**Streptococcus intermedius, Streptococcus constellatus, and Streptococcus anginosus (“Streptococcus milleri Group”) Are of Different Clinical Importance and Are Not Equally Associated with Abscess**

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Difficulties in distinguishing organisms of the “Streptococcus milleri group” (SMG; *Streptococcus intermedius, Streptococcus constellatus, and Streptococcus anginosus*), have caused ambiguity in determining their pathogenic potential. We reviewed 118 cases in which SMG isolates had been identified using 16S rDNA sequence. *S. constellatus* and *S. anginosus* were isolated far more frequently than was *S. intermedius*. Nearly all isolates of *S. intermedius* and most isolates of *S. constellatus*, but only 19% of those of *S. anginosus*, were associated with abscess. Our findings suggest that speciation of the SMG may guide diagnostic evaluation, give insight into the possible role of coinfecting organisms, and help assess the need to search for occult abscess.

The “Streptococcus milleri group” (SMG) has been known by a variety of names [1] and, in the past, has been considered a single species that is loosely synonymous with *S. anginosus* [2]. Members of the SMG are now separated into 3 distinct species—*Streptococcus intermedius, Streptococcus constellatus*, and *Streptococcus anginosus*—with *S. constellatus* and *S. intermedius* being more closely related to each other than to *S. anginosus* [3–5]. However, because many phenotypic tests for the characterization of these species yield similar results, identification of isolates can be difficult.

Possibly because of this difficulty in the identification of isolates, studies that have speciated isolates of SMG and have attempted to correlate them with clinical syndromes have not reached definitive or consistent conclusions; the species seem to have overlapping clinical associations [6–9]. However, some studies that have detailed the site of isolation have suggested that *S. anginosus* is more likely to be isolated from blood, urogenital, and gastrointestinal specimens, whereas *S. intermedius* tends to be associated with infection of the head, neck, and respiratory tract [1, 8–10]. One of the most striking features of species in the SMG is their tendency to cause abscesses. However, both the potential of each of the SMG species to cause abscess and the clinical features of the cases associated with abscess have not been addressed in depth with regard to well-identified strains.

We definitively identified the isolates to species that led to 118 cases of infection due to SMG by use of 16S rRNA gene sequence and biochemical tests, and we evaluated the data for clinical significance by means of careful and complete review of medical records. Cases of infection that were associated with abscess were examined in greater detail for severity, site of abscess, and coisolated organisms.

**Methods.** Identification of clinical isolates, which were recovered by and stored (at a temperature of −70°C) at the Microbiology Laboratory, Veterans Affairs Medical Center, Houston, during 1989–1999, was done as described elsewhere [3]. In brief, strains were characterized as belonging to the SMG by means of biochemical profiling done with the use of the API 20 Strep test (BioMérieux Vitek), and they were characterized as to species by use of the Fluo-Card Milleri test kit (KEY Scientific Products). 16S RNA sequencing was used to definitively identify all strains [3]. The PCR products were sequenced and purified with use of the MicroSeq 500 gene kit protocols and were run on an ABI Prism 377 Sequencer (PE Applied Biosystems). Bacterial identifications based on 16S rRNA gene sequence data were assigned by use of MicroSeq Microbial Identification and Analysis Software (PE Applied Biosystems).

Patients were included in the study if the infecting streptococcus could be assigned unambiguously to a species and if available clinical information allowed for the type of infection to be clearly characterized. To avoid bias, record review and clinical characterization were completed without knowledge of the results of the microbiological studies. For all patients, a careful search was made for evidence of abscess formation. For the purposes of this study, we regarded localized infection in...
closed spaces as abscess; examples include thoracic empyema, subdural abscess, ventriculitis, subcutaneous abscess, and septic arthritis. Certain cases of suppurative soft tissue infection, including gangrene, infection of either a decubitus ulcer or a foot affected by diabetic neuropathy, and cellulitis were not regarded as abscess.

Fisher’s exact test was used to determine whether there were significant differences among the 3 bacterial species. For all tests, $\alpha = .05$.

**Results.** The distribution of individual species of the SMG, stratified according to the type of specimen submitted to the laboratory, is shown in table 1. Of 122 SMG isolates, 58 (48%) were recovered from exudate, aspirate, or fluid samples, and 33 (27%) were recovered from blood samples. The remaining 31 isolates (25%) were recovered from the genitourinary tract, the upper respiratory tract, or other sources. The SMG was isolated from 2 sites in each of 3 patients, and *S. intermedius* and *S. constellatus* both were isolated from the same specimen obtained from 1 patient. Therefore, we analyzed a total of 122 isolates from 118 patients.

