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Clinical and microbiological profile of Viridans group streptococcal bacteraemia; experience from South India

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SUMMARY

Background: Viridans Group Streptococci (VGS) are a group of distinct species that can cause bacteraemia and other invasive infections. They are also among the common organisms causing infective endocarditis. Data on the epidemiology and clinical profile of VGS is limited, especially from India.
Methods: We conducted an electronic medical record-based retrospective analysis of patients with VGS bacteraemia admitted to our hospital between January 2012 to December 2021. Blood cultures were incubated by BacT/ALERT system and bacterial identification and susceptibility testing were done by using the VITEK 2 microbial identification system. Susceptibility test reporting was as per Clinical and Laboratory Standards Institute (CLSI) guidelines. The incidence, clinical profile, source of bacteraemia, co-morbidities and antimicrobial resistance among VGS bacteraemia were analyzed.
Results: VGS were isolated in 219 patients, accounting for 3.2% of positive blood cultures during the period studied. The median age of the patients was 58 years and 69% were males. Diabetes mellitus was the most common co-morbidity (55%) followed by chronic kidney disease and chronic liver disease. Patients with haematological malignancy and neutropenia were few. Intra-abdominal infections were the most common source of infection and was noted in 26%. Infective endocarditis was diagnosed in only 10% of the cases. *Streptococcus mitis* was the most common species isolated followed by *S. gallolyticus* and *S. sanguinis*. 9.58% of the isolates could not be identified up to the species level. Overall penicillin susceptibility was 71% and ceftriaxone susceptibility was 92%, with individual species variation. In-hospital mortality was 19%.
Conclusions: VGS are an important cause of bacteraemia and was associated with 19% mortality in our study. High rates of penicillin and ceftriaxone resistance are a reason of concern. Molecular diagnostics like matrix assisted laser desorption ionization-time of flight (MALDI-TOF) identification must be increasingly applied for species identification considering that a substantial number of isolates were not identified to species level.

Keywords: Viridans group streptococci, bacteraemia, infective endocarditis, *Streptococcus mitis*, *Streptococcus gallolyticus.*

INTRODUCTION

Lancefield group A streptococci (GAS, *Streptococcus pyogenes*) and group B streptococci (GBS, *Streptococcus agalactiae*) are considered the major pathogens amongst streptococci. But the non-group A that include C, G, F, D or group B

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streptococci, are a large group capable of causing significant disease, mainly endocarditis and are grouped under viridans group of streptococci (VGS) [1]. VGS are relatively avirulent, part of the normal microbiota of the oral cavity and gastro-intestinal (GI) tract. VGS comprises a number of distinct species that cause significant community-acquired invasive infections and infections in immune-compromised host with substantial morbidity and mortality. VGS are frequent pathogens in native valve infective endocarditis (IE) and late prosthetic valve endocarditis (PVE). In the pre-antibiotic era, VGS accounted for approximately 75% of cases of IE. Currently their relative frequency in IE has declined to as low as 20% [2]. This change in epidemiology largely reflects an increase in the number of patients acquiring nosocomial staphylococcal IE related to central venous catheters, intra cardiac devices or prosthetic valves and intra-venous drug use [2]. VGS are also commonly isolated in dental, hepatic, or GI abscesses.

There is a large amount of data on the occurrence, clinical profile and resistance pattern of GAS, GBS, pneumococci and enterococci while there is dearth of data on the rest of the streptococcus species, notably from India. A major impediment to the study of VGS has been the inability to consistently and accurately assign VGS strains to specific species, which has resulted in numerous changes in species designation and classification schemes over time. Automated systems have considerable limitations in VGS species identification and needs to be verified by MALDI-TOF system [3-5]. Thus, it is difficult to determine the true burden of VGS infection and clearly understand the clinical characteristics of such infections. Increasing incidence of drug resistance among these streptococcal isolates, not only to macrolides and clindamycin, but even to penicillin and cephalosporins is also of concern. Given the incidence of invasive streptococcal infections, their distinct clinical presentations, and increasing antibiotic resistance, speciation of this heterogeneous group of bacteria is important for optimal clinical management and to improve understanding of VGS epidemiology. With this background, we undertook this study to understand the epidemiology, clinical profile and outcomes of patients with bacteraemia due to VGS.

