**Streptococcus dysgalactiae subsp. equisimilis**

Bacteremia, Finland, 1995–2004

Sari Rantala, Susanna Vähäkuopu, Jaana Vuopio-Varkila, Risto Vuonto, and Jaana Syrjänen

We conducted a retrospective population-based study of 140 episodes of *Streptococcus dysgalactiae* subsp. *equisimilis* bacteremia occurring in Finland during 1995–2004. Rare *emm* types were associated with more severe disease and increased mortality rates. Skin and soft tissue infections were more frequent clinical signs among cases caused by common *emm* types.

Lancefield groups C and G β-hemolytic streptococci (GCS and GGS) may colonize the pharynx, skin, gastrointestinal tract, and female genitourinary tracts (1). According to recent taxonomic studies, large colony-forming groups C and G streptococci that infect humans are classified as *Streptococcus dysgalactiae* subsp. *equisimilis* (2). *S. dysgalactiae* subsp. *equisimilis* and *S. pyogenes* share virulence factors (3,4). The M protein is an important virulence factor because it confers resistance to phagocytosis (5). As with *emm* genes of *S. pyogenes*, the *emm* homologs of groups C and G *S. dysgalactiae* subsp. *equisimilis* are used for sequence-based typing (4,6,7), with >50 sequence types currently described (www.cdc.gov/ncidod/biotech/strep/strepblast.htm). If the *emm* gene could not be amplified with primers 1 and 2, alternative primers MF1/MR1 were used (9). PFGE was performed as described (10). DNA profiles were analyzed by using BioNumerics software (Applied Maths, Kortrijk, Belgium) and interpreted according to the guidelines described (11). Strains with >85% similarity were considered to be related types.

SPSS software version 7.5 (SPSS, Chicago, IL, USA) was used for statistical analyses, and a 2-sided p value <0.05 was regarded as the level for significance. Categorical data were analyzed by the χ² test or Fisher exact test as appropriate. Nonparametric data were analyzed by using the Mann-Whitney U test. Odds ratios were expressed with 95% confidence intervals.

The median age of patients (73 men, 62 women) was 67 years (range 17–90 years). Cardiovascular diseases (41%), diabetes (25%), and malignancies (23%) were the 3 most prominent underlying conditions. We found 18 *emm* types (including 4 subtypes of stG6: stG6.0, stG6.1, stG6.3, and stG6.4). stG480 (27 isolates), stG6 (23 isolates), and stG485 (22 isolates) were the 3 most common *emm* types and represented 51% of all isolates (Figure 1). Eight of group G *S. dysgalactiae* subsp. *equisimilis* isolates remained nontypeable. PFGE analysis showed 2 strains to be related (>85% similarity). The rest of the nontypeable strains were sporadic (6 isolates).

Author affiliations: Tampere University Hospital, Tampere, Finland (S. Rantala, R. Vuonto, J. Syrjänen); National Institute for Health and Welfare, Helsinki, Finland (S. Vähäkuopu, J. Vuopio-Varkila); and Medical School, University of Tampere, Tampere (J. Syrjänen)

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We divided bacteremia episodes into 2 groups: those caused by the 5 most common \textit{emm} types and each representing >5% of all episodes (97 episodes, common \textit{emm} types) and those caused by the less common or nontypable \textit{emm} types (41 episodes, rare \textit{emm} types). We could not find an association between \textit{emm} type and clinical features such as age or underlying disease. Severe disease was caused more often by rare \textit{emm} types than by common \textit{emm} types. Mortality rates were higher in patients with bacteremia caused by rare \textit{emm} types than by common \textit{emm} types. Severe disease was caused more often by rare \textit{emm} types than by common \textit{emm} types. Mortality rates were higher in patients with bacteremia caused by rare \textit{emm} types than by common \textit{emm} types. Severe disease (death or intensive care unit treatment) was also caused more often by rare \textit{emm} types than by common \textit{emm} types. We found also an association between a common \textit{emm} type and cellulitis as a clinical manifestation; the common \textit{emm} types were also associated with skin and soft tissue infections.

Common \textit{emm} types were more frequently manifested as skin and soft tissue infections than were rare \textit{emm} types, 75% vs. 54%, respectively (p = 0.012). The most frequent source of bacteremia was cellulitis (51%). We also found an association between a common \textit{emm} type and cellulitis. Cellulitis was a more frequent clinical sign among patients with infections caused by common \textit{emm} types than by rare \textit{emm} types (p = 0.007); 64% of patients infected by common \textit{emm} types had cellulitis as an initial clinical manifestation versus 39% of patients infected by rare \textit{emm} types.

Conclusions

Our study showed that mortality rates were higher in patients with \textit{S. dysgalactiae subsp. equisimilis} bacteremia caused by rare \textit{emm} types than in those with bacteremia caused by common \textit{emm} types. The reason for this finding is unclear. One explanation for this might be that patients contract certain prevailing bacterial strains (so-called common types) more often, and a prior antigen challenge and subsequent humoral response may play a role. Severe disease (death or intensive care unit treatment) was also caused more often by rare \textit{emm} types than by common \textit{emm} types. We found also an association between a common \textit{emm} type and cellulitis as a clinical manifestation; the common \textit{emm} types were also associated with skin and soft tissue infections.

