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MAJOR ARTICLE

Characteristics of Streptococcal Toxic Shock Syndrome Caused by Different Beta-hemolytic Streptococci Species: A Single-center Retrospective Study

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Background. Streptococcal toxic shock syndrome (STSS) is a life-threatening condition caused by beta-hemolytic streptococci (BHS). *Streptococcus pyogenes* is the main causative agent of this disease; other BHS such as *Streptococcus agalactiae* or *Streptococcus dysgalactiae* could also cause STSS. However, the clinical characteristics of STSS caused by other types of BHS remain poorly understood. In this study, we evaluated the likelihood of STSS development in various streptococcal species.

Methods. We conducted a retrospective observational study using adult medical records of patients with invasive BHS in a tertiary care institution from 2002 to 2022 and classified them into STSS or non-STSS groups. Multivariable analysis of bacterial species adjusted for age and diabetes mellitus was conducted. *S pyogenes* cases were propensity-matched (1:4) to non-pyogenes BHS cases.

Results. A total of 43 STSS and 285 non-STSS cases were identified. *S pyogenes*, *S agalactiae*, and *S dysgalactiae* accounted for 17, 13, and 13 STSS cases, respectively. The crude mortality of STSS was approximately 35% in all groups. A multivariable analysis suggested that STSS was less frequent in *S agalactiae* and *S dysgalactiae* cases with odds ratio 0.24 (95% confidence interval [CI], 0.10–0.54; $P < .001$) and 0.23 (95% CI, .10–.55; $P < .001$), respectively. Propensity score matching showed that *S pyogenes* caused STSS more frequently than other BHS cases with an odds ratio of 3.28 (95% CI 1.21–8.77; $P = .010$).

Conclusions. This study described and compared the clinical characteristics of STSS caused by different BHS. We demonstrated that *S pyogenes* caused STSS more often than other BHS.

Keywords. beta-hemolytic streptococci; streptococcal toxic shock syndrome; streptococcus agalactiae; streptococcus dysgalactiae; *streptococcus pyogenes*.

Beta-hemolytic streptococci (BHS) are pathogens associated with various diseases such as pharyngitis, skin and soft tissue infections (SSTI), necrotizing fasciitis, meningitis, primary bacteremia, and streptococcal toxic shock syndrome (STSS). Most human pathogens associated with STSS are *Streptococcus pyogenes* (Group A *streptococci* [GAS]), *Streptococcus agalactiae* (Group B streptococci [GBS]), *Streptococcus dysgalactiae* (mainly Group G streptococci) [1–3]. *S pyogenes* is a well-known pathogen and a global burden on the general population, including pregnant women and young children [4]. In 2022, the European nations experienced an outbreak of *S pyogenes*, including invasive GAS infections [5–7]. *S agalactiae* is known to lead to invasive GBS infections, including sepsis and meningitis, in infants [8]. It is also a threat to pregnant and nonpregnant adults [9]. Recently the number of patients with invasive *S dysgalactiae* infection has been increasing, and the infection occurs predominantly in very elderly patients [1, 10, 11]. Most developed countries have aging populations; thus, *S dysgalactiae* infection will become a more significant problem. BHS infection is a global problem. Among various BHS infections, STSS (also called toxic shock-like syndrome) is the most severe disease [12, 13].

In the 1980s, several reports described invasive GAS cases similar to those of staphylococcal toxic shock syndrome; these cases are currently known as STSS [14, 15]. Subsequently, the clinical characteristics, pathogenesis, and management of STSS have been vigorously explored based on GAS infections.

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Risk factors include age, skin injury, alcoholism, diabetes, and use of nonsteroidal anti-inflammatory drugs; nevertheless, STSS can occur in anyone [12, 16, 17]. Specific mutations in GAS are known to be related to STSS and other invasive infections [12]; mutations in the negative regulators *csrS*, *csrR,* and *rgg* genes are more often found in STSS cases than in noninvasive cases [18]. The mortality was estimated approximately 30%–70%, and adjunctive use of clindamycin or intravenous immunoglobulin G (IVIG) was found to reduce fatality [19–22]. However, evidence of STSS has been established in GAS infections, as mentioned previously [12, 14, 15, 19, 23–25]. *S agalactiae*–related STSS was first described in 1993 and *S dysgalactiae*–related STSS was first described in 1996 [26, 27]. To the best of our knowledge, most of the *S agalactiae*– or *S dysgalactiae*–related STSS studies were case reports or case series, and there are few descriptions of the clinical characteristics of non-GAS STSS. Therefore, the epidemiology, clinical characteristics, and management of non-GAS STSS have been poorly investigated.

