In-hospital mortality among patients with invasive non-group A β-hemolytic Streptococcus treated with clindamycin combination therapy: a nationwide cohort study

Shoichiro Hamada,1,2 Mikio Nakajima,1,2,3 Richard H. Kaszynski,1 Ryosuke Kumazawa,3 Hiroki Matui,3 Kiyohide Fushimi,4 Hideaki Goto,1 Yoshihiro Yamaguchi,2 and Hideo Yasunaga3

1Emergency and Critical Care Center, Tokyo Metropolitan Hiroo Hospital, 2Department of Trauma and Critical Care medicine, School of Medicine, Kyorin University, 3Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, and 4Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

Aim: Combination treatment with clindamycin is recommended in patients with invasive group A Streptococcus infection; however, whether the same treatment is effective in invasive group B Streptococcus and S. dysgalactiae subspecies equisimilis infections remains unknown. We aimed to investigate whether clindamycin added to standard of care therapy would be effective in patients with invasive non-group A β-hemolytic Streptococcus infections.

Methods: This was a nationwide retrospective cohort study using the Japanese Diagnosis Procedure Combination inpatient database focusing on the period between 2010 and 2018. We extracted data on patients diagnosed with sepsis due to non-group A β-hemolytic Streptococcus. One-to-four propensity score-matching was undertaken to compare patients who were treated with clindamycin within 2 days of admission (clindamycin group) and those who did not (control group). The primary outcome was in-hospital mortality.

Results: We identified 3754 eligible patients during the study period. The patients were divided into the clindamycin (n = 296) and control groups (n = 3458). After one-to-four propensity score matching, we compared 289 and 1156 patients with and without clindamycin, respectively. In-hospital mortality did not significantly differ between the two groups (9.7% versus 10.3%; risk difference 0.3%; 95% confidence interval, –3.5% to 4.2%).

Conclusions: This nationwide database study showed that combination therapy involving the use of clindamycin was not associated with lower in-hospital mortality in patients with invasive non-group A β-hemolytic Streptococcus.

Key words: β-Hemolytic Streptococcus, clindamycin, invasive Streptococcus infection, Streptococcus agalactiae, Streptococcus dysgalactiae subspecies equisimilis

INTRODUCTION

Invasive β-hemolytic Streptococcus infection is defined as the isolation of β-hemolytic Streptococcus from a normally sterile site (i.e., blood, cerebrospinal fluid, joint fluid, or pleural effusion) resulting in a range of severe disease including sepsis syndrome, bacteremia, meningitis, and deep soft tissue infection. Increases in the numbers of patients with invasive β-hemolytic Streptococcus infection have been reported in several countries, including Japan.

Invasive β-hemolytic Streptococcus infection is primarily...
caused by *S. pyogenes*, *S. agalactiae*, and *S. dysgalactiae* subspecies *equisimilis* (SDSE).[9] *Streptococcus pyogenes* has Lancefield group A antigens and is called group A *Streptococcus* (GAS). *Streptococcus agalactiae* has Lancefield group B antigens and is called group B *Streptococcus* (GBS). Streptococci that have Lancefield group C and G antigens include the following: SDSE; *S. canis*, *S. dysgalactiae* subsp. *dysgalactiae*, *S. equi* subsp. *equi*, and *S. equi* subsp. *zeopidemicus.*[7]

Treatment with clindamycin in combination with penicillin is recommended for invasive GAS infection.[6] Previous studies suggest that clindamycin has a longer acting post-antibiotic effect than β-lactams such as penicillin, suppresses bacterial toxin synthesis, inhibits the enzyme associated with cell wall synthesis, disrupts lipopolysaccharide-induced cytokine production, is not affected by inoculum size or stage of growth like penicillin, and facilitates GAS phagocytosis in subinhibitory concentrations.[9–13] These purported mechanisms are based on *in vitro* and animal studies; however, the number of clinical investigations published to date are limited. Observational studies have suggested that clindamycin is effective for invasive GAS infections.[14–17]

While combination therapies are recommended in invasive GAS infections, the fundamental treatment for non-group A β-hemolytic *Streptococcus* (NGAS) remains penicillin monotherapy.[8] Although a number of case reports suggest the potential benefits of adding clindamycin for invasive GBS,[18] no large-scale clinical investigations have interrogated the subject of clinical outcomes in patients treated with combination clindamycin therapy in invasive NGAS infections. Given the drug’s efficacy in GAS infections, we hypothesized that additional clindamycin therapy would be effective in patients with invasive NGAS infections.

