Clinical Significance of Bacteremia Involving the “Streptococcus milleri” Group: 51 Cases and Review

Frédéric Bert, Morgane Bariou-Lancelin, and Nicole Lambert-Zechovsky

Fifty-one cases of bacteremia due to the “Streptococcus milleri” group were analyzed. Among these were 40 patients with underlying diseases, and associated local infections were present in 27 patients. The most frequent sites of infection were the thoracic cavity and the digestive and hepatobiliary tracts. A probable portal of entry related to mucosal-barrier trauma was identified for an additional 16 patients. The origin of bacteremia was unknown for the remaining eight patients. Abscess formation was evident for only six patients, and there were no cases of endocarditis. Multiple positive blood cultures and polymicrobial bacteremia were associated significantly with the presence of local sites of infection. The most common causative species were Streptococcus anginosus and Streptococcus constellatus. Two patients died of bacteremia.

Materials and Methods

The medical records were reviewed for all patients who developed S. milleri bacteremia in our hospital between January 1988 and April 1996. Bacteremia was defined as the isolation of a member of the S. milleri group from one or several cultures of blood from a patient with signs of infection. Data concerning the following were extracted from medical records: age, sex, underlying diseases, predisposing factors, previous antibiotic therapy, associated sites of infection, signs of shock, WBC count, duration of hospitalization before the onset of the bacteremic episode, number of positive blood cultures, associated organisms, treatment, and outcome. Isolates were identified to the species level by use of the Rapid ID 32 Strep system [7]. Hemolysis type was examined on 5% sheep blood agar plates (BioMérieux, Marcy l’Etoile, France). Lancefield serological grouping was carried out using a commercial kit (Streptococcal Grouping Kit, Oxoid, Dardilly, France). MICs were determined by use of the agar dilution method on Mueller-Hinton agar supplemented with 5% sheep blood and interpreted according to the National Committee for Clinical Laboratory Standards (NCCLS) breakpoints.

Results

The clinical findings are shown in table 1. Most patients had one or more underlying conditions, among which the most frequent were the following: cirrhosis of the liver (n = 14); neoplasia (n = 8), including cholangiocarcinoma (n = 3), lung cancer (n = 3), cervical cancer (n = 1), and myeloma (n = 1); and diabetes mellitus (n = 4). There were no cases of bacteremia among patients with neutropenia. The mean duration of hospitalization before the bacteremic episode was 6 days. The first positive blood culture was performed within 48 hours of admission for 24 patients (47%). Local trauma to the mucosal barrier preceded the bacteremic episode in 34 patients (67%). Forty-six patients (90%) had fever, and two patients had hypothermia. Signs of shock were present in four patients. The mean WBC count was 14,926/mm³ (range, 3,280–53,000/mm³). Systemic antibiotics had been administered to nine patients before the bacteremic episodes. The drug was a β-lactam agent in all cases, in combination with an aminoglycoside in two patients, an aminoglycoside and metronidazole in one patient, and vancomycin in one patient.

A local suppurative infection was associated with bacteremia in 27 cases, including six cases with abscess formation. A streptococcal isolate identical to that cultured from the blood was recovered from the associated site in 11 of these 27 episodes. The most common sites of infection were the respiratory tract, the hepatobiliary and digestive tracts, the head and neck area, and the bone and soft tissues. A probable portal of entry related to mucosal-barrier trauma was identified in 16 (66.7%) of the 24 patients with no local suppurative infection. The most frequent causes of mucosal-barrier trauma were gastrointestinal ulceration or bleeding in nine patients, six of whom had esophageal varices, and premature rupture of membranes and cesarean...
in three patients. The origin of bacteremia was not identified for the remaining eight cases.