In this study, we retrospectively reviewed the medical charts of patients with invasive BHS infection and STSS in a tertiary care institution and investigated their characteristics. We explored the likelihood of developing STSS for each bacterial species compared to non-STSS invasive infections.

METHODS

Patients and Case Definition

We retrospectively reviewed a microbiology database and identified patients with invasive BHS infections between 2002 and 2022 at a tertiary care institution, the National Center for Global Health and Medicine. Invasive BHS infection was defined as an infection event caused by *S pyogenes, S agalactiae,* or *S dysgalactiae* identified from normally sterile sites (blood, pleural effusion, ascites, cerebrospinal fluid, joint fluid, and pericardial effusion). The diagnostic criteria of STSS are defined as a condition that meets the following 3 requirements [12]: (1) an infection caused by BHS mentioned previously; (2) hypotension (systolic blood pressure ≤90 mm Hg); and (3) multiorgan involvement characterized by 2 or more of the following: renal impairment (creatinine ≥2 mg/dL, or >2-fold elevation over the baseline level for patients with preexisting renal disease), coagulopathy (platelets ≤100 000 cells/μL or disseminated intravascular coagulation), liver involvement (alanine aminotransferase, aspartate aminotransferase, or total bilirubin levels greater than or equal to twice the upper limit of normal for the patient's age; greater than 2-fold increase over the baseline level for patients with preexisting liver disease), acute respiratory distress syndrome, or a generalized erythematous macular rash or soft tissue necrosis. Three infectious disease physicians retrospectively reviewed the medical records during this study and confirmed STSS diagnosis.

Pediatric patients aged < 16 years and those without detailed medical records were excluded.

Bacterial Identification

Isolated BHS were identified by their morphological and growth characteristics as we reported previously [1]. Serogroup was identified by the streptococcal grouping kit antigen extraction by nitrous acid (Oxoid, Basingstoke, UK) and species were determined by either MicroScan WalkAway (Siemens Healthcare, Bayern, Germany), API 20 Strep (Biomérieux, Marcy l'Etoile, France), or matrix-assisted laser desorption/ionization time-of-flight mass spectrometry MALDI Biotyper (Bruker Daltonik GmbH, Bremen, Germany).

Statistical Analysis

The statistical analysis was done using R software version 4.2.0.

Multivariable analysis of the risk factors for STSS was performed with bacterial species (either *S pyogenes, S agalactiae,* or *S dysgalactiae*) adjusted for age and diabetes mellitus (DM). We limited the number of variables included in the model up to 5 because of the small number of cases included in our dataset.

To clarify the hypothesis that *S pyogenes* is more likely to cause STSS than *S agalactiae* and *S dysgalactiae*, we used the propensity score matching method with variables including age, sex, body mass index, liver cirrhosis, DM, immunocompromised conditions, solid or hematological malignancy, and skin comorbidity for each GAS and non-GAS case. The balance of covariates before and after matching was assessed by the absolute standardized mean differences. Standardized mean difference >0.1 in each variable was regarded as significant imbalance. Matching was performed using nearest-neighbor matching using logistic regression model with a caliper width of 0.2. GAS cases were propensity-matched to non-GAS BHS cases at a 1:4 ratio. No replacement was allowed. After matching, the data were examined using the Fisher exact test.

Ethics Statement

The requirement for formal consent from patients was waived because this was a retrospective study. The design of this study was approved by the Human Research Ethics Committee of the National Center for Global Health and Medicine (NCGM-S-004363-03). All procedures involving human participants were performed according to the principles of the Declaration of Helsinki.

RESULTS

We collected the medical records of 426 patients with invasive BHS. Eight cases were excluded because they were pediatric patients at ages ≤15 years, and 90 cases were excluded because their medical records were unavailable. We identified 328 adult patients with invasive BHS and reviewed their medical records for characteristics, bacterial information, and outcomes. A total

Table 1. The patient characteristics comparing non-STSS and STSS group.

