Epidemiological and Clinical Aspects of Invasive Group A Streptococcal Infections and the Streptococcal Toxic Shock Syndrome

B. K. G. Eriksson, J. Andersson, S. E. Holm, and M. Norgren

In a retrospective study of invasive infections due to group A Streptococcus (GAS) in Stockholm during 1987 to 1995, the average incidence per 100,000 residents per year was 2.3, varying between 3.7 per 100,000 (in 1988) and 1.3 per 100,000 (in 1993). Incidence was 1.8 in the age group of 0–4 years but otherwise increased by age, from 0.48 in the age group of 5–14 years to 6.1 among those over 65 years of age. A review of 151 invasive episodes occurring in 1983–1995 showed cyclic increases of infections due to T1M1-serotype strains during 1986–1990 and 1993–1995. The T1M1 serotype accounted for 27 (20%) of 135 available GAS strains. Streptococcal toxic shock syndrome (STSS) developed in 19 (13%) of the 151 episodes. The case fatality rate was 11% overall but 47% among patients with STSS. In a multivariate logistic regression model, STSS was associated with a history of alcohol abuse (odds ratio [OR], 6.3; \( P = .004 \)) and infection with a T1M1 strain (OR, 6.7; \( P = .007 \)). Case fatality was associated with age (OR, 14.5; \( P = .08 \)), immunosuppression (OR, 4.7; \( P = .02 \)), and STSS (OR, 21.5; \( P < .0001 \)) but not with T1M1 infection. Hypotension was significantly associated with a fatal outcome, regardless of whether STSS developed (\( P < .0001 \)).

The incidence of rheumatic fever and severe invasive infections caused by group A Streptococcus (GAS) decreased in the Western societies during this century, especially after the second World War [1]. Improved socioeconomic conditions and the introduction of penicillin therapy were offered as explanations for this decline [1], which was not paralleled by a reduction in benign streptococcal infections such as pharyngotonsillitis, scarlet fever, and asymptomatic throat carriage of group A streptococci [2].

A dramatic change occurred in the mid 1980s with the reappearance of rheumatic fever in the United States [3], followed by reports from the United States and Europe of GAS-associated severe invasive infections, including necrotizing soft-tissue infections and a toxic shock–like syndrome [4–6]. Epidemiological and clinical studies have since revealed increased incidence and severity of these types of GAS infections [7–13], including among children [14]. A general classification of GAS infections, including a case definition for the streptococcal toxic shock syndrome (STSS), was suggested in 1993 [15], and the pathogenesis and clinical aspects were recently reviewed [16].

The causes of epidemiological changes in GAS infections during the past decade are insufficiently understood [17]. A recent historical review focusing on scarlet fever reported considerable variations in the incidence and severity of that disease over time [18], and outbreaks associated with increased severity of streptococcal disease as well as cyclic variations in GAS bacteremia have been reported [19, 20]. Furthermore, reliable epidemiological data have been scarce since few studies have been population-based [10] and/or prospective [13].

GAS strains causing recent invasive infections have been predominantly of the M1 and M3 serotypes [21]. In particular, the M1 serotype was noted amongst strains submitted to national reference laboratories in the United States and Europe during the 1980s [21–23]. These strains frequently produce streptococcal pyrogenic exotoxins [24, 25], proteins with potent immunomodulatory capacity due to their ability to induce massive T-cell proliferation and subsequent cytokine expression [26]. This may be an important pathogenetic mechanism in severe GAS disease [16]. Some studies indicated a clonal background for most of the M1 and M3 strains causing invasive episodes [27–29]. A recent introduction into the Western population of new serotypes or clones with increased virulence may thus be a possible explanation for the changes in GAS epidemiology [28, 29]. Other studies, however, have shown considerable genetic variation in GAS strains causing invasive disease [30], and some of the retrospective investigations have failed to detect a general increase in invasive GAS disease in recent years [31–34].

