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Original article

Bloodstream infections caused by *Streptococcus anginosus* group bacteria: A retrospective analysis of 78 cases at a Japanese tertiary hospital

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ABSTRACT

Objectives: To investigate the characteristics of *Streptococcus anginosus* group (SAG) bacteremia in recent years, we conducted a retrospective cohort study and compared its findings with the data from previous studies.
Methods: All patients with positive blood cultures from May 2005 to September 2014 in a tertiary care center with 925 beds were included.
Results: There were 78 cases of SAG bacteremia (51 cases men; median age, 68 years) during the study period. The most common comorbidities were solid tumors in 32.1% of the patients. The most common infection source was hepatobiliary in one-third of all cases. Other infection sites included the following: intra-abdominal (12.8%), thoracic (10.3%), musculoskeletal (9%), urinary tract (7.7%), soft tissues (7.7%), and cervicofacial (6.4%). Susceptibility to penicillin, clindamycin and erythromycin were 100% (78/78), 95% (70/74) and 85% (39/46), respectively. Surgery along with systemic antibiotic treatment was administered in 53% of the cases. In-hospital mortality was 14.1%.
Conclusion: The clinical sources of the SAG bacteria were diverse, and hepatobiliary infection was the most common source of infection. In more than half of the patients, surgical treatment was performed. Susceptibility to penicillin was 100%, but susceptibility to erythromycin was lower than that reported in previous studies.
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1. Introduction

Streptococcus anginosus group (SAG) bacteria, formerly referred to as the *Streptococcus milleri* group, consists of three distinct streptococcus species [1]: *S. anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*. SAG bacteria, classified as viridans streptococci, have clinically distinct characteristics from other viridians streptococci in that they cause pyogenic infections in various parts of the body [2]. Bacteremia caused by this group is associated with infections that require surgical treatment [3]. To date, few studies have examined the clinical importance of SAG bacteremia, and most of these studies were conducted before 2000 [4–8]. To investigate the characteristics of SAG bacteremia in recent years, we conducted this retrospective cohort study and compared its findings with the data from previous studies.

2. Patients and methods

We reviewed the medical records of all patients who had SAG bacteremia in Kameda Medical Center, a tertiary care center with 925 beds in Kamogawa, Japan. We also compared the characteristics of the different species. This study was approved by the Committee for Ethics of Kameda Medical Center, Japan under the condition that personal data was kept confidential. Because of the

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retrospective, observational nature of the study, the requirement for informed consent was waived by the Committee.

All patients with positive blood cultures from May 2005 to September 2014 were screened using our laboratory database. SAG-positive blood cultures were identified and investigated using electronic medical records. If more than two blood cultures were positive for SAG, the patient was considered to have had true bacteremia. Also, cases where only one blood culture grew SAG and where the clinical judgement of plural infectious diseases expertise was consistent with SAG bacteremia, the cases were considered to be true bacteremia. If only one blood culture was positive and there was no other sign of sepsis, it was considered to be a result of contamination.

We gathered information on age, sex, number of positive blood cultures, underlying health conditions (solid tumor, lymphoma, leukemia, congestive heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, hemiplegia, dementia, chronic pulmonary condition, connective tissue diseases, peptic ulcer disease, diabetes mellitus, moderate to severe chronic kidney disease, liver disease and AIDs), vital signs on the day of the positive blood culture, source of infection, susceptibility of organism isolated to various antibiotics, choice and duration of antibiotic treatment, performance of surgical treatment and in-hospital mortality. We also calculated the Charlson Comorbidity Index (CCI) [9] using the information about the comorbidities. The source of infection was determined if SAG from another specimen grew or there was a clinically evident site of infection. If there was no clinically evident site of infection in a patient with true bacteremia, it was recorded as primary bacteremia. The severity of the bacteremia on the day of onset was graded by the Pitt Bacteremia Score (PBS) [10].

