agents including penicillin. However, the resistance rates to macrolides, lincosamide, and tetracyclines were substantial. The resistance rates to macrolides (36.1-42.3%), clindamycin

(lincosamide) (34.6%), and tetracyclines (55.8-61.1%) were slightly higher than previous reports (macrolides 9.4-34.8%, lincosamide 3.1-17.4%, and tetracyclines 30.4%).[26, 27] Although the resistance to penicillin, a treatment of choice for SDSE, has not been reported in this study, the resistance rates to other antimicrobial agents seem to be increasing. In this study, the resistance rate of fluoroquinolone to GBS was substantial (26.5%), whereas all of SDSE isolates were susceptible to fluoroquinolone. The resistance rate to fluoroquinolones was reported as less than 1% in North America and Europe,[28] but as high as 12% in Portugal.[29] Since there was no resistance to fluoroquinolones in this study, fluoroquinolones could be considered as a treatment for SDSE bacteremia.

Even though immunocompromised conditions were common in our SDSE patients, the mortality rate of our patients (3.8%) was lower than expected. Some of the SDSE bacteremia studies showed considerable mortalities (12.0-15.0%).[8, 13] I speculate as follows: first, the relatively high proportion of cellulitis patients in our study was responsible for this finding. Cellulitis can be easily detected and treated early with lower mortalities. More serious manifestations, such as pneumonia or toxic shock syndrome,

were rare in this study population. Second, the virulence potentials of SDSE strains may be different depending on the region. It warrants further clinical and micrological investigations.

There are several limitations to this study. First, because this study was performed retrospectively in a single tertiary care hospital, there could be a patients' selection bias. It limits generalization. Second, although I included 52 SDSE bacteremia cases over 5 years, the sample size was still relatively small. Third, since there were only 2 patients died of SDSE bacteremia, I could not evaluate the risk factors associated with bacteremia-related mortality. Finally, I did not analyze pathogenic virulence factors and genes associated with resistance to antimicrobial agents of isolated bacteria.

Conclusion

SDSE bacteremia was commonly associated with cellulitis, especially in elderly patients with comorbid illnesses, during the warm season. However, SDSE bacteremia-related mortality was low. Further studies are needed to reveal risk factors and virulence factors associated with invasive SDSE infections.

References

1. Bennett JE, MD, Dolin R, MD, Blaser MJ, MD. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. (Updated 8th ed); (2015).
2. Facklam R. What happened to the streptococci: overview of taxonomic and nomenclature changes. Clin Microbiol Rev 2002;15(4):613-30.
3. Rato MG, Nerlich A, Bergmann R, Bexiga R, Nunes SF, Vilela CL, et al. 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 2011;49(7):2470-9.
4. Suzuki H, Lefebure T, Hubisz MJ, Pavinski Bitar P, Lang P, Siepel A, et al. Comparative genomic analysis of the *Streptococcus dysgalactiae* species group: gene content, molecular adaptation, and promoter evolution. Genome Biol Evol 2011;3:168-85.
5. Jensen A, Kilian M. Delineation of *Streptococcus dysgalactiae*, its subspecies, and its clinical and phylogenetic relationship to *Streptococcus pyogenes*. J Clin Microbiol 2012;50(1):113-26.
6. Takahashi T, Ubukata K, Watanabe H. Invasive infection caused by *Streptococcus dysgalactiae* subsp. *equisimilis*: characteristics of strains and clinical features. J Infect Chemother 2011;17(1):1-10.
7. Watanabe S, Takemoto N, Ogura K, Miyoshi-Akiyama T. Severe invasive streptococcal infection by *Streptococcus pyogenes* and *Streptococcus dysgalactiae* subsp. *equisimilis*. Microbiol Immunol 2016;60(1):1-9.
8. Rantala S. *Streptococcus dysgalactiae* subsp. *equisimilis* bacteremia: an emerging infection. Eur J Clin Microbiol Infect Dis 2014;33(8):1303-10.
9. Broyles LN, Van Beneden C, Beall B, Facklam R, Shewmaker PL, Malpiedi P, et al. Population-based study of invasive disease due to beta-hemolytic streptococci of groups other than A and B. Clin Infect Dis 2009;48(6):706-12.
10. Ekelund K, Skinhoj P, Madsen J, Konradsen HB. Invasive group A, B, C and G streptococcal infections in Denmark 1999-2002: epidemiological and

clinical aspects. Clin Microbiol Infect 2005;11(7):569-76.