The Scandinavian countries experienced nationwide epidemics of invasive GAS disease due to serotype T1M1 strains during the second half of the 1980s [35–37]. An outbreak of bacteremia due to T1M1 strains occurred in Sweden in the 1988–1989 winter season [36], and T1M1 infections increased again in 1994–1995 [38]. The Swedish T1M1 GAS
strains showed limited genetic variation [39], and T1M1 strains from noninvasive cases were of the same genetic subtypes and produced the same types and amounts of pyrogenic exotoxins as strains from patients with severe disease [40]. A recent study in Finland failed to identify any major genetic differences between T1M1 strains from invasive and superficial infections [41].

On the other hand, patients with invasive disease were shown to have lower levels of antibodies to the M1 antigen, as well as lower levels of antibodies neutralizing the superantigenic activity of streptococcal pyrogenic exotoxin (SPE)-B and SPE-F, than did patients with noninvasive disease [42]. These data point to the importance of host-related factors and lack of acquired immunity to streptococcal antigens in the development of severe invasive disease and death. The importance of host factors was further emphasized by a recent population-based, 2-year prospective study in Ontario, Canada, which indicated increasing age and underlying chronic disease as important risk factors for invasive GAS disease [13].

In the present retrospective study, conducted in Stockholm, we addressed the issue of whether changes in both the incidence and severity of invasive GAS infections have occurred in recent years. The correlation between host factors, bacterial serotypes, and clinical manifestation of streptococcal disease was analyzed.

Materials and Methods

Epidemiological Data

A retrospective population-based study of invasive GAS disease in the southern parts of Stockholm was performed. Cases, defined by the isolation of GAS from a normally sterile site, were identified from the records of the two microbiological laboratories (at Huddinge and South hospitals) that provided bacteriological services for hospitalized patients in the area during the study period, 1983–1995. The Department of Infectious Diseases at Huddinge Hospital is a referral center for infectious disease patients in this area. The study was approved by the ethics committee of Karolinska Institute at Huddinge Hospital.

Clinical and Bacteriologic Data

One of the laboratories (Department of Clinical Bacteriology at Huddinge Hospital) routinely stored bacterial blood culture isolates at −20°C. Cases in which a GAS was isolated from blood or another sterile site during the period of 1 January 1983 to 31 December 1995 were identified. The Oxoid SIGNAL Blood Culture System (Oxoid, Basingstoke, UK) was used from 1983 to 1992, and the Bactec isolation system (Becton Dickinson, Baltimore, MD) was used from 1992 onward. Routinely, two or three blood cultures had been performed for each patient. The proportion of patients who had blood culture specimens submitted to the laboratory that were positive for GAS varied between 1 per 1,000 (in 1995) and 12 per 1,000 (in 1987) and was not related to incidence. Serogrouping of β-hemolytic streptococci was performed by agglutination (Phadebact Streptococcus Test; Boule Diagnostics AB, Huddinge, Sweden).

Clinical and laboratory data were extracted from the medical records. The focus of infection was identified on the basis of clinically recorded symptoms and/or signs in conjunction with culture findings. The clinical course until the patient’s discharge from the acute care facility was recorded. Determination of the T-serotype and the production of opacity factor was performed at the Department of Clinical Bacteriology at Umeå University (Umeå, Sweden) [43].

Statistical Analyses

Statistical analyses were done with the JMP statistical software package (version 3.1.6; SAS Institute, Cary, NC). Continuous variables were analyzed by means of the Student’s t test and categorical variables by the χ² test or Fisher’s exact test when appropriate. Background variables associated (P < .20) in univariate logistic regression with STSS and mortality were further analyzed in a multivariate logistic regression model, with use of backward stepwise regression.