In our comprehensive study with molecular typing data for 138 invasive \textit{S. dysgalactiae subsp. equisimilis} isolates from human infections, we found 18 \textit{emm} types, which is consistent with previous reports by Cohen-Poradosu et al. (12) and Broyles et al. (13). These 2 studies reported stG485.0, or StG6, StG245, and StG2078 as the most common \textit{emm} types, respectively. Thus, \textit{emm} typing provides a useful tool for comparative epidemiologic analysis of GGS isolates from various geographic regions. Our results also suggest that certain \textit{emm} types may prevail among bacteria.

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>No. (%) common \textit{emm} types, n = 97</th>
<th>No. (%) rare \textit{emm} types, n = 41</th>
<th>Odds ratio (95% CI)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality rate</td>
<td>11 (11)</td>
<td>12 (29)</td>
<td>3.2 (1.3–8.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Patient admitted to ICU</td>
<td>5 (5)</td>
<td>6 (15)</td>
<td>3.2 (0.9–11)</td>
<td>0.084</td>
</tr>
<tr>
<td>Patient death or ICU treatment</td>
<td>12 (12)</td>
<td>15 (37)</td>
<td>4.1 (1.7–9.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypotension‡</td>
<td>13 (13)</td>
<td>10 (24)</td>
<td>2.1 (0.8–5.2)</td>
<td>0.113</td>
</tr>
<tr>
<td>DIC§</td>
<td>2 (2)</td>
<td>6 (15)</td>
<td>8.1 (1.6–42.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>2 (2)</td>
<td>4 (10)</td>
<td>5.1 (0.9–29.2)</td>
<td>0.064</td>
</tr>
<tr>
<td>STSS¶</td>
<td>2 (2)</td>
<td>4 (10)</td>
<td>5.1 (0.9–29.2)</td>
<td>0.064</td>
</tr>
</tbody>
</table>

*CI, confidence interval; ICU, intensive care unit; DIC, disseminated intravascular coagulation; STSS, streptococcal toxic shock syndrome. Patients who had both clinical data and isolates available.
†\*x² test or Fisher exact test as appropriate.
‡Hypotensive (BP <90 mm Hg) at least once 0–2 days after positive blood culture.
§Thrombocyte count <100 x 10^9/L.
¶The definition of STSS was based on a consensus definition, including identification of \textit{β}-hemolytic streptococci from a normally sterile site, septic shock, and multiorgan failure.
that cause human infections. Our study did not show any obvious time shifts in the occurrence of certain emm types.

A noteworthy finding in our series was the high frequency of recurrent group G S. dysgalactiae subsp. equisimilis bacteremia as reported earlier (12,14). Clinicians should be alert to this phenomenon, which seems to be more common than recurrent group A streptococcal bacteremia.

The dynamics of interspecies transfer of virulence loci between group A streptococci, GGS, and GCS (3), as well as potential genetic transfer or intragenomic events causing interconversion of group antigen types, remains to be resolved. Further characterization of the strains by multilocus sequence typing would be of interest (15). We conclude that severity of disease and mortality rates were higher in persons with S. dysgalactiae subsp. equisimilis bacteremia caused by rare emm types than that caused by common emm types. Skin and soft tissue infections such as cellulitis were significantly more frequent among episodes caused by common emm types.

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Dr Rantala is a specialist in infectious disease and internal medicine in the Department of Internal Medicine, Tampere University Hospital, and a consultant in infectious diseases at Tampere University Hospital. Her research interests include streptococcal infections.

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References


Table 2. Characteristics of recurrent episodes of group G Streptococcal dysgalactiae subsp. equisimilis bacteremia, Finland, 1995–2004

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Episode 1</th>
<th>Episode 2</th>
<th>Episode 3</th>
<th>Time to recurrence, mo</th>
<th>Clinical signs</th>
<th>PFGE pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>stG6</td>
<td>stG6</td>
<td>stG6</td>
<td>15; 3</td>
<td>Cellulitis</td>
<td>Unique, identical in episodes 1–3</td>
</tr>
<tr>
<td>2</td>
<td>stG6</td>
<td>stG6</td>
<td></td>
<td>68</td>
<td>Cellulitis</td>
<td>Unique, identical in episodes 1 and 2</td>
</tr>
<tr>
<td>3</td>
<td>stG480†</td>
<td>stG480</td>
<td></td>
<td>28</td>
<td>Spondylitis</td>
<td>Unique, identical in episodes 1 and 2</td>
</tr>
<tr>
<td>4</td>
<td>stG480</td>
<td>NA‡</td>
<td>21</td>
<td></td>
<td>Cellulitis</td>
<td>Unique</td>
</tr>
</tbody>
</table>

*PFGE, pulsed-field gel electrophoresis. †Blood culture taken outside Pirkanmaa Health District, isolate available. ‡Blood culture taken outside Pirkanmaa Health District, no isolate available.

Figure 2. Dendrogram and pulsed-field gel electrophoresis (PFGE) profiles of the strains isolated from patients with recurrent group G Streptococcus dysgalactiae subsp. equisimilis bacteremia, Finland. Dendrogram was generated by using BioNumerics software (Applied Maths, Kortrijk, Belgium) with a 1.0% lane optimization and 1.5% band position tolerance.


Address for correspondence: Sari Rantala, Department of Internal Medicine, Tampere University Hospital, PO Box 2000, FIN–33521, Tampere, Finland; email: sari.rantala@uta.fi