11. Kittang BR, Bruun T, Langeland N, Mylvaganam H, Glambek M, Skrede S. Invasive group A, C and G streptococcal disease in western Norway: virulence gene profiles, clinical features and outcomes. Clin Microbiol Infect 2011;17(3):358-64.
12. Liao CH, Liu LC, Huang YT, Teng LJ, Hsueh PR. Bacteremia caused by group G streptococci, taiwan. Emerg Infect Dis 2008;14(5):837-40.
13. Tsai CT, Chi CY, Ho CM, Lin PC, Chou CH, Wang JH, et al. Correlation of virulence genes to clinical manifestations and outcome in patients with *Streptococcus dysgalactiae* subspecies *equisimilis* bacteremia. J Microbiol Immunol Infect 2014;47(6):462-8.
14. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 2002;137(10):791-7.
15. Lim YJ, Park HY, Lee JY, Kwak SH, Kim MN, Sung H, et al. Clearance of carbapenemase-producing *Enterobacteriaceae* (CPE) carriage: a comparative study of NDM-1 and KPC CPE. Clin Microbiol Infect 2018;24(10):1104.e5-.e8.
16. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. 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 2016;315(8):775-87.
17. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 26th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.
18. Rossler S, Berner R, Jacobs E, Toepfner N. Prevalence and molecular diversity of invasive *Streptococcus dysgalactiae* and *Streptococcus pyogenes* in a German tertiary care medical centre. Eur J Clin Microbiol Infect Dis 2018;37(7):1325-32.

19. Blancas D, Santin M, Olmo M, Alcaide F, Carratala J, Gudiol F. Group B streptococcal disease in nonpregnant adults: incidence, clinical characteristics, and outcome. Eur J Clin Microbiol Infect Dis 2004;23(3):168-73.

20. Jackson LA, Hilsdon R, Farley MM, Harrison LH, Reingold AL, Plikaytis BD, et al. Risk factors for group B streptococcal disease in adults. Ann Intern Med 1995;123(6):415-20.

21. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. Jama 2008;299(17):2056-65.

22. Rojas L, Munoz P, Kestler M, Arroyo D, Guembe M, Rodriguez-Creixems M, et al. Bloodstream infections in patients with kidney disease: risk factors for poor outcome and mortality. J Hosp Infect 2013;85(3):196-205.

23. Fram D, Okuno MF, Taminato M, Ponzio V, Manfredi SR, Grothe C, et al. Risk factors for bloodstream infection in patients at a Brazilian hemodialysis center: a case-control study. BMC Infect Dis 2015;15:158.

24. Fysaraki M, Samonis G, Valachis A, Daphnis E, Karageorgopoulos DE, Falagas ME, et al. Incidence, clinical, microbiological features and outcome of bloodstream infections in patients undergoing hemodialysis. Int J Med Sci 2013;10(12):1632-8.

25. Peterson RA, Polgreen LA, Sewell DK, Polgreen PM. Warmer weather as a risk factor for cellulitis: A population-based investigation. Clin Infect Dis 2017;65(7):1167-73.

26. Kim S, Byun JH, Park H, Lee J, Lee HS, Yoshida H, et al. Molecular Epidemiological features and antibiotic susceptibility patterns of *Streptococcus dysgalactiae* subsp. *equisimilis* isolates from Korea and Japan. Ann Lab Med 2018;38(3):212-9.