MATERIALS AND METHODS

We conducted a retrospective analysis of patients with VGS bacteremia admitted to our 750 bedded tertiary care hospital between January 2012 to December 2021, after institutional ethical committee approval. Patients with individual unduplicated VGS blood isolates were enrolled. Bacteraemia due to GAS, GBS, pneumococci and enterococci were excluded. Clinical and laboratory characteristics of the patients were retrieved from the electronic medical record. We looked at the incidence, clinical profile, source of bacteraemia, co-morbidities, antimicrobial resistance among patients with VGS bacteraemia.

Species identification and susceptibility reporting of the blood cultures were done by automated system, BacT/ALERT. Positive samples were inoculated into blood agar, chocolate agar, and MacConkey agar and incubated at 37°C. Once sufficient growth was noted, bacterial identification and susceptibility testing were done by using the VITEK 2 microbial identification system. Susceptibility test reporting was as per Clinical and Laboratory Standards Institute (CLSI) M100 guidelines and reported based on MIC interpretation as susceptible, intermediate and resistant.

RESULTS

A total of 253,419 blood culture samples were processed during the 10 years study period and positive culture was noted in 6836 samples (2.7%). VGS isolates were noted in 219, 3.2% of the positive blood culture samples. The median age of patients was 58 years (IQR: 45-69 years) and 69% were males. Diabetes mellitus (n=117, 55%) was the most common co-morbidity followed by chronic kidney disease (CKD, n=48, 22%) and chronic liver disease (CLD, n=44, 20%). Among those with CKD, 11 were on haemodialysis. Chronic neurological disease (n=32, 14.6%), solid organ malignancy (n=24, 10.9%), chronic lung disease (n=20, 9%), hematological malignancy (n=17, 7.8%) accounted for the rest. One-fourth of the patients (n=55) did not have any co-morbidity. Intra-abdominal infection was the commonest source of bacteraemia identified (n=56, 26%). followed by pulmonary infection (n=40, 18%), skin and soft tissue infection (SSTI, n=36, 16%). Infective endocarditis was noted only in 10% (n=22).

Other focus of infection included bone and joint (n=9), meningitis (n=9), vascular infection (n=4), tonsillitis (n=2), acute suppurative otitis media (n=1) and mastoiditis (n=1). No source was identified in 39 patients (18%). Among these, 16 were considered to have contaminants as the patients had no fever or signs of infection, and improved without appropriate antibiotics. 23 patients with primary bacteremia were considered to have true bacteremia as they had fever and multiple blood culture bottles flagged positive. These were considered to be secondary to gut translocation as majority had underlying neutropenia or CLD or abdominal malignancy.

Table 1 - Comparison of clinical parameters of patients with six commonly isolated VGS groups/species.

Clinical variables	*S. mitis (n=52), (24%)*	*S. gallolyticus ssp gallolyticus/ pasteurianus (n=40, (18%)*	*S. sanguinis n=31, (14%)*	*S. dysgalactiae, equisimilis n=23, (11%)*	*S. salivarius, S. alactolyticus S. infantarius n=22, (10%)*	*S. anginosus, S. constellatus, S. pharyngis n=21 (9.5%)*
Demography						
Age, Median (IQR)	58 (30-68)	61 (51-68)	50 (23-65)	69 (57-79)	51 (45-65)	62 (48-73)
Sex, male	36 (69)	26 (65)	26 (84)	11 (48)	16 (73)	16 (76)
Comorbidities						
DM	29 (57)	24 (60)	13 (42)	16 (70)	9 (41)	12 (57)
Heart failure	1 (2)	–	–	–	–	–
Chronic lung disease	6 (12)	1 (3)	4 (13)	4 (17)	1 (5)	–
Chronic liver disease	10 (19)	19 (48)	4 (13)	2 (9)	2 (9)	2 (10)
Neurological disease	10 (19)	2 (5)	5 (16)	4 (17)	2 (9)	1 (5)
Haematological malignancy (including febrile neutropenia)	–	8 (20)	–	4 (17)	–	–
Solid organ malignancy	4 (8)	6 (15)	2 (7)	2 (9)	2 (9)	5 (24)
Chronic kidney disease	13 (25)	6 (15)	5 (17)	10 (43)	5 (23)	1 (5)
Ongoing significant therapy						
Chemotherapy	1 (2)	6 (15)	–	4 (17)	3 (14)	–
Haemodialysis	1 (2)	–	2 (7)	3 (13)	2 (9)	–
Renal transplant and immune-suppression	1 (2)	1 (3)	–	2 (9)	–	–
Source of infection						
Intra-abdominal infection	9 (17)	21 (53)	7 (23)	–	6 (27)	8 (38)
Pulmonary infection	15 (29)	–	7 (23)	2 (9)	5 (23)	1 (5)
SSTI	4 (8)	5 (13)	2 (6)	15 (65)	3 (14)	2 (10)
IE	6 (12)	1 (3)	6 (19)	–	–	3 (14)
Bone and joint	5 (10)	–	1 (3)	2 (9)	–	1 (5)
Meningitis	4 (8)	1 (3)	4 (13)	–	–	–
Vascular infection	1 (2)	–		1 (4)	1 (5)	–
Tonsillitis	1 (2)	–		–	–	1 (5)
ASOM	1 (2)	–		–	–	–
Mastoiditis	–	–		–	–	1 (5)