Results

Epidemiology

The population of the study area by 31 December 1988 was 875,941. This population and the subpopulations for different age groups were used as denominators. Complete bacteriologic data were available from 1987 onward. During the 9 years from 1987 to 1995, 178 cases of invasive GAS disease were identified. Ages varied between 0 and 94 years; the mean age was 55.4 years (SD, ±23.9 years) and the median age was 60 years. There were 78 women and 97 men (55%). The sex of three patients was unknown because of insufficient data in the laboratory records. The median age of the women was 63 years, and that of the men was 60 years.

The 178 cases corresponded to an average incidence rate of 2.3 per 100,000 residents per year. A peak in incidence was noted in 1988 (3.7 per 100,000; 32 cases), after which it declined to the lowest rate (1.3 per 100,000; 11 cases) in 1993 (figure 1). An age-related increase in incidence was found, especially for those aged >65 years (figure 1). The year-to-year variations for the 0–24 years and 25–64 years age groups were similar and followed the average incidence more closely than did the incidence in the >65 years age group, which persisted at a high level (figure 1).

A division into more narrow age groups showed average incidence rates to be somewhat higher for the 0–4-year-olds than for the 5–14- and 15–24-year-olds (1.8 vs. 0.48 and 0.55

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>No. (%) of episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>46 (30)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>29 (19)</td>
</tr>
<tr>
<td>Peripheral vascular disease/chronic leg ulcer</td>
<td>26 (17)</td>
</tr>
<tr>
<td>Neurological or cerebrovascular disease</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Malignancy²</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Chronic renal failure³</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>5 (3)</td>
</tr>
<tr>
<td>HIV infection and hepatitis C⁴</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other⁵</td>
<td>17 (11)</td>
</tr>
<tr>
<td>Alcoholism#</td>
<td>21 (14)</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
<td>15 (9)</td>
</tr>
<tr>
<td>None</td>
<td>42 (29)</td>
</tr>
</tbody>
</table>

* Some patients had more than one underlying medical condition.
² Seven with a hematologic malignancy and five with solid cancer.
³ Requiring dialysis (6) or renal transplantation (2).
⁴ In three iv drug abusers.
⁵ Lung disease in 6, gastrointestinal or liver disease in 8, and skin disease in 3 patients.
⁶ Patients with known chronic alcoholism or medical and/or social complications of alcohol abuse noted in the medical record.

Clinical and Bacteriologic Findings

GAS strains were available from the laboratory at the Department of Clinical Bacteriology of Huddinge Hospital. Clinical and bacteriologic data were analyzed for 115 episodes identified between 1987 and 1995 (included in the epidemiological analysis above), as well as 37 further episodes recorded during 1983 to 1986. These 152 episodes involved 150 patients (1 male and 1 female had 2 episodes each). Medical records were available for 151 and GAS strains for 135 (89%) of the episodes. Ages varied from 0 to 94 years, with a mean age of 57 years (SD, ±21.7 years) and median age of 60 years. There were 67 women and 84 men (56%). The median age was 65 years for women and 59 years for men. No major changes in treatment regimens were noted during the study period. Patients were regularly treated with intravenous antibiotics, mostly β-lactams, and admitted to intensive care units whenever support of vital functions was needed.

Underlying Medical Conditions

In 109 (71%) of the 151 evaluable episodes, at least 1 underlying medical condition was recorded (table 1). Six of the 12 patients with malignant disease had undergone recent treatment with cytostatic drugs. Four of five patients with an autoimmune disorder were receiving chronic steroid medication. None of the three patients who were infected with the HIV virus had developed AIDS. Nineteen (13%) of the episodes were considered to be nosocomial [44].

Clinical Presentation

The underlying foci of the infections are listed in table 2. Skin and soft tissue were the most frequent clinical focus of infection (80 of 151; 53%), commonly in the form of erysipelas...