	Non-STSS				STSS			
	Overall (n = 285)	*S pyogenes* (n = 34, 11.9%)	*S agalactiae* (n = 121, 42.5%)	*S dysgalactiae* (n = 130, 45.6%)	Overall (n = 43)	*S pyogenes* (n = 17, 39.5%)	*S agalactiae* (n = 13, 30.2%)	*S dysgalactiae* (n = 13, 30.2%)
Demographics								
Age, y	74.0 [63.0–85.0]	65.5 [48.8–71.8]	74.0 [61.0–84.0]	78.0 [69.0–88.0]	68.0 [57.5–76.5]	67.0 [64.0–75.0]	66.0 [51.0–68.0]	73.0 [71.0–86.0]
Sex, male	157 (55.1)	19 (55.9)	67 (55.4)	71 (54.6)	20 (46.5)	7 (41.2)	7 (53.8)	6 (46.2)
BMI	22.5 [19.4–25.3]	22.2 [19.4–25.0]	22.4 [19.5–24.9]	22.5 [19.2–25.4]	22.1 [19.3–25.6]	20.4 [19.6–23.2]	22.1 [19.1–26.7]	23.1 [20.3–26.3]
Underlying diseases								
Hypertension	125 (43.9)	13 (38.2)	46 (38.0)	66 (50.8)	14 (32.6)	4 (23.5)	3 (23.1)	7 (53.8)
Dyslipidemia	38 (13.3)	4 (11.8)	13 (10.7)	21 (16.2)	3 (7.0)	2 (11.8)	0 (0.0)	1 (7.7)
DM	70 (24.6)	8 (23.5)	28 (23.1)	34 (26.2)	7 (16.3)	1 (5.9)	3 (23.1)	3 (23.1)
CKD	31 (10.9)	3 (8.8)	16 (13.2)	12 (9.2)	3 (7.0)	0 (0.0)	2 (15.4)	1 (7.7)
Cirrhosis	32 (11.2)	3 (8.8)	13 (10.7)	16 (12.3)	7 (16.3)	1 (5.9)	2 (15.4)	4 (30.8)
COPD	18 (6.3)	3 (8.8)	9 (7.4)	6 (4.6)	2 (4.7)	1 (5.9)	1 (7.7)	0 (0.0)
Heart diseases	94 (33.0)	9 (26.5)	40 (33.1)	45 (34.6)	11 (25.6)	3 (17.6)	5 (38.5)	3 (23.1)
CVD	56 (19.6)	7 (20.6)	19 (15.7)	30 (23.1)	7 (16.3)	2 (11.8)	3 (23.1)	2 (15.4)
Dementia	35 (12.3)	2 (5.9)	13 (10.7)	20 (15.4)	3 (7.0)	1 (5.9)	0 (0.0)	2 (15.4)
Cancer	36 (12.6)	3 (8.8)	17 (14.0)	16 (12.3)	5 (11.6)	2 (11.8)	3 (23.1)	0 (0.0)
Immunosuppression	12 (4.2)	1 (2.9)	7 (5.8)	4 (3.1)	1 (2.3)	1 (5.9)	0 (0.0)	0 (0.0)
Skin disease	39 (13.7)	4 (11.8)	14 (11.6)	21 (16.2)	4 (9.3)	1 (5.9)	1 (7.7)	2 (15.4)
Gynecological disease	33 (11.6)	4 (11.8)	16 (13.2)	13 (10.0)	4 (9.3)	0 (0.0)	1 (7.7)	3 (23.1)
Focus								
Bacteremia	270 (94.7)	34 (100.0)	114 (94.2)	122 (93.8)	42 (97.7)	16 (94.1)	13 (100.0)	13 (100.0)
polymicrobial[a]	19 (6.7)	1 (2.9)	11 (9.1)	7 (5.4)	3 (7.0)	1 (5.9)	1 (7.7)	1 (7.7)
primary[a]	102 (35.8)	8 (23.5)	54 (44.6)	40 (30.8)	19 (44.2)	7 (41.2)	7 (53.8)	5 (38.5)
Necrotizing fasciitis	3 (1.1)	0 (0.0)	3 (2.5)	0 (0.0)	5 (11.6)	2 (11.8)	2 (15.4)	1 (7.7)
Arthritis	20 (7.0)	6 (17.6)	6 (5.0)	8 (6.2)	6 (14.0)	3 (17.6)	1 (7.7)	2 (15.4)
Meningitis	7 (2.5)	1 (2.9)	4 (3.3)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteomyelitis	25 (8.8)	1 (2.9)	16 (13.2)	8 (6.2)	1 (2.3)	0 (0.0)	1 (7.7)	0 (0.0)
Abscess	7 (2.5)	1 (2.9)	3 (2.5)	3 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	1 (7.7)
SSTI	139 (48.8)	21 (61.8)	45 (37.2)	73 (56.2)	20 (46.5)	8 (47.1)	6 (46.2)	6 (46.2)
Pharyngitis	6 (2.1)	3 (8.8)	3 (2.5)	0 (0.0)	2 (4.7)	2 (11.8)	0 (0.0)	0 (0.0)
Outcome								
Death	26 (9.1)	0 (0.0)	14 (11.6)	12 (9.2)	15 (34.9)	6 (35.3)	4 (30.8)	5 (38.5)

