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Original Research

# Infections Associated with the *Streptococcus Anginosus* Group in Children

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## Abstract

**Objectives:** *Streptococcus anginosus* group (SAG), also known as the *Streptococcus milleri* group, consists of *Streptococcus anginosus*, *Streptococcus intermedius* and *Streptococcus constellatus*. Skin and soft tissue infections, intra-abdominal infections, skeletal infections and ear-nose-throat (ENT) and cervical infections are the most common presentations. This study aimed to evaluate SAG infections in children.

**Methods:** A retrospective review was conducted on patients aged 0-18 years who had cultures positive for *S. anginosus*, *S. intermedius*, or *S. constellatus* between January 1, 2019, and March 1, 2024.

**Results:** SAG bacteria were cultured in 113 patients. SAG was identified as the causative agent of infection in 93 patients. Of a total of 93 patients, 39 were female (41.9%) and 54 were male (58.1%). The median age of the patients at the time of diagnosis was 14 years (IQR: 9-17). Among these, *S. constellatus* was found in 46 patients (49.5%), *S. anginosus* in 36 patients (38.7%), and *S. intermedius* in 11 patients (11.8%). The infections presented primarily as skin and soft tissue infections (63 patients), head and neck infections (23 patients), and intra-abdominal abscesses (7 patients). Additionally, two patients had concomitant bacteremia. Predisposing factors for the development of infection were identified in 52 patients (55.3%). Surgical drainage was required for 70 patients (74.4%).

**Conclusion:** *Streptococcus constellatus* was the most frequently isolated species among the SAG, followed by *S. anginosus* and *S. intermedius*. The most common site of infection was skin and soft tissue, with a significant proportion of patients requiring surgical drainage. The overall incidence of bacteremia was low. *S. intermedius* was more frequently isolated from deep tissue infections.

**Keywords:** Abscess, skin and soft tissue, *Streptococcus anginosus* group, surgical drainage

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Viridans group streptococci include *Streptococcus mutans* group, *Streptococcus salivarius* group, *Streptococcus bovis* group, *Streptococcus mitis* group, *Streptococcus sanguinis* group and *Streptococcus anginosus* group.[1] The *Streptococcus anginosus* group (SAG), also known as the *Streptococcus milleri* group, consists of *S. anginosus*, *S. intermedius* and *S. constellatus*. These organisms are part of the normal human flora and colonize the oropharynx, gastro-

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intestinal tract and vagina. Although they are commensal, they are pathogenic and can cause invasive disease. The most characteristic feature that clinically distinguishes SAG from other viridans streptococci is their tendency to cause invasive pyogenic infections complicated by tissue liquefaction and abscess formation with enzymes such as hyaluronidase, deoxyribonuclease and chondroitin sulphatase.[2,3] Pyogenic infections caused by SAG can be superficial or deep and involve multiple organs.[4] Skin and soft tissue infections, intra-abdominal infections, skeletal infections and ear-nose-throat (ENT) and cervical infections are the most common presentations.[4,5]

The hospitalization rates of complicated sinusitis and otitis due to SAG and the rates of intracranial infections and mastoiditis due to SAG have increased in recent years.[6,7] It has been reported that sinusitis and otitis caused by SAG organisms in children have a more severe course than infections caused by other microorganisms and are associated with multiple surgical interventions.[7]

There is a limited number of studies on the clinical course and optimal treatment of SAG infections in children.[8-10] The aim of this study was to investigate the clinical outcomes and treatment of SAG infections in children.

## Methods

Between January 01, 2019 and March 01, 2024; patients aged 0-18 years with *S. anginosus*, *S. intermedius* or *S. constellatus* growth in any culture at the microbiology laboratory of Ankara Bilkent City Hospital were retrospectively reviewed. For each patient, medical data was evaluated to determine whether the bacteria grown were an infectious agent or a contaminant. Patients were excluded if the culture results were considered to be contamination or if there was growth of SAG in the superficial swab culture. Growth of an additional bacterium together with SAG from the same bottle in blood culture; growth of SAG in blood culture in a patient without clinical signs of bacteremia; mixed growth with other bacteria in bronchoalveolar lavage (BAL) culture was considered as contamination. The patients with missing information in the hospital medical database were also excluded.