**METHODS**

**Data source**

The present study is a retrospective cohort study using the Japanese Diagnosis Procedure Combination inpatient database. Approximately 7 million admissions from over 1,200 health-care facilities are reflected in the database annually. Participating health-care facilities account for approximately 90% of all tertiary-care emergency hospitals, 44% of institutions certified by the Japanese Surgical Society, and 80% of institutions certified by the Japanese Association for Infectious Diseases for board specialist training.[19]

The database contains the following information for each patient: date of admission and discharge, sex, age, height, weight, diagnoses, comorbidities at admission, complications after admission, level of consciousness at admission, procedures, medications and devices used and discharge status. Diagnoses are recorded using the International Classification of Diseases, 10th Revision (ICD-10) codes with text data entered in Japanese. Level of consciousness on admission was evaluated using the Japan Coma Scale. Assessments by the Japan Coma Scale and Glasgow Coma Scale have been evaluated and shown to correlate well.[20] A previous study showed that the validity of diagnoses and procedure records in the database was high in general.[21]

**Patient selection**

We identified data on patients discharged from the hospital between the period of July 2010 to March 2018 with the diagnoses of “sepsis due to *Streptococcus* group B” (ICD-10 code A401) and “other *Streptococcus* sepsis” (A408). The code A408 is classified as “sepsis due to *Streptococcus* group C or G” in Japan. No diagnosis equivalent to invasive NGAS streptococcal infections is available in ICD-10 and therefore we adopted “sepsis due to *Streptococcus* group B” and “sepsis due to *Streptococcus* group C or G” in order to identify invasive streptococcal infections in the database. Because SDSE has been isolated in approximately 80% of patients with group C and G *Streptococcus* sepsis,[4] we defined GBS and SDSE as NGAS. We excluded patients who were under the age of 16 years and who were discharged within 2 days of admission to avoid immortal time bias.

**Patient characteristics and outcomes**

Patient characteristics included age, sex, diagnoses (cellulitis, ICD-10 code L03x; necrotizing fasciitis, M72x; arthritis, M002 and M009; bacteremia, A491 and A499; osteomyelitis, K102, M462, and M86x; empyema, J86x; and endocarditis, I330), procedures performed within 2 days of admission (mechanical ventilation, renal replacement therapy, polymyxin B hemoperfusion, blood transfusion, surgery, and direct measurement of arterial pressure), drugs used within 2 days of admission (vasopressor, i.v. immunoglobulin, penicillin G, combination antibiotics containing penicillin and β-lactamase inhibitor, clindamycin, first-generation cephalosporins, second-generation cephalosporins, third-generation cephalosporins, fourth-generation cephalosporins, carbapenem, glycopeptide, and linezolid), body mass index, level of consciousness at admission (Japan Coma Scale), history of hypertension and diabetes, Charlson comorbidity index (CCI), ambulance use, hospitalization in a teaching hospital, and intensive care unit stay within
2 days of admission. We categorized body mass index into four groups: underweight, <18.5; normal weight, 18.5–24.9; overweight, 25–29.9; and obese, ≥30. Level of consciousness at admission (Japan Coma Scale) was categorized into four groups: 0, alert consciousness; 1–3, awake without any stimuli; 10–30, respond to some stimuli; and 100–300, coma. The CCI is a weighted composite score of comorbidities that is widely used to measure case mixes and disease burdens. We categorized the total score of CCI into four groups as previously reported: 0, 1, 2, and ≥3.

We compared patients who received clindamycin within 2 days of admission (clindamycin group) and those who did not (control group). The primary outcome was in-hospital mortality.

**Statistical analysis**

Propensity score matching was undertaken to minimize confounding by indication and prevent an unbalanced background between the clindamycin and control groups. We estimated the propensity scores by fitting a logistic regression model for clindamycin treatment within 2 days of admission as a function of the background for the above-mentioned patient characteristics, procedures, and treatments. Using the estimated propensity scores, we used nearest-neighbor one-to-four matching with replacement. The caliper width was set at 20% of the standard deviation of the estimated propensity scores. The balance between the two groups was evaluated by the absolute value of standardized differences. We defined unbalanced background as the value of standardized differences more than 10%.