Blood specimens were processed in the microbiology laboratories using the BACTEC blood culture system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). For blood culture bottles, we used BD BACTEC Plus Aerobic/F Culture Vials, BD BACTEC Lytic/10 Anaerobic/F Culture Vials and BD BACTEC Myco/F Lytic Culture Vials (Becton, Dickinson and Company). Bottles were incubated at 37 °C and examined daily for 7 days. Organisms were identified to the species level using the Microscan WalkAway system (Beckman Coulter, Miami, FL, USA) and the Rapid ID32 Strep system (bioMérieux, France). Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Germany) was used to identify species that could not be classified by the Rapid ID32 Strep system. Broth microdilution methodology was used to determine the minimal inhibitory concentrations of the antibiotics that were tested. Isolate susceptibility to various antibiotics was judged according to Clinical and Laboratory Standards Institute (CLSI) M100-S24 [11].

Table 1
Summary of patient demographics, clinical characteristics, microbiological characteristics, treatment and outcomes.

Variables	
Median age, years (IQR) (n = 78)	67.4 (59.3–80.0)
Men, n (%) (n = 78)	51 (65.4)
Comorbidities, n (%) (n = 78)	
Solid tumor	25 (32.1)
Diabetes mellitus	14 (18.0)
Heart failure	10 (13.2)
Liver disease	10 (12.8)
Dementia	10 (12.8)
Hemiplegia	9 (11.5)
Cerebral vascular disease	9 (11.5)
Myocardial infarction	6 (7.7)
Collagen disease	5 (6.4)
Peripheral artery disease	5 (6.4)
Chronic respiratory disease	4 (5.1)
Peptic ulcer disease	3 (3.9)
Chronic kidney disease	3 (3.9)
Leukemia	1 (1.3)
Lymphoma	0
AIDS	0
Charlson Comorbidity Index, n (%) (n = 78)	
0	19 (24.4)
1–2	24 (30.8)
3–4	10 (12.8)
5–	25 (32.1)
Pitt Bacteremia Score, n (%) (n = 75)	
–4	68 (90.7)
5–	7 (9.3)
Source of infection, n (%) (n = 78)	
Hepatobiliary	25 (32.1)
Intra-abdominal	9 (11.5)
Thoracic	8 (10.2)
Urinary tract	6 (7.7)
Soft tissue	6 (7.7)
Musculoskeletal	5 (6.4)
Cervicofacial	5 (6.4)
Infective endocarditis	3 (3.8)
Central nervous system	1 (1.3)
Primary bacteremia	7 (9.0)
Multiple source of infection	3 (3.8)
Polymicrobial bacteremia, n (%) (n = 78)	28 (35.9)
Species, n (%) (n = 78)	
S. constellatus	27 (34.6)
S. intermedius	19 (24.4)
S. anginosus	17 (21.8)
Not identified	15 (19.2)
Susceptibility, susceptible/all (%) (n = 78)	
PCN	78/78 (100)
CLDM	70/74 (94.6)
EM	39/46 (84.8)
Surgical treatment, n (%) (n = 78)	41 (52.6)
Treatment duration, median days (IQR) (n = 78)	19 (14–39)
In-hospital mortality, n (%) (n = 78)	11 (14.1)

3. Results

In total, 136 sets of blood cultures from 83 cases were SAG-positive. Of these, five cases were judged to be the result of contamination. Thus, there were 78 cases in total during the study period. Patient demographics, clinical characteristics, microbiological characteristics, therapy and outcomes are summarized in Table 1. The most common source of infection was hepatobiliary-related (32.1%). Multiple sources of infection were found in three cases (3.8%). One case had infective endocarditis (IE) complicated by vertebral osteomyelitis. Another case had sigmoid cancer with an intra-abdominal abscess extending to the spinal space, then complicated by bacterial meningitis. The last case had concomitant hepatic abscess and iliopsoas abscess. IE was seen in four cases; among these, two cases involved both the mitral and aortic valves. Two other cases involved the mitral valve alone and two cases required valve replacement. Central nervous system (CNS) infection was seen in two cases. One case had a brain abscess and the other had bacterial meningitis. Among the 71 cases whose sources of infection were found, the same organisms were identified as being from a local site in 30 cases (42.2%).