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>No. of cases (%)</th>
<th>STSS</th>
<th>Fatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and soft-tissue infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>28* (19)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cellulitis, erysipelas</td>
<td>40 (26)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>4 (3)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gangrene of lower extremity</td>
<td>8* (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>5* (3)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Lower</td>
<td>6* (4)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bacteremia with no septic focus</td>
<td>39 (26)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Arthritis, bursitis, or osteomyelitis</td>
<td>10 (7)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5 (3)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pelvic infection</td>
<td>3* (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3* (2)</td>
<td>1**</td>
<td>1**</td>
</tr>
<tr>
<td>Total</td>
<td>151 (100)</td>
<td>19</td>
<td>17**</td>
</tr>
</tbody>
</table>

NOTE. STSS = streptococcal toxic shock syndrome.

* Wound infection in 21, local abscess in 3, and infected thrombophlebitis in 4 patients.
1 Infected ulcer developed into vascular gangrene in 5 patients with diabetes and 3 nondiabetics (2 with previously known cardiovascular disease); all 8 patients required amputations.

1 Epiglottitis, sinusitis, septic neck adenitis, tonsillitis, and purulent rhinitis, in one patient each.
1 Two with empyema.
1 Two postpartum and one postabrasio endometritis.
1 Two patients with peritonitis and one with sepsis associated with varicella.
** One patient with peritonitis.
11 Nine with STSS.

or cellulitis. Infection with no identified septic focus was the second most frequent; in 23 of the 39 episodes of nonfocal infection, culture of a nasopharyngeal or throat specimen had been performed and yielded GAS in 11 (48%). This finding indicates the respiratory tract as a possible port of entry in these cases.

Bacteriologic Analysis

One hundred and forty-seven (97%) of the episodes were associated with a positive blood culture. Another four were associated with joint infections. The distribution of T serotypes and associated STSS and fatal episodes is shown in table 3. The T1M1 serotype was prevalent in a cyclic pattern from 1986 to 1990 and again from 1993 to 1995 (figure 3A). In 1994 seven (64%) of 11 strains were of the T1M1 serotype. In contrast, the T3M3, T12M12, and other serotypes showed no specific epidemiologic variation.

STSS

Hypotension with a blood pressure of ≤90 mm Hg and/or shock developed in 31 (21%) of the 151 episodes. The prevalence of organ dysfunction, as defined in the consensus criteria for STSS [15], in patients with or without hypotension is shown in table 4. Nineteen episodes (13%) involved two or more organ systems, thereby fulfilling the STSS consensus definition [15]. The proportion of episodes developing into STSS tended to be greater during 1988–1995 than during 1983–1987 (17 of 104 [16%] vs. 2 of 47 [7%]; \( P = .06 \); figure 3).

It is evident from table 4, however, that classic features of STSS, such as a rash or necrotizing fasciitis, were less common than renal failure and coagulopathy, commonly seen in severe sepsis or septic shock in general. Except for one case each in 1985 and 1986, several STSS cases first appeared in 1988 (figure 3). Classic toxic shock–like syndrome with multiorgan failure and a rash, or necrotizing fasciitis, appeared in three of the four STSS cases due to T1M1 strains in 1988, two in previously healthy young adults. A small cluster again appeared in 1994 and 1995: three STSS episodes were caused by T1M1 infections, one with meningitis and a rash in a previously healthy young adult. In contrast, STSS due to infections with streptococci of other serotypes showed no distinct epidemic variation; the number of cases varied between zero and two per year (figure 3B).

Factors associated in univariate logistic regression with STSS and case fatality are shown in table 5. The male sex was significantly associated with STSS, as was a history of alcohol abuse, which was the only one of the medical conditions listed in table 1 associated with a significantly increased risk of STSS. The clinical presentation commonly associated with STSS was deep-tissue infection such as pneumonia, meningitis, peritonitis, or necrotizing fasciitis, but so was infection with no clinically identified focus (8 of 39 [21%]; table 2). Infection with no identified focus was significantly more often associated with

Table 3. Serotype distribution of 135 group A Streptococcus strains isolated in 151 episodes of invasive infections (1983–1995) and numbers of streptococcal toxic shock syndrome (STSS) and fatal episodes.