Abbreviations: DM: Diabetes Mellitus, SSTI: Skin and Soft Tissue Infections, IE: Infective Endocarditis, ASOM: Acute Suppurative Otitis Media.

Streptococcus mitis group was the most common (n=52, 24%) isolate (Table 1) followed by *Streptococcus gallolyticus* group, Lancefield group D (n=40, 18%). *Streptococcus sanguinis* group was the third most common (group C, G) (n= 31, 14%), followed by *Streptococcus dysgalactiae* group (n=23, 11%), *Streptococcus salivarius* group (n=22, 10%), and *Streptococcus anginosus* group (n=21, 9.5%). Twenty-one isolates were not identified to species level.
Twenty-eight patients (12.8%) belonged to paediatric age group (<18 years). The median age of the pediatric patients was 5 years (IQR 3-8 years). Two had cancer related neutropenia. *S. mitis* (n=11) was the most common species isolated followed by *S. sanguinis* (n=9).
Antibiotic susceptibility of the isolates is depicted in the Figure 1. In some isolates which were uniformly susceptible to penicillin, ampicillin and ceftriaxone, vancomycin susceptibility was not reported, though it was tested. Vancomycin susceptibility report could be retrieved in 44 isolates only. Overall penicillin susceptibility was 71%, ampicillin 76%, ceftriaxone 92%, with individual species variations. Susceptibility to erythromycin and clindamycin was poor; 45% and 66% respectively. 41 (19%) patients expired, 169 (77%) improved and 9 patients were lost to follow-up.
Patient characteristics, clinical manifestations, and outcomes were compared between the 6 commonly occurring species, *S. mitis* group, *S. gallolyticus* group, *S. sanguinis* group, *S dysgalactiae* group, *S. salivarius* group and *S. anginosus* group (Table 1) and is discussed below.

S. mitis

S. mitis was the most common species isolated (n=52, 24%). The median age of patients with *S. mitis* infection was 58 years (IQR: 30-68 years) and the majority were males (69%). The most common identified focus of infection was pulmonary infection (n=15, 29%). Other site of infections included IE (n=6, 12%), bone and joint (n=5, 10%). Fifty-seven percent of patients with *S. mitis* bacteraemia had diabetes mellitus. Other co-morbidities associated were renal impairment (25%), CLD and neurological disease was noted in 19% each; 5

