

# Clinical Features and Outcomes of *Streptococcus anginosus* Group Infective Endocarditis: A Multicenter Matched Cohort Study

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**Background.** Although *Streptococcus anginosus* group (SAG) endocarditis is considered a severe disease associated with abscess formation and embolic events, there is limited evidence to support this assumption.

**Methods.** We performed a retrospective analysis of prospectively collected data from consecutive patients with definite SAG endocarditis in 28 centers in Spain and Italy. A comparison between cases due to SAG endocarditis and viridans group streptococci (VGS) or *Streptococcus gallolyticus* group (SGG) was performed in a 1:2 matched analysis.

**Results.** Of 5336 consecutive cases of definite endocarditis, 72 (1.4%) were due to SAG and matched with 144 cases due to VGS/SGG. SAG endocarditis was community acquired in 64 (88.9%) cases and affected aortic native valve in 29 (40.3%). When comparing SAG and VGS/SGG endocarditis, no significant differences were found in septic shock (8.3% vs 3.5%,  $P = .116$ ); valve disorder, including perforation (22.2% vs 18.1%,  $P = .584$ ), pseudoaneurysm (16.7% vs 8.3%,  $P = .108$ ), or prosthesis dehiscence (1.4% vs 6.3%,  $P = .170$ ); paravalvular complications, including abscess (25% vs 18.8%,  $P = .264$ ) and intracardiac fistula (5.6% vs 3.5%,  $P = .485$ ); heart failure (34.7% vs 38.9%,  $P = .655$ ); or embolic events (41.7% vs 32.6%,  $P = .248$ ). Indications for surgery (70.8% vs 70.8%;  $P = 1$ ) and mortality (13.9% vs 16.7%;  $P = .741$ ) were similar between groups.

**Conclusions.** SAG endocarditis is an infrequent but serious condition that presents a prognosis similar to that of VGS/SGG.

**Keywords.** infective endocarditis; *Streptococcus anginosus*; viridans group streptococci; *Streptococcus gallolyticus*.

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Infective endocarditis is one of the most life-threatening infections encountered in clinical practice and still represents a significant diagnostic and therapeutic challenge. About 40%–50% of patients with endocarditis require valve surgery at some point during the clinical course and mortality remains around 20%–25% in the first year after diagnosis [1].

In recent years, epidemiological changes in endocarditis have been documented in high-income countries, with an increasing rate of episodes caused by staphylococci and enterococci [2, 3]. Nevertheless, streptococci are still a major cause of endocarditis, mostly in developing countries [4]. Concerning streptococcal endocarditis, there is a clear predominance of cases due to viridans group streptococci (VGS), whereas  $\beta$ -hemolytic streptococci [5] and *Streptococcus anginosus* group (SAG)

[1] are identified less often as causative agents. The species encompassing SAG (*Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*) are known for their propensity to cause pyogenic infection and abscess formation in the head, neck, or abdomen. SAG can also cause bacteremia and, more rarely, endocarditis [6, 7].

Although endocarditis caused by SAG is thought to be associated with valve destruction, abscess formation, and embolic events [8], little information is available to support the assumption that it is more severe than other causes. We therefore aimed to characterize the main clinical features and outcomes of endocarditis caused by SAG and compared this with endocarditis and cases due to VGS or *Streptococcus gallolyticus* group (SGG) in a large cohort of patients with infective endocarditis.

## METHODS

### Patient Population and Data Collection

This was a large multicenter cohort study of consecutive adult patients with a definite diagnosis of endocarditis at 27 different Spanish hospitals (24 of them included within the Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España [GAMES] prospective cohort) and 1 Italian hospital. GAMES is a prospective registry into which multidisciplinary teams prospectively record all consecutive episodes of endocarditis since 2008 [9]. We therefore performed a retrospective analysis of prospectively collected data for the period 2008–2017, using a standardized case report form. Data included demographic and clinical variables, echocardiography findings, treatment, and outcomes, namely septic shock, valvular and paravalvular complications, heart failure, embolic events, indication for surgery, and mortality.