Continuous variables were reported as median and interquartile range and categorical variables were reported as count and percentage. The outcomes were compared using the \( \chi^2 \)-test. The threshold for significance was a \( P \)-value of 0.05. All statistical analyses were carried out using Stata/MP 15 (Stata, College Station, TX, USA).

**RESULTS**

The process and flow of patient selection is shown in Figure 1. We identified 3,754 eligible patients during the study period. The patients were divided into the clindamycin group (\( n = 296 \)) and control group (\( n = 3,458 \)). After one-to-four propensity score matching we compared 289 and 1,156 patients with and without clindamycin, respectively. Three patients in the clindamycin group matched the control group at one-to-three. The C-statistic of the logistic regression model was 0.81.

Table 1 shows the baseline characteristics of patients before and after propensity score matching. The patient characteristics were almost balanced between the two groups.
Table 1. Characteristics of patients with invasive non-group A β-hemolytic Streptococcus, treated with or without clindamycin combination therapy, before and after propensity score matching

| Variable                                      | Before propensity score matching | After propensity score matching |
|-----------------------------------------------|---------------------------------|--------------------------------|
|                                               | Control group (n = 3,458)       | Clindamycin group (n = 296)    |
|                                               | ASD (%)                         | ASD (%)                        |
| Age, years; median (IQR)                      | 79 (68–86)                     | 74 (60.5–83)                   |
| Male sex                                      | 1,686 (48.8)                   | 139 (47.0)                     |
| Diagnosis                                     |                                 |                                |
| Cellulitis                                    | 661 (19.1)                     | 132 (44.6)                     |
| Necrotizing fasciitis                         | 23 (0.7)                       | 40 (13.5)                      |
| Arthritis                                     | 67 (1.9)                       | 16 (5.4)                       |
| Bacteremia                                    | 56 (1.6)                       | 10 (3.4)                       |
| Osteomyelitis                                 | 26 (0.8)                       | 4 (1.4)                        |
| Empyema                                       | 9 (0.3)                        | 2 (0.7)                        |
| Meningitis                                    | 34 (1.0)                       | 2 (0.7)                        |
| Endocarditis                                  | 121 (3.5)                      | 3 (1.0)                        |
| Procedures undertaken within 2 days of admission |                               |                                |
| Mechanical ventilation                        | 142 (4.1)                      | 24 (8.1)                       |
| Renal replacement therapy                     | 115 (3.3)                      | 19 (6.4)                       |
| Polymyxin B hemoperfusion                     | 20 (0.6)                       | 7 (2.4)                        |
| Blood transfusion                             | 187 (5.4)                      | 18 (6.1)                       |
| Surgery                                       | 38 (1.1)                       | 35 (11.8)                      |
| Direct measurement of arterial pressure       | 186 (5.4)                      | 46 (15.5)                      |
| Drugs used within 2 days of admission         |                                 |                                |
| Vasopressor                                   | 331 (9.6)                      | 75 (25.3)                      |
| Intravenous immunoglobulin                    | 142 (4.1)                      | 42 (14.2)                      |
| Penicillin G                                  | 86 (2.5)                       | 39 (13.2)                      |
| Penicillin and β-lactamase inhibitor          | 876 (25.3)                     | 93 (31.4)                      |
| First-generation cephalosporins              | 393 (11.4)                     | 59 (19.9)                      |
| Second-generation cephalosporins             | 225 (6.5)                      | 12 (4.1)                       |
| Third-generation cephalosporins              | 912 (26.4)                     | 76 (25.7)                      |
| Fourth-generation cephalosporins             | 98 (2.8)                       | 5 (1.7)                        |
| Carbapenem                                    | 623 (18.0)                     | 85 (28.7)                      |
| Glycopeptide                                  | 297 (8.6)                      | 39 (13.2)                      |
| Linezolid                                     | 15 (0.4)                       | 0 (0.0)                        |
| Body mass index                              |                                 |                                |
| <18.5                                         | 553 (16.0)                     | 40 (13.5)                      |
| 18.5–24.9                                     | 1,684 (48.7)                   | 139 (47.0)                     |
| 25.0–29.9                                     | 563 (16.3)                     | 50 (16.9)                      |
| ≥30.0                                         | 241 (7.0)                      | 36 (12.2)                      |
| Missing data                                  | 417 (12.1)                     | 31 (10.5)                      |
| Japan Coma Scale                              |                                 |                                |
| Alert                                         | 2,302 (66.6)                   | 190 (64.2)                     |
| Awake without any stimuli                     | 768 (22.2)                     | 67 (22.6)                      |
| Responded to some stimuli                     | 245 (7.1)                      | 25 (8.4)                       |
| Coma                                          | 143 (4.1)                      | 14 (4.7)                       |
| Hypertension                                  | 977 (28.3)                     | 69 (23.3)                      |

© 2021 The Authors. Acute Medicine & Surgery published by John Wiley & Sons Australia, Ltd on behalf of Japanese Association for Acute Medicine
after propensity score matching. Patients in the control group were more likely to receive linezolid.