*S. intermedius* was the least commonly isolated member of the SMG (14 [11%] of 122 isolates). Twelve (86%) of these 14 isolates were recovered from an abscess (4 isolates) or from a normally sterile site in association with an abscess (3 of 5 blood isolates and 2 of 2 CSF isolates). The 2 blood isolates that were not definitely associated with abscess were recovered from a paraplegic man who had a deep decubitus ulcer and from a man who had diabetes and gangrene of the foot. *S. intermedius* was not isolated from genitourinary tract or upper respiratory tract sources. Therefore, 12 (86%) of 14 isolates obtained from 10 (83%) of 12 patients were attributed to an abscess.

Fifty-six isolates of *S. constellatus* (46% of the SMG) were recovered from 54 patients. Thirty-nine were recovered from exudate, aspirate, or fluid samples; 38 of these were from an abscess, and 1 was from an area of cellulitis adjacent to a scorpion bite. Only 1 of 7 blood isolates was associated with abscess; the remaining 6 were associated with perforated bowel due to cancer, cholangitis, pancreatitis, and/or gangrene. The genitourinary tract isolates were recovered from a perirectal abscess and a scrotal abscess. Therefore, in 41 (73%) of 56 isolates obtained from 41 (76%) of 54 patients, *S. constellatus* was implicated as the cause of an abscess.

A total of 52 isolates of *S. anginosus* were recovered from 52 patients, representing 43% of SMG. These were obtained from a broader range of sources and were less likely to be associated with abscesses. Eight (67%) of 12 isolates recovered from exudate, aspirate, or fluid samples were from abscesses; as observed for *S. constellatus*, nonabscess sources included gangrenous tissue, decubitus ulcers, and areas of cellulitis. Only 2 (10%) of 21 blood isolates were recovered from patients who had an abscess; the others occurred in patients with decubitus ulcers or conditions that might be associated with translocation from the bowel, such as obstruction, colon cancer, or alcoholic cirrhosis. *S. anginosus* was also isolated from urine samples obtained from 13 patients and from sputum or pharyngeal swab samples obtained from 12 patients without an abscess, as well as from miscellaneous sources. In these patients, *S. anginosus* was isolated as part of mixed flora; an abscess was not present, and, in fact, no infection was attributable to the organism. For example, the $\beta$-hemolytic strains from the pharynx had been identified in a search for group A *Streptococcus*. Only in samples (all urine isolates) obtained from 3 patients did the streptococcus predominate, and the patients were not treated and did not have apparent sequelae. Therefore, of 52 isolates of *S. anginosus*, only 10 (19%) were associated with an abscess, a frequency lower than that associated with *S. intermedius* or *constellatus* ($P < .002$; Fisher’s exact test).

In total, 62 (51%) of 122 SMG isolates were obtained from 60 patients who had an abscess as the presumed source of infection. Abscesses caused by *S. intermedius* tended to be hemogenous and/or extensive, suggesting that, at least in these patients, this organism behaved as a classical, high-grade ex-

<table>
<thead>
<tr>
<th>Streptococcus species</th>
<th>Total no. of Isolates</th>
<th>Patients</th>
<th>Exudate, aspirate, or fluid</th>
<th>Blood</th>
<th>Urine</th>
<th>Sputum or pharynx</th>
<th>CSF</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. intermedius</em></td>
<td>14</td>
<td>12</td>
<td>7 (7)</td>
<td>5 (3)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>S. constellatus</em></td>
<td>56</td>
<td>54</td>
<td>39 (38)</td>
<td>7 (1)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><em>S. anginosus</em></td>
<td>52</td>
<td>52</td>
<td>12 (8)</td>
<td>21 (2)</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>122*</td>
<td>118*</td>
<td>58 (50)</td>
<td>33 (6)</td>
<td>13</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of specimens (no. of isolates associated with an abscess). In some cases of abscess, the causative organism was obtained from blood but not from the abscess material.

* An organism of the “Streptococcus milleri group” was recovered from 2 different sites in each of 3 patients, and 2 different species were recovered from 1 site in 1 patient.
Table 2. Classification of abscesses caused by infection with an organism of the “Streptococcus milleri group.”

<table>
<thead>
<tr>
<th>Classification</th>
<th>S. intermedius</th>
<th>S. constellatus</th>
<th>S. anginosus</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>Odontogenic, neck</td>
<td>1(^a)</td>
<td>2(^a)</td>
<td>—</td>
<td>10(^a)</td>
</tr>
<tr>
<td>Pleuropulmonary</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Intra-abdominal, perirectal(^b)</td>
<td>—</td>
<td>8</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>4</td>
<td>13</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Superficial</td>
<td>1</td>
<td>11</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Extensive</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Indeterminate (isolated from blood only)(^c)</td>
<td>1(^d)</td>
<td>—</td>
<td>2(^b)</td>
<td>1</td>
</tr>
</tbody>
</table>

Total no. of patients with abscess 10 41 10 60\(^a\)

**NOTE.** Data are the no. of patients in whom each species was implicated as a cause of infection.

\(^a\) S. constellatus and S. intermedius were both isolated from 1 abscess.