We analyzed all cases of definite endocarditis due to SAG and compared these with cases due to VGS or SGG using a 1:2 matched analysis. Matching was performed according to the type of valve (native or prosthetic), patient's sex, age ( $\pm 5$  years), year of diagnosis, and when feasible, hospital. Episodes of device-related infection (pacemaker and implantable defibrillators) and isolated right-side valve endocarditis were excluded.

### Definitions

Definite infective endocarditis was defined according to the modified Duke criteria [10, 11]. Acquisition was categorized as community-acquired or non-community-acquired, with the latter including nosocomial-acquired and health care-associated infections [12]. All patients were followed up for up to 1 year and were considered cured in the absence of relapse or death. Relapse during follow-up was defined as positive blood cultures with the same microorganism. A new episode of endocarditis caused by a different microorganism was classified as a reinfection. Embolic events were defined as radiological findings consistent with ischemia of a major organ, either symptomatic

or asymptomatic. Request for imaging tests was made at the discretion of the treating physicians. Acute kidney injury was defined as an abrupt decrease in kidney function with an increase of at least 1.5-fold in serum creatinine levels. Heart conduction disorders were defined as newly identified auriculoventricular blockage or heart bundle blockage. Septic shock was defined as hypotension persisting despite adequate fluid resuscitation [13, 14]. Indication for surgery was considered for heart failure due to valve regurgitation, intracardiac complications, or signs of uncontrolled infection, as listed in both the European and US guidelines [11, 15]. Overall mortality was defined as all-cause death during follow-up. Endocarditis-related mortality was defined as death during active antibiotic treatment at initial hospitalization or when occurring as a complication of valve surgery.

### Microbiological Identification

Identification of microorganisms to the species level was performed according to standard methods in each participating center [16]. Before 2011, bacteria isolated from blood culture isolates were identified using conventional biochemical tests or by 16S polymerase chain reaction and sequencing in cases of inconclusive results. Since 2011, isolates have been identified using matrix-assisted laser desorption/ionization–time of flight in the majority of the participant hospitals. Viridans group streptococci included *Streptococcus mitis* group (*S mitis*, *S oralis*, *S sanguinis*, *S parasanguinis*, *S gordonii*), *Streptococcus mutans* group (*S mutans*), and *Streptococcus salivarius* group (*S salivarius*). *Streptococcus gallolyticus* group included 4 subspecies: *gallolyticus*, *pasteurianus*, *infantarius*, and *lutetiensis*. *Streptococcus anginosus* group included *S anginosus*, *S constellatus*, and *S intermedius*. Antibiotic susceptibility was evaluated according to the Clinical and Laboratory Standards Institute recommendations.

### Statistical Analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as mean and standard deviation (SD). Qualitative variables were compared using  $\chi^2$  or Fisher exact tests, and quantitative variables were compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. Statistical significance was set at  $P < .05$ , and all *P* values were 2-sided. Analyses were performed using IBM SPSS version 20 (IBM Corporation, Armonk, New York).

### Ethical Considerations

This observational study was conducted in accordance with the Declaration of Helsinki and was approved by the regional ethics committee (Comité Ético de Investigación Clínica Regional de la Comunidad de Madrid, approval code 07/18). To protect personal privacy, identifying information in the electronic database was encrypted for each patient. Written informed consent was obtained from all patients reviewed in the GAMES cohort. Informed consent was waived by the

ethics committee in each of the Barcelona Endocarditis Study Team (BEST) participating hospitals because no intervention was involved and no patient-identifying information was included.

## RESULTS

### Clinical Characteristics and Outcomes of SAG Endocarditis

During the study period, 5336 episodes of definite endocarditis were recorded in the participating hospitals. Of these, 72 cases (1.4%) were due to SAG, and these cases were matched with 144 controls of patients with VGS or SGG endocarditis. Characteristics by infective agent are detailed in Tables 1 and 2. Most cases of SAG (76%) occurred in men, and the mean age was 67 years (SD, 16 years). Most cases were community-acquired (90%) and affected native valves (80.6%). The aortic valve was involved most often (40.3%), followed by the mitral valve (38.9%) and the aortic and mitral valves combined (19.4%).