Table 2 shows the outcomes before and after propensity score matching. Before propensity score matching, total in-hospital mortality was 12.4%. In-hospital mortality for the control and clindamycin groups were 12.6% and 9.8%, respectively. After propensity score matching, in-hospital mortality did not significantly differ between the control and clindamycin groups (9.7% versus 10.3%; risk difference, 0.3%; 95% confidence interval, –3.5% to 4.2%).

DISCUSSION

In the present study, we investigated the effectiveness of clindamycin on patients with invasive NGAS using a nationwide inpatient database in Japan. We applied propensity score matching to minimize confounding between the clindamycin and control groups. In-hospital mortality did not significantly differ between the two groups.

Because GAS produce several exotoxins—some of which act as superantigens—previous studies recommended combined treatment with clindamycin and baseline antibiotic therapy for invasive GAS infections with the expectations of suppressing potentially life-threatening bacterial toxin synthesis.10 In addition to producing pyrogenic toxins, GBS is known to possess virulent factors such as alpha C-proteins, pilins, and polysaccharide capsules.24–27 In our study we regarded group C and G Streptococci as SDSE, because the majority of cases resulting in sepsis due to group C and G Streptococci were attributed to SDSE.4 Furthermore, genome sequence analysis indicates that SDSE closely resembles GAS with a 72% genomic similarity.7 Streptococcus dysgalactiae subspecies equisimilis also shares a number of genes that encode virulence factors in GAS, including the antiphagocytic M protein, streptolysin O, streptolysin S, and streptokinase.7 Additionally, NGAS is known to induce Streptococcus toxic shock syndrome in a manner similar to GAS, which supports the theory that certain exotoxins produced by NGAS could act as a superantigen reminiscent of

| Variable                              | Before propensity score matching | After propensity score matching |
|---------------------------------------|----------------------------------|--------------------------------|
|                                       | Control group (n = 3,458)         | Clindamycin group (n = 296)    | ASD (%) | Control group (n = 1,156) | Clindamycin group (n = 289) | ASD (%) |
| Diabetes mellitus                     | 788 (22.8)                       | 86 (29.1)                      | 14.3    | 335 (29.0)                | 82 (28.4)                     | 1.3     |
| Charlson comorbidity index            |                                  |                                |         |                          |                                |         |
| 0                                     | 1,196 (34.6)                     | 109 (36.8)                     | 4.7     | 401 (34.7)                | 106 (36.7)                    | 4.1     |
| 1                                     | 1,059 (30.6)                     | 90 (30.4)                      | 0.5     | 336 (29.1)                | 88 (30.4)                     | 3.0     |
| 2                                     | 658 (19.0)                       | 58 (19.6)                      | 1.4     | 273 (23.6)                | 57 (19.7)                     | 9.4     |
| ≥3                                    | 545 (15.8)                       | 39 (13.2)                      | 7.3     | 146 (12.6)                | 38 (13.1)                     | 1.5     |
| Hospitalization by ambulance          | 1,614 (46.7)                     | 166 (56.1)                     | 18.9    | 641 (55.4)                | 160 (55.4)                    | 0.2     |
| Teaching hospital                     | 2,819 (81.5)                     | 267 (90.2)                     | 25.1    | 1,045 (90.4)              | 260 (90.0)                    | 1.5     |
| Intensive care unit admission         | 201 (5.8)                        | 41 (13.9)                      | 27.2    | 141 (12.2)                | 38 (13.1)                     | 2.9     |

Data are shown as number (%) unless otherwise specified. ASD, absolute standardized difference; IQR, interquartile range.
GAS exotoxins. For these reasons, we hypothesized that clindamycin could also be effective for invasive NGAS infection. To our knowledge, the effect of clindamycin on invasive NGAS infections has never been dissected at the large-scale level. This is the first nationwide study investigating the effects of clindamycin on invasive NGAS infection.