<table>
<thead>
<tr>
<th>T type</th>
<th>Opacity factor</th>
<th>Total no. (%) of episodes</th>
<th>STSS</th>
<th>Fatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>– (T1M1)</td>
<td>27 (20)</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>T12</td>
<td>– (T12M12)</td>
<td>12 (9)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>T3</td>
<td>– (T3M3)</td>
<td>8 (6)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>T8</td>
<td>+</td>
<td>8 (6)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>T28</td>
<td>+</td>
<td>5 (4)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>T6</td>
<td>+</td>
<td>5 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T11</td>
<td>+</td>
<td>5 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nontypeable</td>
<td>±</td>
<td>16 (12)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>±*</td>
<td>49 (36)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>135</td>
<td>19</td>
<td>15</td>
</tr>
</tbody>
</table>

NOTE. – = negative; + = positive; ± = positive or negative.
* Less than five episodes were recorded involving each of these serotypes.
Yearly distribution of 151 episodes of invasive group A streptococcal infections and episodes of streptococcal toxic shock syndrome (STSS) from 1983 to 1995 in southern Stockholm, in relation to serotype of invasive group A Streptococcus (GAS) strain. All STSS episodes conformed with the proposed consensus criteria [15]. GAS strains were available for 135 of the 151 episodes; 2 of 9 strains for 1983 and 3 of 6 for 1984 were available, but 2 strains for 1988 and 1 each for 1987, 1989, 1990, and 1992 were lacking, whereas GAS isolates for all invasive episodes were available for 1985, 1986, 1991, and 1993–1995. A: --- = yearly distribution of all invasive episodes; ♦ = all invasive episodes due to T1M1 strains; ○ = T1M1-associated episodes of STSS. B: --- = yearly distribution of all invasive episodes; 1 = non-T1M1-associated invasive episodes; × = all non-T1M1-associated invasive episodes; + = non-T1M1-associated STSS episodes.

STSS than was erysipelas or cellulitis (OR, 10.6; 95% CI, 1.8–204; P = .03).

The mean leucocyte count for patients with STSS was \(10.9 \times 10^9/L\), and for non-STSS patients, \(16.1 \times 10^9/L\); leucopenia (initial leucocyte count, \(<4.0 \times 10^9/L\)) was significantly associated with STSS (OR, 11.1; \(P = .003\); table 5). Infection with an organism of the T1M1 serotype was associated with an increased risk of STSS (tables 5 and 6). Thirteen (48%) of the 27 patients infected with a T1M1 strain developed hypotension, and 8 of these fulfilled the definition for STSS, compared with 11 of 108 infected with strains of other serotypes. No other serotype was significantly associated with hypotension or STSS.

Table 4. Organ involvement in episodes with or without hypotension (blood pressure, \(<90\) mm Hg) in patients with invasive group A streptococcal infections.

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>Hypotension(n = 31) [22%]</th>
<th>No hypotension(n = 109) [78%]</th>
<th>(P) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>17/29</td>
<td>7/98</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>19/29</td>
<td>8/92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Liver</td>
<td>13/27</td>
<td>16/83</td>
<td>.005</td>
</tr>
<tr>
<td>ARDS(^i)</td>
<td>2/31</td>
<td>0/109</td>
<td>.05</td>
</tr>
<tr>
<td>Exanthema</td>
<td>3/31</td>
<td>1/109</td>
<td>.03</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>2/31</td>
<td>2/109</td>
<td>.21</td>
</tr>
<tr>
<td>Gangrene of extremity</td>
<td>0/31</td>
<td>8/109</td>
<td>.20</td>
</tr>
</tbody>
</table>

* According to the consensus criteria for the streptococcal toxic shock syndrome regarding organ involvement [15]. Laboratory values were not available for all patients.

\(^i\) Blood pressure of \(<90\) mm Hg (30 patients) or shock with no recorded blood pressure (one patient).

\(^\dagger\) In 11 episodes, blood pressure had not been recorded.