Polymicrobial bacteremia was seen in 28 cases (35.9%). Table 2 shows the microorganisms identified along with the SAG bacteria. Gastrointestinal flora was the most frequently identified group, followed by obligate anaerobes, skin and nasopharynx flora and oral flora. *S. constellatus*, *S. intermedius* and *S. anginosus* were identified in 27, 19 and 17 cases, respectively. In 15 cases, we could not identify the organism at the species level (reported as *S. milleri* group or SAG). Three cases of *S. anginosus* and one case of *S. constellatus* were identified by MALDI-TOF MS. Surgical treatment and systemic antibiotics were used in 53% of the cases. The

Table 2
Microorganisms identified along with SAG bacteria.

Classification	Number
Gastrointestinal flora	
Escherichia coli	7
Klebsiella spp.	7
Enterobacter spp.	2
Enterococcus spp.	2
Proteus mirabilis	1
Citrobacter koseri	1
Obligate anaerobes	
Bacteroides spp.	2
Clostridium spp.	2
Fusobacterium sp.	1
Bifidobacterium sp.	1
Anaerobes, not identified	6
Skin and nasopharynx flora	
Corynebacterium spp.	3
Staphylococcus aureus	2
Coagulase-negative staphylococci	2
Oral flora	
Eikenella corrodens	2
Viridans streptococci	2
Others	
Pseudomonas aeruginosa	1

type of surgical treatment performed included endoscopic biliary drainage (EBD), percutaneous drainage, surgical debridement or valve replacement. In-hospital mortality was 14.1%. The median number of days from the onset of bacteremia to death was 29 days (3–96 days). Among the 11 cases that died during hospitalization, seven had advanced cancer (gastric cancer, three cases; cholangiocarcinoma, ureteral cancer, ovarian cancer and hypopharyngeal cancer, one case each). Among the seven cases with advance cancer, four of them died during treatment for bacteremia and three died after treatment completion. Among the four cases without advanced cancer, one had IE and died after valve replacement. The other three cases had septic shock, which did not respond to treatment. In eight cases, mortality was related to SAG bacteremia. Table 3 shows the sources of infection for the individual SAG species. *S. anginosus* and *S. intermedius* were associated frequently with hepatobiliary infections. In contrast, the presence of *S. constellatus* was more evenly distributed among the various infection sources.

4. Discussion

We conducted a retrospective analysis of SAG bacteremia to describe its risk factors, treatment, and prognosis at a Japanese tertiary-care hospital. A total of 78 cases were diagnosed with SAG bacteremia over the past 9 years, 3 months at the hospital. To date, our study is the largest single-center study of SAG bacteremia.

We compared our findings with those of previous studies (Table 4) [3–8,12]. The mean age of the patients in our cohort, 67.4 years, was higher than that of all the previous studies. This high mean age reflects the typical demographics of rural areas in Japan.

The most common underlying diseases involved solid tumors (25 cases, 32.1%). Most of the previous studies [3,5,6,12] also reported the presence of a solid tumor as the most frequent underlying disease. In 18 cases (73.9%), the infection source was associated with an underlying tumor. We speculate that disruption of normal anatomical structure by a solid tumor causes local infection, which subsequently leads to SAG-related bacteremia. Furthermore, there have recently been suggestions that SAG plays a significant role in the carcinogenic process of some types of cancer [13–16]. Sasaki et al. investigated whether *S. anginosus* is associated with various types of cancer using polymerase chain reaction (PCR) and Southern blot analyses to detect *S. anginosus* DNA sequences from various cancer tissues. These researchers frequently found *S. anginosus* DNA sequences in samples from patients with esophageal cancer and gastric cancer, but not in lung, cervical and renal cancers [14]. The association between cancer and SAG may partly explain why solid tumors are seen frequently in patients with SAG bacteremia.