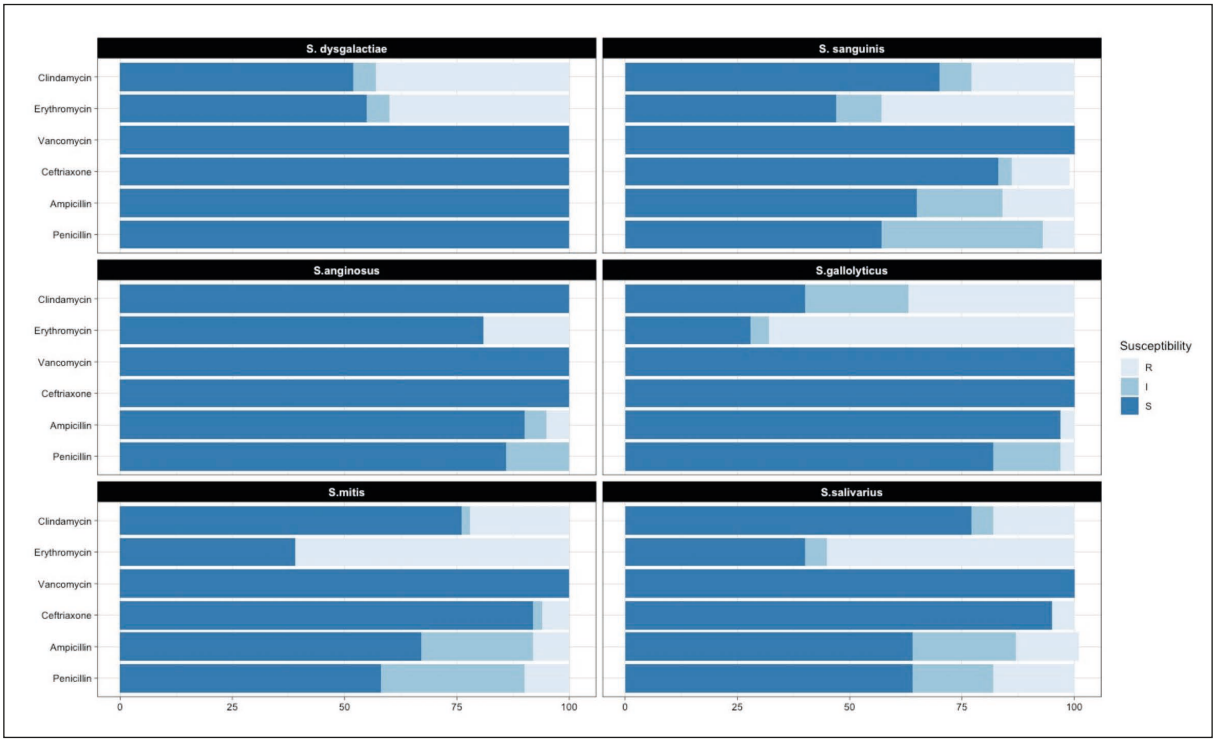

Figure 1 - Antibiotic susceptibilities of six commonly isolated VGS groups/species (R: resistant, I: intermediate susceptibility, S: susceptible; all expressed in percentages).

patients (9.6%) had underlying cancer, none had neutropenia. Only 58% isolates were susceptible to penicillin; resistance to penicillin was noted in 5 isolates, and intermediate susceptibility was noted in 17 isolates. Ampicillin susceptibility was 67%, while erythromycin and clindamycin susceptibility were 67% and 39% respectively. Ceftriaxone susceptibility was noted in 92% (Figure 1). The number of isolates tested for levofloxacin were 12 and 9 showed susceptibility. All the isolates were susceptible to vancomycin.

S. gallolyticus

S. gallolyticus was the second common species (18%) in our study. The majority were *S. gallolyticus subsp. pasteurianus.* The median age group was 61years (IQR: 51-68 years) and majority were males (65%). Intra-abdominal infection was the most common source of bacteremia. Only one had IE. CLD was the most common underlying co-morbidity (n=19, 48%). Eight patients had underlying haematological malignancy, while six had solid organ malignancy. However, none of them had colonic malignancy. Penicillin susceptibility was 82%; susceptibility of rest of the antibiotics were as follows: ampicillin: 97%, ceftriaxone: 100%, erythromycin: 28% and clindamycin: 40%.