Additional clindamycin treatment was not associated with lower in-hospital mortality in the present study and there are three possible reasons for this outcome. The first conceivable reason is antibiotic resistance. Group B Streptococcus resistance to clindamycin has been reported as in Japan as 5.3% in 2015. With regard to SDSE, resistance to clindamycin was 14.1–16.2% in Japan and 17.4% in Korea. The increasing rate of resistance might have inadvertently influenced the results. Second, in the present study there was an underlying prevalence of broad-spectrum antibiotics such as carbapenem, third- and fourth-cephalosporins, and β-lactamase inhibitor antibiotics being adopted for treatment. The use of such potent antibiotics could have overshadowed the additional benefits of combined clindamycin. The third possible reason for the achieved outcome stems from the inherent limitation of clindamycin for treatment of β-hemolytic Streptococcus infections. Although the scientific evidence in support of clindamycin combination therapy in GAS patients is documented to some degree, the same cannot be said for NGAS. Perhaps as a result of a mechanism still unknown, clindamycin could simply be ineffective on NGAS.

There are several limitations associated with this study that should be acknowledged. First, the extracted data do not reflect all cases involving invasive NGAS because the data extraction was based on the ICD-10 codes. Invasive NGAS infections are not specifically included in the ICD-10 codes and therefore the system inherently fails to place a distinction on sepsis and invasive forms of NGAS. This could inadvertently result in a skewed patient population. However, a previous observational study undertaken in Japan showed that mortality among the adult population (≥15 years old) was 16.7% in invasive GAS, 10.8% in invasive GBS, and 12.7% in invasive SDSE infections. The overall mortality in the present study (12.4%) is consistent with the population data reported previously. The second limitation is the absence of key clinical factors from the database. Although we used propensity score matching to adjust for various confounders, there are several factors that the database does not include, such as vital signs at admission, laboratory data, and degree of surgical intervention. Finally, we did not have a standardized protocol for the administration of clindamycin. The effects of dose or duration of clindamycin are ultimately unknown. Furthermore, we defined the exposure time window for clindamycin treatment to be within 2 days of admission. This decision was grounded upon the recommendations of a previous review suggesting early intervention yields positive outcomes. The justification for the adopted criteria is relatively poor due to a lack of published scientific reports on the subject.

This nationwide cohort study showed that combination therapy with clindamycin was not associated with lower in-hospital mortality in patients with invasive NGAS infection. Additional prospective studies are warranted to examine the efficacy of clindamycin in greater detail.

DISCLOSURE

A PROVAL OF THE research protocol: The present study was approved by the Institutional Review Board at the University of Tokyo (approval number: 3501-1).

Informed consent: Due to the anonymous nature of the data, the requirement for patient informed consent was waived.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

Conflict of interest: None.

REFERENCES

1 Waddington CS, Snelling TL, Carapetis JR. Management of invasive group A streptococcal infections. J. Infect. 2014; 69: S63–9.
2 Ikebe T, Tominaga K, Shima T et al. Increased prevalence of group A streptococcus isolates in streptococcal toxic shock syndrome cases in Japan from 2010 to 2012. Epidemiol. Infect. 2015; 143: 864–72.
3 Phares CR, Lynfield R, Farley MM et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. JAMA 2008; 299: 2056–65.
4 Broyles LN, Van Beneden C, Beall B et al. Population-based study of invasive disease due to β-hemolytic Streptococci of groups other than A and B. Clin. Infect. Dis. 2009; 48: 706–12.
5 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: 1–10.
6 Takahashi T, Sunaoshi K, Sunakawa K, Fujishima S, Watanabe H, Ubukata K. Clinical aspects of invasive infections with Streptococcus dysgalactiae ssp. equisimilis in Japan: differences with respect to Streptococcus pyogenes and Streptococcus agalactiae infections. Clin. Microbiol. Infect. 2010; 16: 1097–103.
7 Shimomura Y, Okumura K, Murayama SY et al. Complete genome sequencing and analysis of a lancefield group G
Streptococcus dysgalactiae subsp. equisimilis strain causing streptococcal toxic shock syndrome (STSS). BMC Genom. 2011; 12(1): 17.