As with previous studies, our data showed that various infection sources were associated with SAG bacteremia. The most common entry was hepatobiliary infection in 26 cases (33.3%), followed by intra-abdominal infection in 10 cases (12.8%). This finding is not surprising because SAG bacteria are considered part of the normal gastrointestinal flora. Thoracic infections were seen in eight cases (10.3%). Aspiration of oropharyngeal secretions is associated with pleural empyema and pulmonary abscess caused by SAG [17]. Musculoskeletal infections, which were seen in seven cases (9.0%), included an iliopsoas abscesses and vertebral osteomyelitis; they were considered to be related to hematogenous inoculation secondary to bacteremia rather than the primary source of infection, except in one case, which had an iliopsoas abscess caused by invasion of adjacent sigmoid cancer. Soft tissue infection was seen in six cases (7.7%); these were either diabetic foot infections or decubitus infections. Urinary tract infections (UTIs) were seen in six cases (7.7%). Although SAG is considered to be part of the normal urogenital flora, it is rarely reported as a pathogen responsible for UTIs.

Polymicrobial bacteremia was seen in 37% of patients with SAG bacteremia in this study. Previous studies have reported that the incidence of polymicrobial bacteremia was 12.5–51.0%. Organisms frequently seen along with SAG were gastrointestinal flora and obligate anaerobes; this may be explained, at least in part, by the fact that hepatobiliary infections, which frequently involve various types of organisms including gastrointestinal flora and obligate anaerobes, were the most common source of infection. Clarridge

Table 3
Association of individual species with infection sources.

Variables	*S. constellatus* (n = 27)	*S. intermedius* (n = 19)	*S. anginosus* (n = 17)	Total number
Source of infection, n (%)				
Hepatobiliary	4 (14.8)	8 (42.1)	6 (35.3)	18
Intra-abdominal	4 (14.8)	1 (5.3)	3 (17.6)	8
Thoracic	2 (7.4)	3 (15.8)	1 (5.9)	6
Urinary tract	1 (3.7)	2 (10.5)	3 (17.6)	6
Soft tissue	4 (14.8)	2 (10.5)	0	6
Musculoskeletal	3 (11.1)	2 (10.5)	0	5
Cervicofacial	3 (11.1)	1 (5.3)	1 (5.9)	5
Central nervous system	1 (3.7)	0	0	1
Infective endocarditis	0	0	0	0
Primary bacteremia	3 (11.1)	0	2 (11.8)	5
Multiple sources of infection	2 (7.4)	0	1 (5.9)	3

Table 4
Comparison of our data with the data from previous studies.

	This study	Stelzmueller et al. [3], 2009	Weightman et al. [12], 2004	Bert et al. [4], 1998	Salavert et al. [7], 1996	Casariego et al. [5], 1996	Jacobs et al. [6], 1994
Cases, n	78	24	29	51	33	32	19
Age, mean	67.4	50.6	67.0	52.0	57.8	64.0	48.8
Solid tumor, %	32.1	16.7	25.0	15.7	21.2	21.9	21.1
Source of infection, %							
Hepatobiliary	32.1	8.3	44.8	11.8	33.3	31.3	21.1
Intra-abdominal	11.5	20.8	6.9	3.9	27.3	9.4	31.6
Thoracic	10.2	0	13.8	15.7	9.1	9.4	26.3
Urinary tract	7.7	0	3.4	0	3.0	0	0
Soft tissue	7.7	29.2	17.2	3.9	9.1	3.0	5.3
Musculoskeletal	6.4	0	3.4	3.9	0	3.0	0
Cervicofacial	6.4	4.2	3.4	11.8	3.0	6.3	10.5
Infective endocarditis	3.8	0	3.4	0	3.0	15.6	0
Central nervous system	1.3	12.5	0	3.9	3.0	3.0	0
Polymicrobial, %	35.9	12.5	13.8	51.0	27.3	15.6	15.8
Species, %							
S. constellatus	34.6		20.7	43.1		43.8	10.5
S. intermedius	24.4		6.9	2.0		43.8	10.5
S. anginosus	21.8		48.3	54.9		12.5	78.9
Not identified	19.2		24.1	0		0	0
Susceptibility, %							
PCN	100	100	100	100	100	100	100
CLDM	94.6		100		97	100	100
EM	84.8		95	88.2	94	100	100
Surgical treatment, %	52.6	91.7		31.4	54.5	31.3	63.2
In-hospital mortality, %	14.1	20.8	10.3	19.6	15.2	12.5	26.3