Forty-one patients (80.4%) had a single blood culture positive for *S. milleri*, five other patients had two positive blood cultures, and the remaining five patients had three or more positive cultures. Patients with several positive blood cultures were more likely to have a local infection than were those with a single positive culture (100% vs. 41.5%, *P* < .01). Twenty-six bacteremic episodes (51%) were polymicrobial. In 15 cases (29.4%), the associated organism was recovered from the same blood culture as the streptococcal isolate, and in 11 additional cases the associated organism was recovered from another blood culture performed on the same day. The pathogens associated most frequently with the bactereamic episodes were members of the family Enterobacteriaceae and anaerobes. There was a statistically significant difference in the frequency of association of polymicrobial blood cultures with local infections when compared with the frequency of association with monomicrobial cultures (86.7% vs. 38.9%, *P* < .01). The isolate was identified as *S. anginosus* in 28 cases (54.9%), *S. constellatus* in 22 cases (43.1%), and *S. intermedius* in one case. Ten isolates (19.6%) were β-hemolytic. Seventeen isolates (33.3%) belonged to Lancefield group F, nine to group C, five to group A, one to group G, and the remaining 19 isolates (37.3%) were nongroupable. All isolates were susceptible to penicillin G, amoxicillin, cefotaxime, imipenem, and vancomycin; 88.2% were susceptible to erythromycin and 80.4% to doxycycline. None of the isolates exhibited high-level resistance to gentamicin.

In 42 (87.5%) of the 48 cases for which treatment data were available, systemic antibiotics were given. Forty patients received a β-lactam agent, associated with an aminoglycoside in 16 cases and metronidazole in 11 cases. The drug administered most frequently was amoxicillin/clavulanate (*n* = 21). Two further patients received vancomycin. The duration of antibiotic therapy varied from 7 days to 5 months, according to the associated site of infection. Sixteen patients with a local suppurative process required surgical or transcortaneous drain- age. Thirty-five (77.8%) of the 45 patients for whom outcome data were available were treated successfully. Ten patients died during their hospital stays. Death was attributed to the infection for two of these patients and was related to an underlying condition in the other cases.

### Discussion

We compared our findings with those from 158 *S. milleri* bacteremic episodes reported previously in the French- and English-language literature (table 1). The mean age, male predominance, and frequency of underlying conditions found among our patients were similar to those reported previously. Hepatic and biliary disease, mostly cirrhosis of the liver, were the most prevalent conditions. Among patients with neoplasia, most had solid tumors. In contrast to increasing reports on the leading role of viridans streptococci in bactereemic episodes in patients with neutropenia [14], there were no cases of *S. milleri* bacteremia in the hematology department during the study period. Similarly, Jacobs et al. [15] found that *S. milleri* isolates occurred significantly more frequently in the general hospital population and less frequently in the hematology unit than other viridans streptococci.

A local site of infection was identified for 53% of our patients, but abscess formation was significantly less frequent than described previously. The gastrointestinal and hepatobiliary tracts and the thoracic cavity were the two most common foci of infection. As in other studies [4, 13], none of our patients had endocarditis. Salavert et al. [6] compared the characteristics of bacteremia caused by *S. milleri* and other viridans streptococci and found that *S. milleri* bacteremia was associated more frequently with an abdominal origin, whereas endocarditis was more frequent in the viridans streptococci group. In contrast, Casariego et al. [5] found nine cases of endocarditis among 32 patients with *S. milleri* bacteremia. To assess the significance

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients with indicated finding/total no. (%) in the previous study</th>
<th>No. of patients with indicated finding/total no. (%) in the present study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y) (range)</td>
<td>52 (16–77)</td>
<td>57.2 (2–88)</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>Underlying condition</td>
<td>40/51 (78.4)</td>
<td>81/131 (61.8)</td>
</tr>
<tr>
<td>Associated sites of infection¹</td>
<td>27/51 (52.9)</td>
<td>116/152 (76.3)</td>
</tr>
<tr>
<td>Abdominal/hepatobiliary</td>
<td>8</td>
<td>52</td>
</tr>
<tr>
<td>Thoracic</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Cervicofacial</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>CNS</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Bone</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Abscess formation</td>
<td>6/51 (11.8)</td>
<td>50/158 (31.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Abdominal/pelvic</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Brain</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Unknown origin of infection</td>
<td>8/51 (15.7)</td>
<td>14/152 (9.2)</td>
</tr>
<tr>
<td>Polymicrobial bacteremia</td>
<td>26/51 (51)</td>
<td>15/101 (14.9)</td>
</tr>
<tr>
<td>Death related to <em>S. milleri</em> infection</td>
<td>2/51 (3.9)</td>
<td>31/114 (27.2)</td>
</tr>
</tbody>
</table>

