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Original article

# Microbiology and clinical characteristics of viridans group streptococci in patients with cancer

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ABSTRACT

This study assessed the microbiology, clinical syndromes, and outcomes of oncologic patients with viridans group streptococci (VGS) isolated from blood cultures between January 1st, 2013 and December 31st, 2016 in a referral hospital in Mexico using the Bruker MALDI Biotyper. Antimicrobial sensitivity was determined using BD Phoenix 100 according to CLSI M100 standards. Clinical information was obtained from medical records and descriptive analysis was performed.

Forty-three patients were included, 22 females and 21 males, aged 42 ± 17 years. Twenty (46.5%) patients had hematological cancer and 23 (53.5%) a solid malignancy. The VGS isolated were *Streptococcus mitis*, 20 (46.5%); *Streptococcus anginosus*, 14 (32.6%); *Streptococcus sanguinis*, 7 (16.3%); and *Streptococcus salivarius*, 2 (4.7%). The main risk factors were pyrimidine antagonist chemotherapy in 22 (51.2%) and neutropenia in 19 (44.2%) cases, respectively. Central line associated bloodstream infection was diagnosed in 18 (41.9%) cases. Septic shock occurred in 20.9% of patients, with an overall mortality of 18.6%. Only four *S. mitis* revealed penicillin-resistance.

Our results are similar to those of other series, identifying these bacteria as emerging pathogens with significant morbidity and mortality in oncologic patients. The MALDI-TOF system increased the rate of VGS isolation in this population.



## Introduction

Viridans group streptococci (VGS) comprise five categories of microorganisms that are part of the human microbiome. They are usually found in oropharynx and in gastrointestinal and genitourinary tracts. These bacteria have been difficult to classify due to the variability and overlapping of their microbiological characteristics. They were originally named "*viridans*" (Latin for green) because they were α-hemolytic. However,

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their hemolysis is variable, as well as their Lancefield group (A, C, F, or G).

Traditionally described as commensal bacteria, the virulence of VGS was considered to be low. However, VGS can become opportunistic pathogens under common circumstances in patients with cancer, such as neutropenia, antimicrobial prophylaxis with fluoroquinolones, mucosal barrier injury, and high-dose chemotherapy, especially with cytarabine.[1] It is also important to consider that mortality due to VGS bacteremia ranges between 2 and 21%,[2] mainly as a result of septic shock and acute respiratory distress syndrome.

VGS have been difficult to study, since automated systems and molecular techniques such as 16S RNA sequencing have limitations in species identification.[3] The superoxide dismutase gene (*sodA*) is currently the most accurate method for distinguishing among VGS species.[4] Techniques with greatest availability, such as MALDI-TOF, are a reliable option for identification at the group level, although it can misidentify closely related species such as *Streptococcus mitis* and *Streptococcus pneumoniae*.[4]

Due to the challenge in identification, their clinical manifestations, distant foci, and outcomes have scarcely been described for each of the five groups. The best-known group is that of *Streptococcus anginosus*, which has been identified in invasive infections such as deep-seated abscesses and endocarditis. In the *S. anginosus* group, several virulence factors have been described, but there is no similar description for the remaining groups.

In the present study, we sought to describe the epidemiology, clinical syndromes, and outcomes of VGS bacteremia in a retrospective cohort of adult patients with cancer. The goal was to distinguish risk factors and clinical manifestations for each of the five VGS groups, identifying the antimicrobial susceptibility patterns in our setting.

## Methods

### *Study setting and cultures*

All patients from the Instituto Nacional de Cancerología (INCan) who had VGS isolated from blood between 01/01/2013 and 12/31/2016 were evaluated. INCan is a 135-bed cancer referral, teaching hospital for adult patients in Mexico City.

### *Microbiology*

Blood samples were cultured in BD BACTEC 9240 System™ (Becton Dickinson Microbiology Systems, USA), and plated on blood, chocolate and MacConkey agar using standard microbiological techniques. Isolated bacteria were identified using the Bruker Daltonics IVD MALDI Biotyper software package (version 2.2). The Brucker bacterial test standard (Bruker Daltonik) was used for calibration according to manufacturer's instructions. Identification scores ≥2.000 indicated species-level identification, scores of 1.700–1.999 indicated genus-level identification, and scores of <1.700 were considered unreliable.[3] Only microorganisms with scores ≥2 were included. Differentiation with *S. pneumoniae* was performed employing the optochin test. Antimicrobial resistance was determined in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines utilizing BD Phoenix™ 100 automated identification and susceptibility testing. Microbiological data was correlated with relevant clinical information from the patients' medical electronic records and nursing files. A standardized database was constructed and descriptive analysis was conducted. Student *t* test or Wilcoxon non-parametric tests was used for continuous variables. For qualitative variables, Fisher and $X^2$ tests were used as appropriate.

### *Definitions*

Information on infection sites were obtained from the diagnoses established in the clinical records. Central-line associated bloodstream infection (CLABSI), mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI) and primary bacteremia were classified using the U.S. Centers for Disease Control and Prevention (CDC)/National Nosocomial Infections Surveillance (NNIS)/Healthcare Infection Control Practices Advisory Committee definitions.[5]

## Results

During the study period from January 1, 2013 to December 31, 2016, a total of 10,417 blood cultures were drawn, among which, 1715 (16.5%) turned out positive. Of these, 44 blood cultures were positive for any VGS (2.6%), but only 43 patients were included, since two cultures were from a sole patient with persistent bacteremia. Twenty-two patients (51%) were female and 21 (49%), male. The mean age was 42 ± 17 years. Twenty (46.5%) patients had hematological malignancies and 23 (53.5%) a solid malignancy. The most frequent cancer was acute lymphoid leukemia ($n = 11$), followed by solid organ cancers of the digestive tract ($n = 9$). Six patients (13.9%) were obese, six (13.9%) had diabetes mellitus, and two (4.6%) had valvular heart disease.

The most common VGS isolated were *S. mitis*, 20 (46.5%); *S. sanguinis*, seven (16.3%), and *S. salivarius*, two (4.7%). No *S. mutans* were found. *S. anginosus* were isolated in 14 (32.6%) patients.

The most frequent risk factors related to bacteremia by a VGS were chemotherapy with pyrimidine antagonists ($n = 22$, 51.2%), severe neutropenia < 500 cell/mm$^3$ ($n = 19$, 46.5%), and steroid use ($n = 15$, 34.9%). Among 13 patients who had neutrophil counts less than 100 cells/mm$^3$ at diagnosis of bacteremia, nine were from the *S. mitis* group (69%). The risk factors identified in VGS are depicted in Table 1. The only significant differences between risk factors for *S. mitis* and non-mitis VGS bacteremia were the association of diabetes mellitus favoring non-mitis VGS with six patients *vs.* none in the *S. mitis* group ($p = 0.01$). For *S. mitis* bacteremia, the presence of hematological malignancy ($p = 0.02$) and treatment with pyrimidine antagonists ($p = 0.02$) were both statistically significant.

The frequency of distant infection sites is presented in Table 2. Significant correlation between VGS group and infection site was only found between *S. anginosus* and abdominal abscesses ($p = 0.01$).



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