The patients' demographics, underlying comorbid conditions, site of infection, presence of any predisposing factors for the development of infection, and prior antibiotic use for the existing infection were recorded. The oral or parenteral antibiotic treatments given for the current infection and the duration of treatment were investigated, along with any antibiotic escalation/de-escalation or changes based on culture results and whether surgical drainage was performed. Antibiogram sensitivity and resistance patterns were also examined. It was investigated whether there was a predisposing factor for the development of infection.

Pus samples included in the study were Gram stained (PREVI®COLOR, bioMerieux, France) and analyzed before being cultured. Gram-positive cocci arranged in pairs and in chains of varying lengths were observed. Pus samples were inoculated into 5% sheep blood agar, MacConkey agar and chocolate agar and incubated for 24-48 hours at 37 degrees under suitable atmospheric conditions. Blood samples, taken in accordance with our hospital's standard clinical blood culture procedures were collected in BACT-ALERT culture bottles (bioMérieux, France). Samples were then loaded onto the BACT/ALERT 3D (bioMerieux, France) device for incubation. Gram staining was performed from the bottles giving positive signals and gram-positive cocci arranged in pairs and in chains of varying lengths were observed. Inoculation on 5% sheep blood agar, MacConkey agar and chocolate agar was performed and incubated for 24-48 hours at 37 degrees under suitable atmospheric conditions. In plates where significant growth was detected, identification was performed by using VITEK® MS (bioMérieux, France) with MALDI-TOF technology. The bacterial colony was removed with a loop and spread Into the wells on MALDI-TOF MS slides. 1 ml of CHCA (α-cyano-4-hydroxycinnamic acid) matrix solution was dropped onto it. After the slides dried, they were placed in the VITEK® MS (bioMérieux, France) device and evaluated. Antibiotic susceptibility tests of isolates were performed in accordance with the manufacturers' recommendations using the VITEK® 2 (bioMérieux, France) automatic system and the VITEK® 2 AST-ST03 card. A 0.5 McFarland standard suspension was prepared from the colonies in the medium and inoculated onto VITEK cards. Doubtful results were confirmed manually by the disk diffusion method.

This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Ankara Bilkent City Hospital Ethics Committee (date of approval: 24.04.2024, protocol no: 1-24-170).

IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY) was used for statistical analysis. Descriptive statistics are presented with numbers and percentages for qualitative data and with mean and standard deviation or median (IQR) for quantitative data. The conformity of the variables to the normal distribution was examined by histogram and probability graphs and the Shapiro-Wilk test.

## Results

SAG was cultured in 113 patients. Twenty patients were excluded due to inappropriate sampling or contamination.

Twelve patients were excluded because only a superficial

swab was taken. One patient had a mixed growth with a dominant co-isolate in the bronchoalveolar lavage (BAL) culture, while three patients had two different bacterial growths in blood culture, and four had bacterial growth in blood culture without clinical signs of bacteremia. After applying these exclusion criteria, SAG was identified as the causative agent of infection in a total of 93 patients.

Of a total of 93 patients, 39 were female (41.9%) and 54 were male (58.1%). The median age of the patients at the time of diagnosis was 14 years (IQR: 9-17). Sixty-four (68.8%) patients were outpatient, while twenty-nine (31.2%) were inpatient. The duration of symptoms before presentation was 4 days (2.25-7.75). Thirty-one patients (33.3%) had used oral antibiotics prescribed at the initial medical center before presenting to our hospital, while sixty-two patients (66.7%) had not received any prior treatment. *S. constellatus* grew in 46 (49.5%), *S. anginosus* in 36 (38.7%) and *S. intermedius* in 11 (11.8%) patients.