¹ Associated sites of infection: 8 pneumonias, 5 liver abscesses, 2 sinusitis, 2 extradural empyemas with sinusitis, 2 cellulitis, 1 asetic infection, 1 cholangitis, 1 pancreatic cyst, 1 tracheotomy wound, 1 cervical abscess, 1 spondylodiskitis, 1 postsurgical osteitis, and 1 vascular graft.
of *S. milleri* bacteraemia as an indicator of the presence of a
deep-seated infection, we compared the microbiological find-
ings in bacteraemic episodes with and without an associated site
of infection. The greater frequency of multiple positive blood
cultures and polymicrobial cultures among patients with foci
of infections than among other patients was statistically sign-
ificant. A portal of entry, often related to a mucosal disruption
in the gastrointestinal tract, was identified in most patients with
no associated suppurative infection. The most frequent cause
was esophageal ulceration or bleeding. The prophylactic use
of drugs with poor antibacterial activity such as amingly-
cosides or metronidazole, which was previously suspected to
predispose to *S. milleri* bacteraemia [16], was found in only
three of our patients.

As reported previously [4], *S. anginosus* was the most fre-
quent species, and *S. intermedius* was uncommon. Species
identification by use of the API 20 Strep system (bioMérieux),
which often misidentifies *S. anginosus* and *S. constellatus* as
*S. intermedius* [15], probably explains the high incidence of *S.
intermedius* in the study by Casariego et al. [5]. The Rapid ID
32 Strep system is the preferred method for identification of
species within the *S. milleri* group [7]. The hemolytic and
antigenic properties of the isolates were in agreement with
those of other studies. We did not observe any particular rela-
tionship between species and source of infection.

The emergence of penicillin resistance as a therapeutic prob-
lem among streptococci seems to be less frequent for the
*S. milleri* group than for other viridans streptococci [17]. In
our study, none of the isolates showed decreased susceptibility
to β-lactams. Thus, β-lactam agents remain the treatment of
choice for *S. milleri* infections. Despite the excellent in vitro
activity of penicillin G, amoxicillin/clavulanate was the agent
most frequently chosen. The frequent recovery of anaerobes
from patients with *S. milleri* infections probably explains this
finding, as well as the combination with metronidazole in a
number of patients. Surgery and antibiotics was the treatment
for the majority of patients with a local suppurative infection.

In conclusion, our findings indicate that bacteraemia due to
the *S. milleri* group is often associated with a local site of
infection, mostly in the hepatobiliary and bronchopulmonary
tracts, and reflects the presence of a deep-seated abscess for
only a minority of patients. Multiple positive blood cultures
and polymicrobial bacteraemia strongly suggest a suppurative
focus of infection and should prompt clinicians to initiate a
thorough investigation of the abdominal and thoracic cavities.
However, bacteraemia also occurs frequently in the absence of
an associated infection site among patients with a disruption of
the mucosal digestive barrier. These transient bacteraemias
should not be overlooked, since they may be complicated by
metastatic purulent lesions and, therefore, a single positive
blood culture should be considered clinically significant. In
contrast to other viridans streptococci, the *S. milleri* group
is seldom responsible for bacteraemia in neutropenic patients and
for endocarditis, and most isolates remain fully susceptible to
penicillin G.

References

1. Murray HW, Gross KC, Masur H, Roberts RB. Serious infections caused
2. Admon D, Ephros MA, Gavish D, Raz R. Infection with Streptococcus
3. Dossou-Gbité L, Christmann D, Picard A, Scheftel P. Streptococcus angi-
nosus: A propos de dix cas d’infections graves. Sem Hôp Paris 1993;
69:68–70.
4. Jacobs JA, Pietersen HG, Stobberingh EE, Soeters PB. Bacteraemia involv-
ing the ‘‘Streptococcus milleri’’ group: analysis of 19 cases. Clin Infect
5. Casariego E, Rodriguez A, Corredora JC, et al. Prospective study of
Garau J. Seven-year review of bacteraemia caused by Streptococcus
milleri and other viridans streptococci. Eur J Clin Microbiol Infect Dis
7. Jacobs JA, Stobberingh EE. Species identification of ‘‘Streptococcus mill-
eri’’ with the Rapid ID 32 Strep system. Med Microbiol Lett 1994;3:
315–22.
8. Shlaes DM, Lerner PI, Wolinsky E, Gopalakrishna KV. Infections due to
Streptococcus miller-
i

References