Serious Complications of Bacteremia Caused by Viridans Streptococci in Neutropenic Patients with Cancer

Anna Marron, Jordi Carratalà, Eva González-Barca, Alberto Fernández-Sevilla, Fernando Alcaide, and Francesc Gudiol

We prospectively studied 485 episodes of bacteremia in neutropenic patients with cancer. Viridans streptococci caused a total of 88 episodes (18%). Ten (11%) of these 88 cases were associated with serious complications: acute respiratory distress syndrome (ARDS) plus septic shock (5 cases), ARDS (3), and septic shock (2). *Streptococcus mitis* was the species most frequently isolated (7 of 10 episodes). Four viridans streptococci showed a diminished susceptibility to penicillin (MICs ranged from 0.25 to 4 μg/mL), and 5 strains were resistant to ceftazidime (MICs ranged from 2 to >32 μg/mL). Patients with viridans streptococcal bacteremia (VSB) who developed serious complications were compared with patients with VSB without complications. Severe oral mucositis (70% vs. 32.5%, respectively; *P* = .036), high-dose chemotherapy with cyclophosphamide (60% vs. 25%, respectively; *P* = .043), and allogeneic bone marrow transplantation (40% vs. 10%, respectively; *P* = .040) were the only variables found to be significantly associated with the development of complications. Neither a specific species of viridans streptococci nor resistance to penicillin was associated with the occurrence of complications. The mortality rate was higher in case patients than in control patients (80% vs. 17.5%, respectively; *P* < .001). Serious complications associated with VSB occur mainly in patients receiving high-dose chemotherapy with cyclophosphamide before allogeneic bone marrow transplantation who develop severe oral mucositis; these complications are associated with a high mortality rate.

Viridans streptococci have become a significant cause of bacteremia in neutropenic patients with cancer [1–4]. These infections have traditionally been associated with limited morbidity, but serious complications such as septicemic shock and adult respiratory distress syndrome (ARDS) have been described sporadically in recent years [5–8]. Moreover, viridans streptococcal bacteremia (VSB) has been associated with the development of α-hemolytic streptococcal shock syndrome, which is characterized by shock, ARDS, rash, and acute renal failure [9, 10]. A combination of the effects of cytotoxic chemotherapy and the infection itself, either through production of an exotoxin or induction of the release of certain cytokines, has been suggested as a pathogenic mechanism. In particular, a high concentration of IL-6 has been found in patients who have VSB-associated shock [11].

The clinical features of patients with VSB at risk for developing serious complications have not been precisely defined to date. Recently, the emergence as well as the spread of multidrug-resistant strains of viridans streptococci is becoming an additional problem for empirical antibiotic therapy and prevention of these infections [12–17]. The aims of the present study were to determine the incidence, clinical characteristics, risk factors, antimicrobial susceptibility, and outcome of serious complications of VSB in adult neutropenic patients with cancer.

Patients and Methods

The study was conducted in a 1000-bed university hospital for adults in Barcelona, Spain. Prospective surveillance of all cases of bacteremia is regularly carried out at our institution, and all cases are recorded with use of a computer-assisted protocol. Prophylactic noroxacin is given orally (400 mg twice daily) to patients with hematologic malignancy who are neutropenic or those likely to develop cytotoxic therapy–induced neutropenia lasting >7 days. Cefazidime or imipenem plus amikacin was the empirical antibiotic regimen most commonly used to treat febrile episodes that occurred during the study period. Vancomycin was added to the therapeutic regimens of patients in whom infection with gram-positive bacteria was initially suspected and also those whose conditions had not improved after initial therapy for 48 hours or had worsened before that time. Bone marrow transplant recipients received high-dose chemotherapy with cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy) as conditioning regimens.

For the purposes of this study, we analyzed data on all episodes...
of VSB in neutropenic patients with cancer that were documented from January 1986 through December 1996. The diagnosis of VSB was established by the presence of ≥2 sets of blood cultures positive for viridans streptococci. Those cases in which a single blood culture yielded these bacteria were included only when signs of sepsis were present. Neutropenia was defined as a granulocyte count of <500 cells/mm³. Severe mucositis was defined as the presence of multiple ulcerations covering >25% of the oral mucosa. Serious complications of VSB included the following: septic shock (defined as a systolic blood pressure <90 mm Hg and evidence of peripheral hypoperfusion) and ARDS (defined as respiratory failure with bilateral pulmonary infiltrates and neither evidence of cardiac failure nor isolation of organisms from respiratory specimens). We defined α-hemolytic streptococcal shock syndrome as shock, ARDS, cutaneous rash, and acute renal failure.