\(^b\) Patients had uncultured epidural or lung abscess.

\(^c\) Although we assumed that the source of the blood isolate was the concurrent abscess, data for these patients were not used in the calculation of statistical differences.

\(^d\) Only *Staphylococcus aureus* was isolated from an abscess on the arm.

tracellular bacterial pathogen (table 2). There were 2 cases of intracerebral abscess (1 case each of subdural abscess and ventriculitis) and 2 cases of thoracic empyema. An abscess of the mouth required surgical drainage of pus, as did 3 deep abscesses of soft tissue or muscle. The soft tissue infections were more likely to be extensive or deep than were those due to *S. constellatus* or *S. anginosus* (*P* = .015). Only 1 of the 10 abscesses, which was located at the site of injection in a drug abuser, was amenable to superficial drainage. Furthermore, of the 8 abscesses for which full microbiological data were available, *S. intermedius* was the only isolate recovered from 7 of them (83%; table 3).

Abscesses caused by *S. constellatus* tended to present somewhat differently. Two patients had multiple brain abscesses suggesting a hematogenous source. Although a larger percentage of patients experienced abscess located in the mouth, throat, and neck (22% vs. 10% for *S. intermedius* and 0 for *S. anginosus*), the difference was not significant. *S. constellatus* was also more likely to be isolated from intra-abdominal or perirectal/perianal abscesses: 8 isolations, compared with 0 such isolations in the case of *S. intermedius* and 1 for *S. anginosus* (*P* < .33; not significant). There were 7 cases of lung abscess and/or empyema, which is comparable to findings for the other species. In contrast to observations of soft tissue infection due to *S. intermedius*, 11 of 13 *S. constellatus* infections of skin and soft tissues were superficial. Five infections were related to self-injection of illegal drugs, and 1 infection was related to injection of insulin; 1 case each involved the nose, the forehead, and the breast, and 1 case involved a bite from a human. The remaining 2 isolates were recovered from wound infections at the site where elective surgery of the gastrointestinal tract had been performed.

For 10 cases of abscess caused by *S. anginosus*, the spectrum appeared to be similar to that of *S. constellatus*; there was 1 case of epidural abscess, 3 cases of pleuropulmonary abscess (1 case each of lung abscess, postobstructive pneumonia, and empyema), 5 cases of superficial abscess, and 1 case of intra-abdominal abscess. In no abscess was *S. anginosus* isolated as the sole organism.

Of the 53 patients for whom sufficient bacteriologic information was available, *S. intermedius* was isolated in pure culture more often than was either *S. constellatus* or *S. anginosus* (83%, 22%, and 0%, respectively, were sole isolates; *P* = .001; difference significant among groups). Organisms found with *S. constellatus* and *S. anginosus* reflected the site from which the specimen was obtained. Respiratory flora (e.g., *Eikenella corrodens*, *Haemophilus influenzae*, and *Bacteroides melaninogenicus*) and skin flora (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*, and diphtheroids) were identified in abscesses located on the upper parts of the body, whereas colonic flora (e.g., *Bacteroides fragilis* group and *Escherichia coli*) were coisolated from abscesses found on the lower parts of the body. *E. corrodens* was coisolated most often with *S. constellatus*.

**Discussion.** The application of molecular biologic techniques has allowed for more precise speciation of organisms that comprise the SMG, thereby eliminating ambiguous or er-
E. corrodens, Eikenella species stimulates the growth of S. constellatus, which is consistent with the observation that the or infections, including odontogenic and intra-abdominal dis-

S. anginosus that of S. intermedius which is found with approximately the same frequency; each of these species is found ∼4 times more often than is S. intermedius.

Our data support earlier observations that a striking feature of the SMG is its members’ tendency to cause abscesses [1, 6, 8, 9]. Overall, half the isolates in our series were implicated in abscess formation. Our results show, however, that the members of this group do not cause abscesses with an equal frequency. S. intermedius and S. constellatus were more likely to cause deep abscess (86% and 73% of isolates of each species, respectively) than was S. anginosus (19%). Abscesses caused by S. intermedius tended to be associated with hematogenica spread or were deep-seated, whereas those due to S. constellatus were more often superficial. S. constellatus also seemed to cause a broader range of infections, including odontogenic and intra-abdominal dis-

Whereas S. intermedius was found as a solitary isolate in specimens obtained from 8 of 9 patients for whom necessary microbiologic data were available, abscesses caused by S. constellatus or S. anginosus were more likely to be polymicrobial. E. corrodens, the most common coisolate, was often found with S. constellatus, which is consistent with the observation that the Eikenella species stimulates the growth of S. constellatus but not that of S. anginosus [11]. In all but 3 patients in whom the mixed respiratory flora was not further identified, S. anginosus was isolated with an organism known to cause abscesses, most commonly S. aureus.