S. sanguinis

The third most common species was *S. sanguinis* (14%). The median age of infection was 50 years (IQR 23-65); majority were males (n=26, 84%). Intra-abdominal (n=7, 23%) and pulmonary (n=7, 23%) infections were the common source. Six patients had IE, 5 (16%) had underlying neurological disease, chronic lung and liver disease were noted in 4 each (13%), 2 had underlying solid organ malignancy. Drug resistance was noted in *S. sanguinis*. Only 57% were susceptible to penicillin, 36% were intermediate susceptible and 7% were resistant. Ampicillin susceptibility was similar to penicillin and was noted in 65%, while erythromycin and clindamycin susceptibility were 47% and 70% respectively. Ceftriaxone susceptibility was noted only in 83%. Vancomycin susceptibility was reported for seven isolates, and all were susceptible.

S. dysgalactiae

S. dysgalactiae was the fourth most common species n=23 (11%). The median age of occurrence was 69 years (IQR: 57-79 years) and noted equally in both genders. Majority had SSTI as the focus of infection. Renal impairment was a common underlying disease. All isolates were susceptible to penicillin, ampicillin and ceftriaxone. Erythromycin and clindamycin susceptibility were 55% and 52% respectively.

S. salivarius

The fifth most common species identified was *S. salivarius* (n=22, 10%). The median age of occurrence was 51 years (IQR: 45-65 years) and occurred commonly in males n=16 (73%). Abdominal and pulmonary infection were the common site of infection. Renal impairment was the most common underlying illness. Penicillin and ampicillin susceptibility was 64%, while susceptibility for other antibiotics were as follows: ceftriaxone 95%, clindamycin 77% and erythromycin 40%.

S. anginosus

S. anginosus was isolated in 21 patients (9.5%), and median age of occurrence was 62 years (IQR: 48-73 years); majority were males (n=16, 76%). Abdominal infection was the common identified focus of infection, IE was noted in 3 patients. Susceptibility profile of *S. anginosus* was as follows- penicillin: 86%, ampicillin: 90%, ceftriaxone: 100, clindamycin: 100 and erythromycin: 81%.

Nutritionally variant streptococci (NVS)

In our study we found 6 NVS isolates: 4 *Granulicatella adiacens*, 1 *Granulicatella elegans*, 1 *Abiotrophia defectiva*. Two patients had SSTI and one had IE. No focus was identified in 3 patients and the isolates were considered as contaminants. None were neutropenic.

S. pseudoporcinus

Bacteremia due to *S. pseudoporcinus* was noted in 3 patients. One had orbital cellulitis, while 2 were considered contaminants.

DISCUSSION

Viridans streptococci accounted for 3.2% of blood culture isolates during the study period. The median age of patients was 58 year and 69% were males. Diabetes mellitus was the most common co-morbidity (55%). Almost one-fifth (18.7%) had an underlying cancer. Solid organ malignancy

was noted in 10.9% of patients and 7.8% of patients had underlying haematological malignancy. VGS was noted as an important cause of primary bacteraemia in neutropenic hosts. In previous studies, haematological malignancies were identified as a common co-morbidity and frequent occurrence of *S. mitis* bacteraemia in neutropenic or cancer hosts [6-9]. In the study by Shelburne SA et al. among 118 VGS strains causing bacteraemia in cancer patients, *S. mitis* (68 patients) and *Streptococcus oralis* (22 patients) were the most frequently identified strains [10]. In another study from Mexico, 43 patients with VGS bacteraemia in cancer patients were studied between 2013 and 2016. In this study group also *S. mitis* was the most common VGS isolated (n=20, 46.5%) [4]. This is contrast to our study, where we found *S. gallolyticus* as the most common pathogen in those with underlying solid or hematological malignancies. *S. gallolyticus* bacteraemia usually affects the elderly and has a strong association with colonic malignancy. This association is stronger for *S. bovis* biotype I (*S. gallolyticus subsp. gallolyticus*) when compared to *S. bovis* biotype II (*S. gallolyticus subsp. pasteurianus*) [11]. Bacteraemia in our study was more often caused by *S. bovis* II, underlying CLD was noted in nearly half the patients, none had colonic malignancy and only one had IE.

Among paediatric patients, we observed *S. mitis* as the most common species, though numbers were few. Basaranoglu et al. in his study analysed 53 VGS bacteraemia in paediatric patients with febrile neutropenia in haematology and bone marrow transplantation unit and found 34% were caused by *S. mitis/S. oralis* [12]. Patients with *S. salivarius* bacteraemia were associated with non-colon cancer and *S. sanguinis* with gastrointestinal carcinoma in previously published studies though we did not find any association in our study [13].