When classified according to the region of infection, there were 63 patients with skin and soft tissue infections (gluteal/sacral abscess, omphalitis, paronychia, bursitis), 23 patients with head and neck infections (brain abscess, deep neck infection, odontogenic infection, orbital abscesses), 7 patients with intra-abdominal abscesses. The relationship between bacterial type and involvement of any region is mentioned in Table 1. Two patients with brain abscesses had their immunology background checked, and neither was found to have an immune deficiency. Blood cultures were obtained from 26 patients. In two cases, the same bacterial pathogen was identified in both wound and blood cultures: an 8-year-old girl with a dental abscess and a 6-year-old boy with a peritonsillar abscess.

There were predisposing factors for the development of infection in 52 patients (55.3%). Among patients with skin/soft tissue infections, underlying predisposing factors were examined as follows: Twenty-five patients had skin abscesses due to pilonidal sinus, one patient had purulent discharge around percutaneous endoscopic gastrostomy (PEG), one patient had purulent discharge around tracheostomy site, one patient had purulent discharge from C/S scar, one patient developed a tooth abscess after dental filling, three patients had tooth abscesses due to dental caries, one patient had an infection related to a thyroglossal cyst, one patient had an infection related to a branchial cleft cyst, one patient had an infection related to preauricular sinus, four patients developed omphalitis based on umbilical granuloma, and two patients had paronychia secondary to ingrown toenails. One patient developed a skin abscess at the surgical site following appendectomy. Among patients with intra-abdominal abscesses, 7 patients developed abscesses in the abdomen after appendectomy, and SAG was isolated in cultures obtained. No predisposing factor for infection was found in the remaining 41 patients.

All patients in the cohort recovered and there were no deaths. Drainage was applied to 70 patients (74.4%). Drainage was required in 25 patients (69.4%) with *S. anginosus*, 36 patients (78.3%) with *S. constellatus* and 9 patients (81.8%) with *S. intermedius*. Ten patients required repeated drainage procedures. The SAG species grown in these patients were S.constellatus in 5 patients and S.anginosus in 5 patients.

**Table 1.** Distribution of patients with SAG infection according to clinical presentation and SAG type

| Infection site | *S. Anginosus* n (%) | *S. Constellatus* n (%) | *S. Intermedius* n (%) | Total number of strains |
|---|---|---|---|---|
| Skin-soft tissue infection | | | | |
| Gluteal/sacral abscess | 6 (50.0) | 4 (33.3) | 2 (16.6) | 12 |
| Skin abscess due to ingrown hair or pilonidal sinus | 8 (32.0) | 17 (68.0) | 0 (0) | 25 |
| Omphalitis | 4 (57.1) | 2 (28.5) | 1 (14.2) | 7 |
| Other (paronychia, bursitis, postauricular abscess, puru-lent discharge around PEG or tracheostomy or surgical site infections) | 7 (46.7) | 8 (53.3) | 0 (0) | 15 |
| Head and neck infections | | | | |
| Deep neck infection | 3 (27.2) | 4 (36.3) | 4 (36.3) | 11 |
| Brain abscess | 0 (0) | 1 (50.0) | 1 (50.0) | 2 |
| Orbital abscess | 0 (0) | 1 (25.0) | 3 (75.0) | 4 |
| Dental abscess | 5 (62.5) | 3 (37.5) | 0 (0) | 8 |
| Otitis | 0 (0) | 2 (100) | 0 (0) | 2 |
| Intraabdominal abscess | 3 (42.8) | 4 (57.1) | 0 | 7 |
| Total no. of strains of each species identified | 36 | 46 | 11 | 93 |

SAG: Streptococcus anginosus; PEG: Percutaneous endoscopic gastrostomy.