To assess factors associated with the development of serious complications, we carried out a case-control study in which control patients were neutropenic patients with cancer and VSB without complications. Each case of VSB was matched with 4 control patients by date of infection (± 1 year). Viridans streptococci recovered from blood cultures were identified by phenotypic methods [18] and classified according to the taxonomy and nomenclature proposed by Bruckner and Colonna [19]. Antibiotic susceptibility testing (to determine MICs) was performed by a microdilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [20]. Susceptibility to penicillin was defined according to NCCLS criteria [21] as follows: susceptible (MIC of <0.12 µg/mL); intermediate resistant, MIC of 0.25–2 µg/mL; and highly resistant, MIC of ≥4 µg/mL. Viridans streptococci were considered resistant to extended-spectrum cephalosporins when the MIC was ≥2 µg/mL. Streptococcus pneumoniae ATCC 49619 and Staphylococcus aureus ATCC 29213 were used for quality control.

For analysis of categorical variables, we used the χ² test with Yates’ correction or Fisher’s exact test, as appropriate, and for analysis of continuous variables we used the Student’s t test. P < .05 was considered statistically significant.

### Results

During the study period, a total of 485 episodes of bacteremia in neutropenic patients with cancer were documented. Eighty-eight (18%) of these cases of bacteremia were caused by viridans streptococci. Strains were identified as Streptococcus mitis (72 cases), Streptococcus salivarius (7), Streptococcus sanguis (5), Streptococcus milleri (3), and Streptococcus mutans (2). One case of bacteremia was caused by S. mitis and S. salivarius. Results of antimicrobial susceptibility testing for these strains are shown in table 1.

Serious complications associated with VSB occurred in 10 (11%) of 88 episodes. The characteristics of the patients with these cases are detailed in table 2. The mean age of the patients was 38.5 years (range, 16–71 years). All patients had hematologic malignancies, and one-half had undergone bone marrow transplantation (allogeneic, 4; autologous, 1). All patients but one were severely neutropenic (granulocyte count, <100 cells/mm³) at the time of bacteremia. Bone marrow transplant recipients became bacteremic a mean of 8.6 days after transplantation (range, 5–13 days). In 8 patients (80%), complications occurred within 24 h of the onset of bacteremia. Serious complications were ARDS plus septic shock (5 patients), ARDS (3), and septic shock (2). Cutaneous rash was present in 3 case patients (30%); 1 patient had erythematous macules and papules scattered over the face and trunk, and the other two had generalized rash. Only 1 (10%) of 10 patients had all features of α-hemolytic streptococcal shock syndrome.

S. mitis was the most frequent causative agent (7 of 10 episodes). Four (36%) of 11 isolates showed a diminished susceptibility to penicillin (MICs ranged from 0.25 to 4 µg/mL), and 5 strains (45%) were resistant to ceftazidime (MICs ranged from 2 to >32 µg/mL). A highly penicillin-resistant strain (MIC, 4 µg/mL) of S. mitis was isolated from a patient with bacteremia and ARDS who had had a previous episode of bacteremia without complications that was caused by a susceptible strain. Empirical antibiotic therapy included appropriate antibiotics (vancomycin or imipenem) for all but 2 patients. Overall, 8 patients (80%) died after developing multiorgan failure. Two of these 8 had a fulminant course and died rapidly after bacteremia.

Results of the comparison between case patients (neutropenic patients with cancer and VSB who developed serious complications) and control patients (neutropenic patients with cancer and VSB without complications) are shown in table 3. The variables found to be significantly associated with complications were severe oral mucositis (70% vs. 32.5%, respectively; \(P = .036\)), high-dose chemotherapy with cyclophosphamide (60% vs. 25%, respectively; \(P = .043\)), and allogeneic bone marrow transplantation (40% vs. 10%, respectively; \(P = .040\)). Neither a specific species of viridans streptococci nor resistance to penicillin was associated with the occurrence of complications (\(P > .05\)). The mortality rate was significantly higher in case than in control patients (80% vs. 17.5%, respectively; \(P < .001\)).