et al. reported that *S. intermedius* tends to be isolated as a sole pathogen, whereas *S. anginosus* and *S. constellatus* are associated with polymicrobial infections [18]. In our study, the percentage of each species identified from the polymicrobial infections was 47.4% in *S. intermedius*, 35.3% in *S. anginosus* and 33.3% in *S. constellatus*. Although the results from our study contrast with that of Clarridge et al., it is difficult to draw a definitive conclusion in terms of the association between species and polymicrobial infection because of the limited number of samples in our study.

A relationship between certain species of SAG and particular infection sources has not yet been adequately established. Clarridge et al. reported that *S. intermedius* was associated with CNS infections and deep soft-tissue infections, whereas *S. anginosus* and *S. constellatus* were associated with intra-abdominal infections, respiratory infections and superficial infections [15]. Whiley et al. reported that *S. intermedius* was associated with CNS infections, *S. anginosus* was associated with intra-abdominal infections and genitourinary infections and *S. constellatus* was associated with most infection sources without particular predominance [16]. In contrast, Casariego et al. did not find any relationship between bacterial species and infection sources in their case series on SAG bacteremia [5]. Here, *S. anginosus* and *S. intermedius* were associated frequently with hepatobiliary infections, but *S. constellatus* did not exhibit such an association. Also, all isolates associated with CNS infection were *S. constellatus*. This result is similar to that of Whiley et al. except for the association between *S. constellatus* and CNS infections. However, because of the limited number of samples, it is difficult to draw a definite conclusion concerning any association between species types and infection sources.

Susceptibility to penicillin (PCN), clindamycin (CLDM) and erythromycin (EM) was 100%, 95% and 85%, respectively. In all other studies, susceptibility to PCN was 100% [3–7,12]. Although PCN susceptibility was retained in our study, susceptibility to EM was lower than that found in other studies [4–7,12]. Similarly, *Streptococcus pneumoniae* has lower susceptibility to EM in Asia compared with other regions [19]. This low susceptibility to erythromycin is partly explained by the over-prescription of macrolide antibiotics at outpatient settings in Japan, as described in the study by Gu et al. [20].

Surgical treatment and antibiotics were administered to 53% of the patients in our study. Previous studies have reported a high rate of surgical treatment for SAG bacteremia (29–63%). There are two possible reasons for this high rate. First, SAG bacteria have a tendency to form abscesses. Second, hepatobiliary infections, which frequently require EBD, have been reported to be the most common infection sources [5,7,12].

In-hospital mortality in this study was 14.1%; this finding is comparable to previous studies (10.3–26.3%). In our study, most of the patients who died during hospitalization had advanced cancer. Infection in patients with advanced cancer is often problematic because it may not be possible to perform complete source control because of the cancer. SAG-related mortality from bacteremia may be greatly affected by the presence of active cancer rather than the severity of the bacteremia itself.

Our study has some limitations. First, not all isolates were identified by the same method. Most of the isolates were identified with phenotypical methodology using the rapid ID32 strep system. Additionally, we found four isolates that could not be identified phenotypically with MALDI-TOF MS. Woods et al. showed that MALDI-TOF MS could identify *S. anginosus* and *S. constellatus* reliably to the species level, but not *S. intermedius* [21]. Among four isolates identified by MALDI-TOF MS, three were *S. anginosus* and one was *S. constellatus*. Second, our investigation was conducted in a single-center; therefore, the patient population may not accurately reflect the general demographics of Japan.

In conclusion, our case series of SAG bacteremia has shown that the clinical sources of the bacteria were diverse, and hepatobiliary infections were the most common sources of infection. In more than half of the patients, surgical treatment was performed.

Susceptibility to penicillin was 100%, but susceptibility to erythromycin was lower than that reported in previous studies [4–7,12].

Conflict of interest

The authors declare that they have no competing interests.

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