Data are presented as median [interquartile range] or number (percentage).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; SSTI, skin and soft tissue infection; STSS, streptococcal toxic shock syndrome.

[a]n = proven bacteremia cases.

of 285 cases were diagnosed as non-STSS invasive BHS infection and 43 cases as STSS during this retrospective review.

Table 1 summarizes the clinical characteristics of the non-STSS and STSS cases caused by overall and each BHS species. The overall median [interquartile range] age was 74.0 [63.0–85.0] and 68.0 [57.5–76.5], and the percentage of men was 55.1% and 46.5% in the non-STSS group and STSS groups, respectively. Asian race accounted for 99.1% of the ethnicity in this study. *S pyogenes* comprised 11.9% of non-STSS cases, whereas *S agalactiae* and *S dysgalactiae* comprised 42.5% and 45.6%, respectively. In contrast, *S pyogenes* comprised 39.5% of STSS cases and it was the most frequently identified pathogen, followed by *S agalactiae* and *S dysgalactiae,* both comprising 30.2%. Infection caused by overall BHS occurred commonly as soft and skin tissue infections, primary bacteremia, and arthritis in both the STSS and non-STSS groups. The overall mortality was 9.1% and 34.9% in the non-STSS and STSS groups, respectively.

We then focused on STSS and causative bacterial species. The median [interquartile range] age was 67.0 [64.0–75.0], 66.0 [51.0–68.0], and 73.0 [71.0–86.0] in the *S pyogenes*, *S agalactiae*, and *S dysgalactiae* groups, and the mortality was 35.3%, 30.8%, and 38.5%, respectively (Table 1). There was no statistically significant difference in the mortality rates. For each *S pyogenes*, *S agalactiae*, and *S dysgalactiae* infection in the STSS group, the primary bacteremia occurrence rate (95% confidence interval [CI]) was 41.2 (18.4–67.1), 53.8 (25.1–80.8), and 38.5 (13.9–68.4), and the SSTI occurrence rate was 47.1 (23.0–72.2), 46.2 (19.2–74.9), and 46.2 (19.2–74.9), respectively. The mortality rate (95% CI) of primary bacteremia was 28.6 (3.7–71.0), 42.9 (9.9–81.6), and 100 (47.8–100), and of SSTI was 25.0 (3.2–65.1), 16.7 (0.4–64.1), and 0 (0–45.9), respectively. In our study, approximately one third of the patients did not have any comorbidities in the *S pyogenes* group, whereas all patients had at least 1 comorbidity in the *S agalactiae* or *S dysgalactiae* groups (Table 1).

Approximately 30% of *S pyogenes* STSS cases showed acute respiratory distress syndrome, necrosis, and diffuse skin rash; whereas 0%–23.1% of *S agalactiae* or *S dysgalactiae* STSS cases showed these presentations (Table 2). For each *S pyogenes*–, *S agalactiae*–, and *S dysgalactiae*–STSS group, clindamycin was administered in 23.5%, 23.1%, and 38.5% patients, and IVIG was administered in 29.4%, 15.4%, and 7.7% patients, respectively (Table 2). Three patients died despite IVIG administration in the *S. pyogenes*–STSS group; there were no other deaths.

No underlying disease was a significant risk factor for STSS development when comparing STSS and non-STSS cases caused by overall BHS or each bacterial species, whereas *S pyogenes* infection appeared to be associated with STSS development (Table 1). To explore the differences in the likelihood of STSS development among the bacterial species,

Table 2. The comparison among STSS groups caused by different bacteria.