New valve regurgitation developed in 20 (27.8%) patients, with severe mitral regurgitation being the most frequent. Notably, 15 patients (20.9%) suffered some form of intracranial hemorrhage and 14 (19.4%) suffered splenic emboli. Acute heart failure occurred in 34.7%, with 26.4% of cases having a New York Heart Classification III or IV. Acute kidney injury

occurred in 20.8%, heart conduction disorders in 15.3%, and septic shock in 8.3%, but there were no cases of symptomatic osteoarticular involvement.

All patients received  $\beta$ -lactams as backbone antibiotic therapy, in 37 cases (51%) in synergic combination with gentamicin. The mean antibiotic treatment length was 34.5 days (SD, 12.6 days). Although more than two-thirds of cases had an indication for surgery, it was eventually not performed in 14% due to a poor prognosis and/or lack of patient consent. There was an elective indication in 33% of surgeries. Ultimately, 83% of cases were deemed to have been cured. Overall mortality occurred in 10 patients (14%), all cases considered endocarditis-related mortality due to peri- or postoperative complications, severe bleeding, multiorgan failure, and septic or cardiogenic shock.

### Microbiology

The most frequently isolated microorganism in SAG endocarditis was *S anginosus* (n = 40 [55%]), followed by *S constellatus* (n = 15 [20%]) and *S intermedius* (n = 7 [10%]). In 10 (14%) cases, a SAG microorganism was isolated but not identified to the species level. Among the cases of VGS/SGG endocarditis, *S mitis* was the most commonly isolated microorganism (n = 40 [28%]), followed by *S oralis* (n = 22 [15%]), *S sanguinis* (n = 20 [14%]), and other species (Table 3). In 29 (20%) cases of VGS/

**Table 1. Comparative Analysis of General Characteristics and Clinical Manifestations of Infective Endocarditis Caused by *Streptococcus anginosus* Group and Viridans Group *Streptococci*/*Streptococcus gallolyticus* Group**

| Characteristic                            | SAG Endocarditis (n = 72) | VGS or SGG Endocarditis (n = 144) | PValue |
|---|---------------------------|-----------------------------------|--------|
| Male sex                                  | 55 (76.4)                 | 106 (73.6)                        | .846   |
| Mean age, y (SD)                          | 67 (16)                   | 68 (15)                           | .845   |
| Chronic lung disease                      | 12 (16.7)                 | 23 (16)                           | 1.000  |
| Diabetes mellitus                         | 16 (22.2)                 | 22 (15.3)                         | .283   |
| Chronic kidney disease                    | 6 (8.3)                   | 18 (12.5)                         | .491   |
| Age-adjusted Charlson index, y, mean (SD) | 3.8 (2.6)                 | 3.7 (2.5)                         | .960   |
| Acquisition                               |                           |                                   | .834   |
| Community-acquired                        | 64 (88.9)                 | 133 (92.4)                        | .552   |
| Non-community-acquired                    | 6 (8.4)                   | 9 (6.3)                           | .776   |
| Type of endocarditis                      |                           |                                   | .951   |
| Native                                    | 58 (80.6)                 | 118 (81.9)                        | .951   |
| Prosthetic                                | 14 (19.4)                 | 26 (18.1)                         | .951   |
| Affected valve                            |                           |                                   | .876   |
| Aortic                                    | 29 (40.3)                 | 60 (41.7)                         | .961   |
| Mitral                                    | 28 (38.9)                 | 52 (36.1)                         | .803   |
| Mitral and aortic                         | 14 (19.4)                 | 26 (18.1)                         | .950   |
| Embolitic phenomena                       | 30 (41.7)                 | 47 (32.6)                         | .248   |
| Central nervous system emboli             | 18 (25)                   | 22 (15.3)                         | .122   |
| Echocardiographic findings                |                           |                                   |        |
| Perforation or valve rupture              | 16 (22.2)                 | 26 (18.1)                         | .584   |
| Pseudoaneurysm                            | 12 (16.7)                 | 12 (8.3)                          | .108   |
| Abscess                                   | 18 (25)                   | 27 (18.8)                         | .264   |
| Intracardiac fistula                      | 4 (5.6)                   | 5 (3.5)                           | .485   |
| Prosthesis dehiscence                     | 1 (1.4)                   | 9 (6.3)                           | .170   |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: SAG, *Streptococcus anginosus* group; SD, standard deviation; SGG, *Streptococcus gallolyticus* group; VGS, viridans group streptococci.