### Discussion

Our prospective study involving a large series of adult neutropenic patients with cancer and VSB found that 11% of pa-

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC range, µg/mL</th>
<th>Susceptibility breakpoint</th>
<th>Susceptible strains, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>≤0.03 to 8</td>
<td>≤0.12</td>
<td>60</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≤0.12 to 16</td>
<td>≤1</td>
<td>76</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≤0.03 to &gt;256</td>
<td>≤1</td>
<td>44</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤0.12 to 4</td>
<td>≤1</td>
<td>93</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≤0.25 to &gt;32</td>
<td>≤0.5</td>
<td>64</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>≤0.25 to 1</td>
<td>≤4</td>
<td>100</td>
</tr>
</tbody>
</table>
Clinical outcomes among patients with VSB are frequently fatal, with mortality rates associated with VSB in neutropenic patients along with the emerging problems of resistance to antimicrobial agents have become a problem for current empirical regimens for febrile episodes. In our study, 36% of viridans streptococci isolated from patients with complications showed diminished susceptibility to penicillin, and more importantly, approximately one-half of these strains were resistant to ceftazidime (MIC, \( \geq 2 \mu g/mL \)), which is frequently administered as empirical therapy. Thus, at institutions where VSB is frequent and resistant strains are prevalent, empirical antibiotic treatment for febrile episodes should include drugs active against these strains, such as imipenem, fourth-generation cephalosporins, and vancomycin [12, 28]. Importantly, a recent study of the outcomes of bacteremia in patients with cancer and neutropenia found that patients with VSB who did not receive vancomycin as part of their initial empirical regimen were more likely to die than patients who did receive it [29].

Our study and other experiences [10], however, highlight the fact that in spite of appropriate empirical antibiotic coverage the mortality rate among patients with complicated cases of VSB is too high. Therefore, it can be speculated that antibiotic treatment is unable to modify the course of the events once the pathogenic mechanisms implicated in serious complications are triggered. We thus believe that adjunctive therapy with immunomodulating drugs might merit evaluation.

Over the last decade, quinolones have been widely used as a predisposing factor as long as it produces severe damage of oral mucosa, which is a major portal of entry for VSB [27].

The mortality rate among patients with VSB who develop complications is high. In fact, only 2 of 10 patients survived in the present study. The increase in morbidity and mortality rates associated with VSB in neutropenic patients along with the emerging problems of resistance to antimicrobial agents has become a problem for current empirical regimens for febrile episodes. In our study, 36% of viridans streptococci isolated from patients with complications showed diminished susceptibility to penicillin, and more importantly, approximately one-half of these strains were resistant to ceftazidime (MIC, \( \geq 2 \mu g/mL \)), which is frequently administered as empirical therapy. Thus, at institutions where VSB is frequent and resistant strains are prevalent, empirical antibiotic treatment for febrile episodes should include drugs active against these strains, such as imipenem, fourth-generation cephalosporins, and vancomycin [12, 28]. Importantly, a recent study of the outcomes of bacteremia in patients with cancer and neutropenia found that patients with VSB who did not receive vancomycin as part of their initial empirical regimen were more likely to die than patients who did receive it [29].

In our study, the most frequent complications associated with VSB were ARDS and septic shock, which occurred concomitantly in one-half of the patients. It is interesting to note that the complete features of \( \alpha \)-hemolytic streptococcal shock syndrome were observed only in one case. Thus, although this syndrome is regarded as a characteristic complication of VSB, it appears to be rather infrequent.

To our knowledge, only one previous study has specifically analyzed predisposing factors for the development of serious complications in patients with VSB [10]. In that study, which dealt with a population of bone marrow transplant recipients, only patients younger than 15 years of age were found to be at increased risk for developing shock. In fact, no complications were documented for adult patients. Our study found that severe oral mucositis, high-dose chemotherapy with cyclophosphamide, and allogeneic bone marrow transplantation were the only factors significantly associated with the development of complications. It should be noted that the administration of cyclophosphamide was identified as a predisposing factor for complications rather than the administration of cytosine arabinoside, which has been the drug more frequently related to the increase in streptococcal infections [1, 25]. Our finding concurs with a previous report describing five patients who had received cyclophosphamide therapy as a conditioning regimen for marrow transplantation and died of VSB and shock [26].

We therefore believe that any chemotherapy regimen might act as a predisposing factor as long as it produces severe damage of oral mucosa, which is a major portal of entry for VSB [27].

Table 2. Characteristics of 10 neutropenic patients with cancer who had viridans streptococcal bacteremia and developed serious complications.