\(^\ddagger\) Per Fisher’s exact test.

\(^\S\) Adult respiratory distress syndrome.

Table 5. Univariate logistic regression analysis of factors associated with the streptococcal toxic shock syndrome (STSS) and death among patients with invasive group A streptococcal disease. For comparison, figures for both outcomes are included for each characteristic that was significantly associated with one of the two outcomes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>STSS (OR [95% CI])</th>
<th>(P) value</th>
<th>Fatal outcome (OR [95% CI])</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.66 (0.1–5.5)</td>
<td>&gt;.2</td>
<td>5.5* (0.55–72.9)</td>
<td>.16</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>4.8 (1.5–21.6)</td>
<td>.02</td>
<td>1.2 (0.42–3.4)</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>Alcohol abuse(^\dagger)</td>
<td>3.4 (1.1–9.9)</td>
<td>.03</td>
<td>0.81 (0.12–3.2)</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>Malignancy(^\ddagger)</td>
<td>3.5 (0.46–19.6)</td>
<td>.16</td>
<td>6.9 (1.3–34.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Immunosuppression(^\S)</td>
<td>0.9 (0.2–3.2)</td>
<td>&gt;.2</td>
<td>3.1 (0.9–9.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Leukopenia(^\S)</td>
<td>11.1 (2.2–61.7)</td>
<td>.003</td>
<td>15.7 (3.6–72.3)</td>
<td>.0002</td>
</tr>
<tr>
<td>Nonfocal infection</td>
<td>2.6 (0.9–7.1)</td>
<td>.06</td>
<td>5.2 (1.8–15.4)</td>
<td>.002</td>
</tr>
<tr>
<td>T1M1 strain infection</td>
<td>3.5 (1.2–9.9)</td>
<td>.02</td>
<td>0.58 (0.1–2.3)</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Not applicable</td>
<td>38.6 (9.7–261)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>STSS</td>
<td>Not applicable</td>
<td>13.9 (4.5–45.7)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

* For each 1-year increase in age.

\(^\dagger\) Patients with known chronic alcoholism or medical and/or social complications from alcohol abuse noted in the medical record.

\(^\ddagger\) Malignancy recently treated with cytostatic drugs.

\(^\S\) Twenty-six patients with malignancy (11), autoimmune disease (4), chronic renal failure (6), HIV infection (3), or chronic renal failure with either malignancy (1) or autoimmune disease (1).

\(^\ddagger\) Peripheral leukocyte count of \(<4.0 \times 10^9/L\) recorded <48 hours after admission or blood culture.
Recent studies have shown a high prevalence of asymptom-
tors associated with the streptococcal toxic shock syndrome (STSS) (26 patients); malignancy recently treated with cytostatic drugs; leukopenia; and nonfocal infection (table 5). Mortality was strongly associated with STSS but also with hypotension gener-
ally, regardless of whether organ failure developed (table 5). Thirteen of the 31 patients with recorded hypotension died, in contrast to only 2 of 109 with no recorded hypotension ($P < .0001$). No particular T-serotype was associated with excess mortality; e.g., only two of the 27 episodes due to a T1M1 strain ended fatally.

In the multivariate model, age, immunosuppression, and
STSS remained significantly associated with a fatal outcome (table 6). Hypotension, regardless of whether a full picture of
STSS developed, also remained strongly associated with a fatal outcome (data not shown).

### Discussion

Several reports have emphasized the serious nature and high
fatality rate of severe invasive GAS disease, although not spe-
cifically addressing the issue of long-term changes in incidence
or severity [45–51]. In the present report, incidence increased with age and was particularly high in the oldest age group
throughout the study period, whereas incidence peaked in 1988
and 1989 in the younger age groups, congruent with the in-
creased prevalence of T1M1 strains. This would indicate in-
creased susceptibility in the elderly for invasive disease due to
endemic as well as more epidemic GAS strains.