–n	*S pyogenes* 17	*S agalactiae* 13	*S dysgalactiae* 13
Clinical scores			
–qSOFA 0	0 (0.0)	2 (15.4)	0 (0.0)
–1	6 (35.3)	4 (30.8)	2 (15.4)
–2	7 (41.2)	5 (38.5)	6 (46.2)
–3	3 (17.6)	2 (15.4)	3 (23.1)
–NA	1 (5.9)	0 (0.0)	2 (15.4)
–LRINEC score	8.0 [6.0–9.0]	6.5 [4.0–9.0]	6.0 [3.5–7.0]
Organ involvement			
–AKI	10 (58.8)	5 (38.5)	8 (61.5)
–Coagulopathy	10 (58.8)	10 (76.9)	8 (61.5)
–Liver damage	12 (70.6)	10 (76.9)	12 (92.3)
–ARDS	5 (29.4)	3 (23.1)	0 (0.0)
–Rash	5 (29.4)	0 (0.0)	3 (23.1)
–Necrosis	6 (35.3)	2 (15.4)	0 (0.0)
Interventions			
–CLDM	4 (23.5)	3 (23.1)	5 (38.5)
–IVIG	5 (29.4)	2 (15.4)	1 (7.7)

Data are presented as median [interquartile range] or number (percentage).

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CLDM, clindamycin; IVIG, intravenous immunoglobulin; LRINEC, laboratory risk indicator for necrotizing fasciitis; NA, not applicable; SOFA, sequential organ failure assessment; STSS, streptococcal toxic shock syndrome.

Table 3. Multivariable Regression Analysis for STSS Development

Variables	Odds Ratio [95% CI]	*P* Value
Age	0.991 [0.972–1.011]	.368
DM	0.669 [0.258–1.532]	.370
S agalactiae	0.236 [0.101–0.540]	<.001
S dysgalactiae	0.233 [0.097–0.548]	<.001

CI, confidence interval; DM, diabetes mellitus; STSS, streptococcal toxic shock syndrome.

we performed a multivariable logistic regression analysis. When adjusted for age and DM, the odds ratios of *S agalactiae* infection for STSS was 0.24 (95% CI, .10–.54) and the odds ratio of *S dysgalactiae* was 0.23 (95% CI, .10–.55) (Table 3).

As for the effect of *S pyogenes* compared with other species, the Fisher exact test after propensity score matching estimated that *S pyogenes* caused STSS more often than non-GAS BHS and its odds ratio was 3.28 (95% CI, 1.21–8.77; $P = .010$). The absolute standardized mean differences of covariables between the GAS and non-GAS groups was within 0.1 (Figure 1).

DISCUSSION

This retrospective study described the clinical characteristics of STSS cases classified by the causative bacterial species: *S pyogenes*, *S agalactiae,* and *S dysgalactiae*. Among the 43 patients with STSS included in this study, more than half

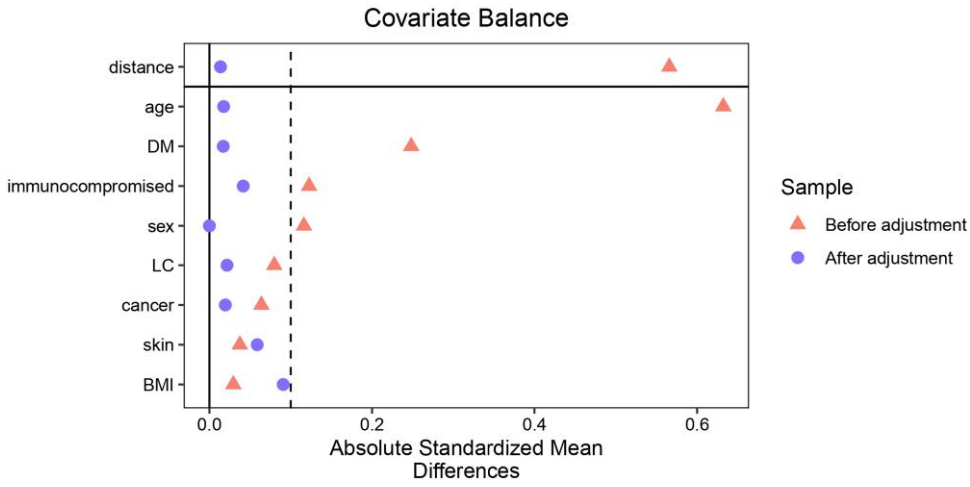

Figure 1. Balance of covariates before and after propensity score matching. Red triangles represent absolute standardized mean differences (SMDs) before adjustment and blue circles represent SMDs after adjustment. BMI, body mass index; DM, diabetes mellitus; LC, liver cirrhosis; sex, male; skin, skin diseases.