<table>
<thead>
<tr>
<th>Age (y), sex</th>
<th>Underlying disease(s)</th>
<th>Predisposing factors</th>
<th>Streptococcus species isolated</th>
<th>MIC, µg/mL</th>
<th>Clinical presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>71, M</td>
<td>Lymphoma</td>
<td>Cyph therapy</td>
<td>( S. mitis )</td>
<td>0.06 0.25</td>
<td>Shock, ARDS</td>
<td>Empirical</td>
</tr>
<tr>
<td>51, M</td>
<td>CML, BMT</td>
<td>Cyph therapy</td>
<td>( S. sanguis )</td>
<td>0.06 0.05</td>
<td>ARDS, RF</td>
<td>Definitive</td>
</tr>
<tr>
<td>30, M</td>
<td>AML, BMT</td>
<td>Cyph therapy, oral mucositis</td>
<td>( S. mitis )</td>
<td>0.25 2</td>
<td>Shock, ARDS, rash, RF</td>
<td>Definitive</td>
</tr>
<tr>
<td>46, F</td>
<td>ALL</td>
<td>Cy-Ara therapy, oral mucositis</td>
<td>( S. mitis )</td>
<td>4 16</td>
<td>ARDS</td>
<td>Definitive</td>
</tr>
<tr>
<td>47, F</td>
<td>ALL, BMT</td>
<td>Cyph therapy, oral mucositis</td>
<td>( S. milleri )</td>
<td>0.12 16</td>
<td>Shock, ARDS, rash</td>
<td>Definitive</td>
</tr>
<tr>
<td>26, M</td>
<td>Lymphoma</td>
<td>Cy-Ara therapy, oral mucositis</td>
<td>( S. mitis )</td>
<td>&lt;0.03 0.25</td>
<td>Shock, ARDS, rash</td>
<td>Definitive</td>
</tr>
<tr>
<td>16, F</td>
<td>AML</td>
<td>Cy-Ara therapy, oral mucositis</td>
<td>( S. mitis )</td>
<td>4 4</td>
<td>Shock</td>
<td>Definitive</td>
</tr>
<tr>
<td>20, M</td>
<td>Hodgkin's lymphoma</td>
<td>Oral mucositis</td>
<td>( S. salivarius )</td>
<td>&lt;0.03 0.25</td>
<td>Shock</td>
<td>Definitive</td>
</tr>
<tr>
<td>42, M</td>
<td>CML, BMT</td>
<td>Cyph therapy, oral mucositis</td>
<td>( S. milleri )</td>
<td>&lt;0.03 1</td>
<td>Shock, ARDS, RF</td>
<td>Definitive</td>
</tr>
<tr>
<td>36, F</td>
<td>CML, BMT</td>
<td>Cyph therapy, oral mucositis</td>
<td>( S. mitis )</td>
<td>4 &gt;32</td>
<td>ARDS, RF</td>
<td>Definitive</td>
</tr>
</tbody>
</table>

NOTE: ALL, acute lymphoid leukemia; AMI, amikacin; AML, acute myeloblastic leukemia; ARDS, adult respiratory distress syndrome; BMT, bone marrow transplantation; C-Ara, cytosine arabinoside; CML, chronic myelogenous leukemia; Cyph, cyclophosphamide; Czid, ceftazidime; Gm, gentamicin; Imi, imipenem; Pen, penicillin; RF, renal failure; Rif, rifampin; Vm, vancomycin.

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prophylactic agents for neutropenic patients and have been effective in preventing bacteremia due to gram-negative organisms, but an increased frequency of streptococcal bacteremia has been noted [30, 31]. Thus, different antibiotic regimens have been used to prevent these infections. Oral penicillin V or oxacillin added to fluoroquinolone treatment has resulted in reduction of VSB cases [32, 33]. Nevertheless, the increasing incidence of infection with viridans streptococci that are resistant to penicillin and macrolides limits the utility of these drugs as prophylactic agents [12–14, 34]. On the other hand, our study identified severe oral mucositis as an important predisposing factor for life-threatening complications of VSB. Therefore, although some prophylactic measures have been studied [35], more effective strategies to prevent chemotherapy-induced oral mucositis are needed.

In summary, serious complications associated with VSB occur mainly in patients with severe oral mucositis secondary to high-dose therapy with cyclophosphamide as a conditioning regimen for allogeneic bone marrow transplantation. Because the mortality rate associated with these complications is high, new strategies for treatment and prophylaxis for this patient population should be promptly investigated.

References