27. Uh Y, Hwang GY, Jang IH, Cho HM, Noh SM, Kim HY, et al. Macrolide resistance trends in beta-hemolytic streptococci in a tertiary Korean hospital. Yonsei Med J 2007;48(5):773-8.

28. Biedenbach DJ, Toleman MA, Walsh TR, Jones RN. Characterization of fluoroquinolone-resistant beta-hemolytic *Streptococcus* spp. isolated in North America and Europe including the first report of fluoroquinolone-resistant *Streptococcus dysgalactiae* subspecies *equisimilis*: report from the SENTRY Antimicrobial Surveillance Program (1997-2004). Diagn Microbiol Infect Dis 2006;55(2):119-27.

29. Pinho MD, Melo-Cristino J, Ramirez M. Fluoroquinolone resistance in *Streptococcus dysgalactiae* subsp. *equisimilis* and evidence for a shared global gene pool with *Streptococcus pyogenes*. Antimicrob Agents Chemother 2010;54(5):1769-77.

국문요약

연구 배경: *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE)에 의한 침습적 감염은 그 보고가 점차 증가하고 있다. 본 연구에서는 SDSE 균혈증의 발생률, 임상적 특징, 그리고 예후에 대해 보고하고자 하였다.

연구 방법: 2012 년 8 월부터 2016 년 12 월까지 국내의 3 차 의료기관인 서울아산병원에 입원한 SDSE 혹은 *Streptococcus agalactiae* (Group B streptococci, GBS) 균혈증이 있었던 성인 환자들을 대상으로 후향적 연구를 진행하였다. 이 연구에서 SDSE 균혈증 환자의 발생률, 임상적 특징, 그리고 예후를 GBS 균혈증 환자와 비교하였다.

연구 결과: SDSE 와 GBS 균혈증의 발생률을 각각 100,000 인년당 1.28 과 4.22 였다. 최종적으로는 SDSE 균혈증 52 건과 GBS 균혈증 151 건을 분석하였다. 대부분의 SDSE 균혈증은 지역사회에서 시작된 감염이었다 (SDSE 94.2% vs GBS 83.4%, p = 0.052). 란세필드 항원으로 SDSE 의 유형을 분류했을 때, G 가 91.5% (43/47) 로 가장 흔했다. SDSE 균혈증 환자들은 나이 중앙값이 68.0 세로 GBS 균혈증 환자들 (61.0 세)보다 나이가 더 많았고 SDSE 균혈증은 남자에서 더 흔했다. 두 군

모두에서, 고형 종양 (40.4% vs 42.4%)이 가장 흔한 기저 질환이었고, 환자의 절반 이상이 면역저하 (51.9% vs 54.3%)였다. 투석을 받지 않는 만성 신부전이 SDSE 군에서 GBS 군에 비해 더 흔했다 (19.2% vs 5.3%, $p < 0.01$). 가장 흔한 임상 증후군은 SDSE 군과 GBS 군 모두에서 봉와직염이었으나 이는 SDSE 군에서 더 흔했다 (59.6% vs 29.1%, $p < 0.01$). SDSE 균혈증은 GBS 균혈증에 비해서 추운 계절보다는 6-9 월까지 따뜻한 계절에 더 자주 발생하였다 (65.4% vs 37.1%, $p < 0.01$). 병원내 사망률 (3.8% vs 10.6%, $p = 0.17$)과 균혈증에 의한 사망률 (3.8% vs 7.9%, $p = 0.53$) 모두 두 군간에 통계적으로 유의한 차이를 보이지 않았다.

연구 결론: SDSE 균혈증은 특히 따뜻한 계절에 고령이고 면역저하 환자들에서 봉와직염의 임상양상으로 나타났다. 그러나 이러한 면역저하 환자들에서도 SDSE 균혈증에 의한 사망률은 높지 않았다.

중심 단어: *Streptococcus dysgalactiae* subspecies *equisimilis*, *Streptococcus agalactiae*, 균혈증, 봉와직염