The majority of the patients with *S. dysgalactiae* had SSTI as source and this is similar to previous studies. *S. dysgalactiae subsp. equisimilis* disease can mimic *S. pyogenes* and can cause wound infection, erysipelas, and cellulitis, life-threatening necrotizing fasciitis and streptococcal toxic shock syndrome. Invasive forms of this infection are most commonly found in elderly patients with underlying comorbidities and skin breakdown. The case fatality in bacteraemia has been reported to be 15-18% [14].

S. anginosus group, though an oral commensal, differs from other VGS in its ability to cause invasive pyogenic infections like head and neck abscesses, visceral abscesses and behaves like *Staphylococcus aureus* [15]. It is a rare cause of IE, but when it does, infection is often complicated by myocardial abscess with heart block [16]. We noted 8 cases of *S. anginosus* related abdominal infection, 2 had IE.

VGS are commonly associated with IE. Infective endocarditis was noted only in 10% of the patients and commonly caused by *S. sanguinis* and *S. mitis* group. In a study from Denmark, the risk of IE related to streptococcal species was studied in all patients with streptococcal bacteraemia from 2008 to 2017. Among 6506 cases with streptococcal bacteraemia, IE prevalence was 7.1% and was species dependent, with *S. mutans, S. gordonii, S. sanguinis, S. gallolyticus*, and *S. mitis/oralis* having the highest IE prevalence [17].

It is important to understand that VGS can also be commensals and frequently isolated in blood without clinical significance. In our study 7.3% of isolates were considered contaminants.

Viridans streptococci are usually susceptible to penicillin. Resistance, if present, is "relative resistance" and MICs are easily exceeded in blood and cardiac vegetations with the high-dose β-lactam therapies [18]. However, penicillin resistance is increasingly reported among VGS and variable between the species. In our study the overall non-susceptibility to penicillin was 29% and non-susceptibility to ceftriaxone was 8%. We found *S. dysgalactiae* to be 100% susceptible to penicillin while high rates of resistance among *S. mitis, S. sanguinis, S. salivarius* group was noted. This was similar to the study by Chun et al in which susceptibility of the streptococcal species to penicillin were as follows: *S. anginosus* 86%, *S. gallolyticus* 82%, *S. salivarius* 64%, *S. mitis* 58%, *S. sanguinis* 57%, respectively [19]. Resistance to erythromycin and clindamycin was high and susceptibility was only 45% and 66% respectively. High rates of penicillin resistance were noted among *S. mitis*, *S. sanguinis* and *S. salivarius* isolates in previous studies as well [4, 8, 10, 20].

Almost one fifth (19%) of patients affected by Group B Streptococcus bacteremia died, while 77% improved and 4% were lost to follow-up in our study. The mortality rates in previous studies were variable depending on the population and

species analyzed. Mortality was 15.1% in the study by Su TY et al. Longer stay in intensive care unit, underlying solid organ malignancy and shorter treatment duration were independent risk factors for 30-day mortality [5]. Marron A et al. observed a mortality of 30% in VGS bacteraemia in neutropenic patients with cancer [11+. In adult cancer patients with VGS bacteraemia, Spanik et al. observed a mortality of 20%. Fatality rates were higher in bacteraemia due to penicillin-resistant VGS when compared to penicillin-susceptible strains [21].

CONCLUSIONS

Understanding infections caused by VGS is difficult due to its complex classification, difficulty in identification to species level, paucity of data on clinical presentation and risk factors. Molecular diagnostics like MALDI-TOF identification must be increasingly applied for species identification as 9.58% were not identified to species level in our study. *S. mitis* was the most common VGS species noted in our study. Patients with haematological malignancy and neutropenia were less common. Intra-abdominal, pulmonary and skin and soft tissue infections were the most common source of bacteraemia while IE was noted only in 10% of patients. Penicillin and ceftriaxone resistance were noted commonly among *S. mitis, S. sanguinis and S. salivarius* group and it is important to be aware of antibiotic resistance rates when considering antibiotic choices in immune-compromised host and in IE.

Conflict of interests
None to declare.

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