8 Parks T, Barrett L, Jones N. Invasive streptococcal disease: a review for clinicians. Br. Med. Bull. 2015; 115: 77–89.

9 Yan S, Bohach GA, Stevens DL. Persistent acylation of high-molecular-weight penicillin-binding proteins by penicillin induces the postantibiotic effect in Streptococcus pyogenes. J. Infect. Dis. 1994; 170: 609–14.

10 Mascini EM, Jansze M, Schouls LM, Verhoef J, Van Dijk H. Penicillin and clindamycin differentially inhibit the production of pyrogenic exotoxins A and B by group A streptococci. Int. J. Antimicrob. Agents 2001; 18: 395–8.

11 Stevens DL, Bryant AE, Hackett SP. Antibiotic effects on bacterial viability, toxin production, and host response. Clin. Infect. Dis. 1995; 20: S154–S157.

12 Stevens DL, Yan S, Bryant AE. Penicillin-binding protein expression at different growth stages determines penicillin efficacy in vitro and in vivo: an explanation for the inoculum effect. J. Infect. Dis. 1993; 167: 1401–5.

13 Gemmell CG, Peterson PK, Schmeling D et al. Potentiation of opsonization and phagocytosis of Streptococcus pyogenes following growth in the presence of clindamycin. J. Clin. Invest. 1981; 67: 1249–56.

14 Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive Streptococcus pyogenes infection. Pediatr. Infect. Dis. J. 1999; 18: 1096–100.

15 Linnér A, Darenberg J, Sjölín J, Henriques-Normark B, Norby-Teglund A. Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study. Clin. Infect. Dis. 2014; 59: 851–7.

16 Carapetis JR, Jacoby P, Carville K, Ang SJJ, Curtis N, Andrews R. Effectiveness of clindamycin and intravenous immunoglobulin, and risk of disease in contacts, in invasive group A streptococcal infections. Clin. Infect. Dis. 2014; 59: 358–65.

17 Mullá ZD, Leaverton PE, Wiersma ST. Background: invasive group A Streptococcal infections in Florida. South Med. J. 2003; 96: 968–73.

18 Begley JS, Barnes RC. Group B streptococcus toxic shock-like syndrome in a healthy woman: a case report. J. Reprod. Med. 2007; 52: 323–5.

19 Yasunaga H. Real world data in Japan: chapter II the diagnosis procedure combination database. Ann. Clin. Epidemiol. 2019; 1: 76–9.

20 Ono K, Wada K, Takahara T, Shirotani T. Indications for computed tomography in patients with mild head injury. Neurol. Med. Chir (Tokyo) 2007; 47: 291–7.

21 Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. J. Epidemiol. 2017; 27: 476–82.

22 Lundgren RS, Kramer CB, Rivara FP et al. Influence of comorbidities and age on outcome following burn injury in older adults. J. Burn Care Res. 2009; 30: 307–14.

23 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav. Res. 2011; 46: 399–424.

24 Schlievert PM, Gocke JE, Deringer JR. Group B streptococcal toxic shock-like syndrome: report of a case and purification of an associated pyrogenic toxin. Clin. Infect. Dis. 1993; 17: 26–31.

25 Madoff LC, Michel JL, Gong EW, Kling DE, Kasper DL. Group B streptococci escape host immunity by deletion of tandem near elements of the alpha C protein. Proc. Natl. Acad. Sci. USA 1996; 93: 4131–6.

26 Konttio-Ghiorgi Y, Mairey E, Mallet A et al. Dual role for pilus in adherence to epithelial cells and biofilm formation in Streptococcus agalactiae. PLoS Pathog. 2009; 5(5): e1000422.

27 Uchiyama S, Sun J, Fukahori K et al. Dual actions of group B Streptococcus capsular sialic acid provide resistance to platelet-mediated antimicrobial killing. Proc. Natl. Acad. Sci. USA 2019; 116: 7465–70.

28 Ikebe T, Chiba K, Shima T et al. Evaluation of streptococcal toxic shock-like syndrome caused by group B streptococcus in adults in Japan between 2009 and 2013. J. Infect. Chemother. 2014; 20: 207–11.

29 Kim S, Byun J, Park 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: 212–9.

30 Ikebe T, Okuno R, Sasaki M et al. Molecular characterization and antibiotic resistance of Streptococcus dysgalactiae sub-species equisimilis isolated from patients with streptococcal toxic shock syndrome. J. Infect. Chemother. 2018; 24: 117–22.