**Table 2. Comparative Analysis of Treatment and Outcomes of Infective Endocarditis Caused by *Streptococcus anginosus* Group and Viridans Group Streptococci/*Streptococcus gallolyticus* Group**

| Characteristic                        | SAG Endocarditis (n = 72) | VGS or SGG Endocarditis (n = 144) | PValue |
|---------------------------------------|---------------------------|-----------------------------------|--------|
| Treatment duration, d, mean (SD)      | 34.5 (12.6)               | 33.8 (10.8)                       | .854   |
| Combination treatment with gentamicin | 37 (51)                   | 82 (56.9)                         | .494   |
| Complications                         |                           |                                   |        |
| Acute heart failure                   | 25 (34.7)                 | 56 (38.9)                         | .655   |
| Persistent bacteremia                 | 4 (5.6)                   | 8 (5.6)                           | .602   |
| Heart conduction disorder             | 11 (15.3)                 | 18 (12.5)                         | .739   |
| Acute kidney injury                   | 15 (20.8)                 | 44 (30.6)                         | .177   |
| Septic shock                          | 6 (8.3)                   | 5 (3.5)                           | .116   |
| Surgery                               |                           |                                   |        |
| Surgery indicated                     | 51 (70.8)                 | 102 (70.8)                        | 1      |
| Elective                              | 24 (33.3)                 | 47 (32.6)                         | 1      |
| Urgent                                | 12 (16.7)                 | 19 (13.2)                         | .618   |
| Emergent                              | 5 (6.9)                   | 7 (4.9)                           | .749   |
| Surgery indicated but not performed   | 10 (13.9)                 | 29 (20.1)                         | .348   |
| Prognosis <sup>a</sup>                |                           |                                   |        |
| Definitely cured                      | 60 (83.3)                 | 114 (79.2)                        | .584   |
| Overall mortality                     | 10 (13.9)                 | 24 (16.7)                         | .741   |
| Endocarditis-related mortality        | 10 (13.9)                 | 16 (11.1)                         | .711   |
| Relapse                               | 0                         | 1 (0.7)                           |        |
| Reinfection                           | 0                         | 2 (1.4)                           |        |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: SAG, *Streptococcus anginosus* group; SD, standard deviation; SGG, *Streptococcus gallolyticus* group; VGS, viridans group streptococci.

<sup>a</sup>There were 2 and 3 losses to follow-up among SAG and VSG/SGG endocarditis, respectively.

SGG endocarditis, identification was not performed to the species level.

#### Comparative Analysis of SAG and VGS/SGG Endocarditis

Tables 1 and 2 show the comparison between SAG and VGS/SGG endocarditis. There were no statistically significant differences in either valve involvement (perforation: 22.2% vs 18.1%,  $P = .584$ ; pseudoaneurysm: 16.7% vs 8.3%,  $P = .108$ ; prosthesis dehiscence: 1.4% vs 6.3%,  $P = .170$ ) or paravalvular complications (abscess: 25% vs 18.8%,  $P = .264$ ; intracardiac fistula: 5.6% vs 3.5%,  $P = .485$ ). Equally, no significant differences were detected between SAG and VGS/SGG endocarditis when comparing the rate of acute heart failure (34.7% vs 38.9%,  $P = .655$ ), heart conduction disorders (15.3% vs 12.5%,  $P = .739$ ), septic

shock (8.3% vs 3.5%,  $P = .116$ ), indication for surgery (70.8% vs 70.8%,  $P = 1$ ), or overall mortality (13.9% vs 16.7%,  $P = .741$ ). There was 1 case of relapse due to *S. oralis*. No molecular typing was performed.