**Table 2.** Antibiotic susceptibility rates of SAG isolates

| | Susceptible % | Intermediate % | Resistant % |
|---|---|---|---|
| Ampicillin | 88.2 | 2.1 | 9.7 |
| Sulbactam-ampicillin | 91.4 | 4.3 | 4.3 |
| Ceftriaxone | 65.6 | 0 | 34.4 |
| Cefotaxime | 81.7 | 0 | 18.3 |
| Clindamycin | 89.2 | 0 | 10.8 |
| Linezolid | 90.4 | 7.5 | 2.1 |
| Vancomycin | 100 | 0 | 0 |

The median duration of antibiotic treatment for the patients was 11 days (IQR: 10-15.75 days). In 10 patients (10.6%), treatment was changed because the culture results showed resistance to the empirically started antibiotic. Ten patients (10.7%) recovered with drainage alone, without antibiotic therapy. The antibiotic susceptibility rates are shown in Table 2. SAG bacteria were highly susceptible to sulbactam-ampicillin, vancomycin, and linezolid.

## Discussion

In the presented study, within the SAG, *S. constellatus* was the most commonly isolated species, followed by *S. anginosus*. The most frequent site of infection was the skin and soft tissue. More than three-quarters of the patients required surgical drainage.

*S. constellatus* and *S. anginosus* were isolated from clinical samples at approximately equal frequencies, each being four times more common than *S. intermedius*.[11] In a study involving 463 cultures positive for the SAG, *S. anginosus* was isolated in 54.86% of cases, *S. constellatus* in 37.37%, and *S. intermedius* in 7.77%.[4] Similarly, in this study, *S. intermedius* was significantly less frequently isolated compared to S. constellates and *S. anginosus*.

In a study of 332 adult patients with SAG growth over 5 years, the most common site of infection was skin and soft tissue, with a rate of 72%.[5] In the study, which included both adult and child patients, the most common site of infection was the abdomen, followed by the chest, ear, nose and throat.[4] Different studies have reported different results regarding the most common site of infection caused by each SAG species. One series reported that *S. constellatus* (73%) or *S. intermedius* (86%) were more likely to cause deep abscesses than *S. anginosus* (19%). *S. constellatus* has been reported to be the most common cause of skin/soft tissue infections.[12] In another study, *S. constellatus* was more likely to cause infections in the thorax than in other parts of the body; *S. anginosus* was closely associated with perianal abscesses; *S. intermedius* was most commonly isolated in cranial infections.[4] In a study of 133 cases of SAG bacterial infections, *S. intermedius* was isolated significantly more often in head and neck infections, *S. anginosus* and *S. constellatus* in intra-abdominal infections.[9] In presented study, the most common site of infection was skin and soft tissue. In accordance with the literature, *S. constellatus* was most isolated from skin and soft tissues. The number of deep tissue infections (deep neck infection, intra-abdominal abscess, brain abscess) was low, it was therefore not possible to make an assessment between the groups. When examining patients with infections caused by *S. intermedius*, it was found that it was more frequently isolated from deep tissue infections, while skin and soft tissue infections were less common.

The incidence of bacteremia was reported to be 6% in one study of SAG infection. In another series, blood was identified as the second most frequently isolated sample type for SAG.[5,11] More than one-third of SAG infections caused by *S. intermedius* were found to have bacteremia.[11] In 61% of bacteremia cases, there was no primary infection site. For patients with a primary infection site, the primary focus was identified as liver abscess, osteomyelitis, intra-abdominal abscess, lower extremity soft tissue abscess, and complicated urinary tract infection.[5] In this study, two patients presented with bacteremia, each originating from a distinct primary site of infection outside of the bloodstream. Among patients for whom blood cultures were requested, the frequency of bacteremia was found to be 7.7%, which supports the literature data.