Blood was second to abscess fluid as the most common sample from which the SMG was recovered. S. anginosus predominated: it was identified in 64% of blood isolates of the SMG. This result is similar to that of 2 earlier studies [10, 12].

Table 3. Distribution of “Streptococcus milleri group” microorganisms isolated either in pure culture or with companion organisms from an abscess.

<table>
<thead>
<tr>
<th>Variable</th>
<th>S. intermedius</th>
<th>S. constellatus</th>
<th>S. anginosus</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases in which enough information was given so that coisolates could be assessed</td>
<td>9</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>Percentage of cases in which the isolate was recovered in pure culture</td>
<td>89</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>No. of cases with respiratory flora (no. with Eikenella)</td>
<td>1 (1)</td>
<td>10 (4)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>No. of cases with fecal or gastrointestinal flora (no. with Bacteroides species or Escherichia coli)</td>
<td>0</td>
<td>6 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>No. of cases with skin flora (no. with Staphylococcus aureus)</td>
<td>0</td>
<td>10 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Other, unclassified</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

raneous identification that may have been unavoidable in the past. Such misidentification may have altered the frequency with which individual species are reported to be associated with disease [3]. Most studies that have identified the SMG to the species level have suggested that S. anginosus is the most common isolate [6, 8–10]. Data presented in this report, which were based largely on sequential isolates recovered from all body sites in the laboratory of a single adult tertiary-care hospital, show that S. constellatus and S. anginosus are isolated from clinical specimens with approximately the same frequency; each of these species is found ∼4 times more often than is S. intermedius.

Variable  
No. of cases in which enough information was given so that coisolates could be assessed  
Percentage of cases in which the isolate was recovered in pure culture  
No. of cases with respiratory flora (no. with Eikenella)  
No. of cases with fecal or gastrointestinal flora (no. with Bacteroides species or Escherichia coli)  
No. of cases with skin flora (no. with Staphylococcus aureus)  
Other, unclassified  

A study performed in our laboratory showed that all members of the SMG are susceptible to these antibiotic regimens, as demonstrated by the favorable outcomes achieved in most of the cases. Bantar et al. [6] evaluated the susceptibilities of each strain to penicillin, erythromycin, vancomycin, gentamicin, and streptomycin, and they found decreased susceptibility in 12.5% of S. anginosus, 5.5% of S. constellatus, and 33.3% of S. intermedius. A study performed in our laboratory has shown that all members of the SMG are susceptible to levels of penicillin, amoxicillin, cefotaxime, or ceftriaxone achieved by the usual dosage [13]. Variable susceptibility to tetracycline, clindamycin, and erythromycin has been reported elsewhere [14] and was confirmed for clindamycin in our study.

Some type of drainage procedure was required in most cases of abscess. For infections due to S. constellatus or S. anginosus,
a simple incision and drainage procedure accompanied by appropriate antibiotic treatment was sufficient. For those due to S. intermedius, more extensive surgery or CT-guided aspiration was used for both therapeutic and diagnostic purposes. There were only 2 deaths among 60 patients with abscess; in contrast, the mortality rate in the other series of patients (those who had bacteremia with or without abscess) has been as high as 26% [12], mostly among seriously compromised patients.

A simplified scheme for the identification of the SMG has been suggested [3]. Identification of the SMG strains by use of widely available laboratory methods, such as the Vitek GPI card or API 20 Strept test, is reliable for identification of the group but not for that of the species. If additional tests (e.g., the Fluocard Milleri test kit) are done, the percentage of correct identification to the species level can be increased to 93% [3, 10]. Furthermore, it was shown that β-hemolytic strains that were presumed to be S. intermedius on the basis of the aforementioned scheme were actually S. constellatus genetically [3]. With this correction, the percentage of correct identification to the species level was increased to 96% [3] (S.A. and J.E.C., unpublished data).

S. intermedius, S. constellatus, and S. anginosus tend to be associated with different clinical syndromes. If clinical considerations mandate that the source of infection, the probable coinfecting organisms, and, in the case of blood isolates, the probability of an occult abscess be known, then identification of the SMG to the species level is important.

Acknowledgment

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References