were associated with *S agalactiae* or *S dysgalactiae*. STSS caused by non-pyogenes BHS accounted for the majority of the cases; it could be worth considering the differences in STSS caused by *S pyogenes*.

The effects of the bacterial species on the clinical presentation of STSS have not been well described to date. For example, the incidence rate is almost unknown except for 1 study. A prospective Danish nationwide study aimed to survey a broad spectrum of invasive BHS infections, including STSS, and described GAS as an independent predictor of the development of STSS without adjustment for confounders [28]. In our research, we compared *S pyogenes* and others (*S agalactiae* and *S dysgalactiae*) by propensity score matching and showed that *S pyogenes* developed STSS more frequently than other BHS species with an odds ratio of 3.28. Although the reason why *S pyogenes* frequently causes STSS remain unclear, 1 possible explanation is that *S pyogenes* has various kinds of superantigens compared with other streptococci [29–31].

We shed light on several clinical aspects of STSS caused by *S agalactiae* or *S dysgalactiae*. The 30-day mortality of STSS by *S pyogenes* was 35.3%, which is consistent with previous reports [12, 32, 33]. As discussed previously, *S agalactiae* and *S dysgalactiae* invasive infections develop into STSS less frequently; however, the mortality rate of STSS was similar to that of *S pyogenes*. STSS caused by *S dysgalactiae* appeared to occur in elderly individuals. *S agalactiae* and *S dysgalactiae* appeared to require at least 1 comorbidity in patients for STSS development, whereas approximately one third of GAS STSS cases had no comorbidities.

Several unanswered questions remain regarding the similarities and differences in STSS caused by different BHS, as discussed previously. One clinically important question is whether adjunctive clindamycin and IVIG reduces the mortality of non-GAS STSS, as shown in GAS STSS cases. Some researchers have investigated the effect of adjunctive clindamycin or IVIG in invasive GAS, GBS, or non-GAS non-GBS infection groups and showed efficacy only in the GAS infection groups [34, 35]. These invasive infections include both STSS and non-STSS cases; thus, if the population was focused only on STSS cases, clindamycin or IVIG could be effective in non-GAS cases. In our study, 3 patients died after IVIG administration in the *S pyogenes* group; there was no other patient who died after clindamycin or IVIG treatment. Researchers have suggested the importance of conducting clinical trials to treat invasive BHS infections [36].

Our study has several limitations. First, it had a retrospective design and was conducted at a single center. Because STSS is a rare and acute disease, a prospective study design does not seem feasible. The generality of this study should be examined to obtain more robust evidence. Second, the sample size was relatively small. We were interested in whether streptococcal species affect mortality, but we could not evaluate this using our dataset. Additionally, we had to limit the number of variables in multivariable logistic regression model because of this small size of the number of cases. A multicenter study is desirable to gain more cases and generalizability. Third, we could not identify further microbiological information, such as *emm* type or toxin production, because bacterial pathogenic factors are not usually analyzed; our retrospective study did not reveal these findings.

Despite these limitations, this study statistically demonstrated that *S pyogenes* developed STSS more frequently than other BHS, such as *S agalactiae* or *S dysgalactiae*. Further research is needed to evaluate the differences in STSS caused by *S pyogenes*,

S agalactiae, and *S dysgalactiae,* particularly regarding the risk factors, prognostic factors, and effective therapy.

Notes

Author contributions. Conceptualization. M.I., N.I., H.N. Data collection: M.I., N.I., H.N., N.F., A.M. Formal analysis: M.I., S.T. Funding acquisition: N.I., N.T. Supervision: N.O. Writing: M.I. All authors contributed to the writing of the final manuscript.

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Potential Conflicts of Interest. The authors declare that there is no conflict of interest.

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