An increase in acute complicated sinusitis and otitis associated with the SAG has been reported.[7,12] In pediatric patients, SAG rhinosinusitis has a significantly higher likelihood of leading to severe intracranial complications and neurological disorders compared to infections caused by other bacteria.[1] In children, intracranial infections caused by SAG related to sinusitis, otitis media, and mastoiditis tend to have a more severe clinical course and a higher likelihood of requiring neurosurgical intervention.[7] In a series of 95 pediatric patients with complicated otitis/sinusitis caused by SAG, *S. intermedius* was most commonly isolated (80%), followed by *S. constellatus* (12.6%) and *S. anginosus* (7.4%).[6] In another series containing 153 strains from different laboratories, 21 strains were isolated from the central nervous system (CNS); 20 strains were from brain abscesses, and one was from cerebrospinal fluid. Of the strains isolated from the CNS, 2 (10%) were *S. anginosus*, 1 (5%) was *S. constellatus* and 18 (86%) were *S. intermedius*. These results support an association of *S. intermedius* with infections involving the CNS.[13] In patients with intracranial infections associated with sinusitis, otitis media, and mastoiditis, 97.4% underwent

surgical intervention, and 34.4% required multiple surgical encounters due to SAG bacteria.[7] In this cohort, there were two patients observed with brain abscess secondary to sinusitis, with *S. intermedius* cultured from one abscess and *S. constellatus* from the other. In these patients, the brain abscess was drained once and then a second surgical intervention was performed by neurosurgery because the size of the abscess had grown again, and the clinical findings had worsened.

Streptococcal strains belonging to the SAG are reported to be almost universally susceptible to penicillin, ampicillin, ceftriaxone, cefotaxime, and vancomycin. However, susceptibility to macrolides, clindamycin, and/or tetracyclines has been found to be variable in some case series.[6,14,15] Penicillin susceptibility has been reported as 84%, with 15% of isolates being intermediately susceptible, and 1% resistant.[5] SAG, particularly *S. anginosus*, may be resistant to clindamycin.[13] Another important consideration when determining antibiotic therapy is that up to 70% of SAG infections are polymicrobial.[5] In this cohort, resistance rates were higher than those reported in the literature, such as ceftriaxone susceptibility 65% and cefotaxime 81%. These results may indicate that resistance rates are gradually increasing in SAG group bacteria.

Most abscesses required drainage. However, not all members of this group cause abscesses with the same frequency.[11] While simple incision and drainage along with appropriate antibiotic therapy were sufficient for infections caused by *S. constellatus* or *S. anginosus*, more extensive surgical drainage was required for infections caused by *S. intermedius*, both for therapeutic and diagnostic purposes. *S. intermedius* is considered the most pathogenic species within the SAG group due to its higher frequency of causing deep-seated infections, more frequent bacteremia, and often requiring more complicated drainage procedures.[11] Three-quarters of the cases required surgical drainage. Among these patients, the need for drainage was most common in patients with *S. intermedius* infection, at 81% of cases. In the presented study, three-quarters of the cases required surgical drainage. Several patients recovered with drainage alone, without antibiotics. The need for drainage was most common in patients with *S. intermedius* infection, at 81% of cases. However, *S. intermedius* was not etiological in any patient undergoing multiple surgical drainage.

## Conclusion

In conclusion, SAG bacteria primarily cause skin and soft tissue infections, but they are also capable of leading to more severe conditions, such as deep tissue infections and bacteremia. SAG infections often occur in the presence of an underlying predisposing factor. Surgical drainage is frequently required in the treatment of infections caused by SAG. As shown in our study, *S. constellatus* was the most frequently isolated species among the SAG, followed by *S. anginosus* and *S. intermedius*. The most common site of infection was skin and soft tissue, with a significant proportion of patients requiring surgical drainage. Notably, resistance rates to ceftriaxone and cefotaxime were higher than previously reported in the literature, suggesting a potential increase in antimicrobial resistance among SAG bacteria. Despite these challenges, all patients in this cohort recovered, highlighting the effectiveness of appropriate antibiotic therapy and surgical intervention when necessary. Clinicians should keep in mind that severe infections caused by SAG, such as brain abscesses, may require multiple instances of drainage.

### Disclosures

**Ethics Committee Approval:** The study was approved by the Ankara Bilkent City Hospital Ethics Committee (date: 24.04.2024, no: 1-24-170).

**Conflict of Interest:** None declared.

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