#### DISCUSSION

In this largest study of SAG endocarditis to date, we found that SAG accounted for 1.4% of all definite cases of endocarditis in our cohort. This figure concurs with that reported in a previous study of 18 patients [17]. Also in accordance with previous observations, we found that *S. anginosus* was the most commonly identified causative species in SAG endocarditis [8, 18].

Controversy remains about the true virulence of SAG in infective endocarditis. Some sporadic case reports depict SAG endocarditis as an aggressive infection with frequent intracardiac complications, embolic events, and abscess formation [19–21]. In a retrospective study of 56 cases of endocarditis caused by  $\beta$ -hemolytic streptococci, 29 cases of SAG endocarditis had a less aggressive presentation and fewer extracardiac complications [1]. However, the conclusions in previous studies are limited by the limited by the small number of cases of endocarditis caused by SAG.

We observed no statistically significant differences when comparing SAG with VGS/SGG endocarditis regarding either local complications (valve perforation or abscess, pseudoaneurysm, prosthesis dehiscence, or intracardiac fistula) or systemic

**Table 3. Distribution of Viridans Group Streptococci or *Streptococcus gallolyticus* Group Isolates Causing Endocarditis, by Species**

| Species of Microorganism                          | Frequency (%) |
|---|---------------|
| <i>Streptococcus mitis</i>                        | 40 (27.8)     |
| Nonidentified <i>Streptococcus viridans</i> group | 29 (20.1)     |
| <i>Streptococcus oralis</i>                       | 22 (15.3)     |
| <i>Streptococcus sanguinis</i>                    | 20 (13.9)     |
| <i>Streptococcus salivarius</i>                   | 12 (8.3)      |
| <i>Streptococcus mutans</i>                       | 9 (6.3)       |
| <i>Streptococcus gordonii</i>                     | 8 (5.6)       |
| <i>Streptococcus gallolyticus</i> group           | 3 (2.1)       |
| <i>Streptococcus parasanguinis</i>                | 1 (0.7)       |



complications (heart failure and septic shock). Similarly, we found no differences in the proportion of patients with surgical indications nor in mortality. These results are consistent with those of a previous study in which SAG endocarditis had a comparable prognosis to VGS/SGG endocarditis [17]. It could be hypothesized that prior observations reporting a higher virulence of SAG endocarditis may have been biased toward describing the most severe cases. It should be noted, however, that higher rates of pseudoaneurysms, intracardiac abscess, and central nervous system emboli were actually identified, although without achieving statistical significance. Anatomic damage and prognostic differences may ultimately be subtle and difficult to detect; thus, the non-statistically significant differences observed could reflect a type II statistical error due to the limited number of SAG endocarditis cases in our cohort.

Our study has some limitations that should be acknowledged. Due to its retrospective design, some information such as the formation of extracardiac abscesses was not available for comparison between groups. Moreover, the small number of cases with certain complications, such as prosthesis dehiscence or intracardiac fistula, diminishes the power of these analyses. On the other hand, the well-known difficulties for the accurate identification of streptococcal species and some changes in the microbiological tools used for this task throughout the study period should be recognized as another potential limitation. We believe, however, that the multicenter nature of this study and the contemporary period of data collection strengthen our results.

In conclusion, SAG endocarditis is an infrequent but serious condition that follows a similar clinical course to VGS/SGG endocarditis, regarding valvular complications and prognostic variables such as indication for surgery or endocarditis-related mortality.

## Appendix

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## Notes

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