Recent studies have shown a high prevalence of asymptom-
atic throat carriage of the invasive GAS clone in pediatric
populations in social settings close to the index cases with
invasive disease [52, 53]. The expansion of an epidemic clone
can thus take place primarily among children, who are often
asymptomatic, with secondary cases occurring mainly in the
parent generation. For elderly patients, especially those with
chronic diseases, infection with any GAS strain, epidemic or
endemic, may constitute a higher risk of invasive disease.

Whether the T1M1 strains showed higher invasive potential
than other serotypes, i.e., a higher prevalence among invasive
cases than noninvasive cases, cannot be inferred from our
study, since all our cases were invasive and no control group
was available. To our knowledge, no such controlled study has
been performed, although T1M1 strains submitted to reference
laboratories have been more prevalent among invasive than
noninvasive infections [22]. However, data based on referred
strains are often subject to bias [13].

In fact, a high prevalence of T1M1 strains was noted among
patients with tonsillitis in Sweden in 1988–1989 [36], and
parallel changes of the T1M1 serotype prevalence among blood
and pharyngeal isolates was noted in Uppsala County, Sweden,
in 1989–1995 [38]. Therefore, the prevalence of a particular
GAS serotype in invasive infections (i.e., infection within a
normally sterile compartment) may largely represent the gen-
eral spread of that serotype in a population. However, the par-

### Table 6. Multivariate logistic regression analysis of underlying factors associated with the streptococcal toxic shock syndrome (STSS) and death for patients with invasive group A streptococcal infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STSS Alcohol abuse*</td>
<td>6.3 (1.8–22.9)</td>
<td>.004</td>
</tr>
<tr>
<td>T1M1 strain infection</td>
<td>4.6 (1.5–14.7)</td>
<td>.007</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>14.5 (0.9–389)</td>
<td>.08</td>
</tr>
<tr>
<td>Immunosuppression$^*$</td>
<td>4.7 (1.2–18.9)</td>
<td>.02</td>
</tr>
<tr>
<td>STSS</td>
<td>21.5 (5.9–89.9)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* Patients with known chronic alcoholism or medical and/or social complica-
tions from alcohol abuse noted in the medical record.

$^*$ Twenty-six patients with malignancy (11), autoimmune disease (4), chronic renal failure (6), HIV infection (3), or chronic renal failure with either malign-
ancy (1) or autoimmune disease (1).
ticular ability to induce specific complications of invasive infections, such as STSS or necrotizing fasciitis, may vary due to strain- or clone-specific virulence factors or to host immunity to these factors [54].

Risk factors operating in patients developing STSS during infection with GAS strains are not fully understood. Unlike in the staphylococcal toxic shock syndrome, an invasive infection is usually required, although noninvasive GAS pharyngitis has been reported to precipitate STSS [55]. By multivariate logistic regression analysis, STSS was shown to be significantly associated with alcohol abuse and infection with T1M1 strains (table 6). Alcohol overconsumption has previously been reported to be related to STSS [4]. M1 and M3 strains, which produce SPE-A, have been reported to be particularly prone to induce STSS [25]. This association has been questioned, since considerable genetic variability has been demonstrated among strains causing STSS [30]. Furthermore, no significant correlation was found between the M1 serotype or SPE-A and STSS or fatality in a prospective study [13].

However, in our study nearly half (13 of 27) of the patients infected with a T1M1 strain developed hypotension, and about 30% (8 of 27) developed full-blown STSS. This relation remained highly significant in the multivariate model as well. The long observation time of our study may have revealed this association between T1M1 infection and STSS more clearly. Furthermore, episodes with classic clinical features of toxic shock, such as an exanthema, as well as episodes of necrotizing fasciitis, were generally uncommon but clustered among T1M1 infections, whereas the majority of episodes of hypotension and organ failure did not differ clinically from the syndromes of severe sepsis and septic shock in general [56].

Risk factors for STSS in univariate regression, other than a T1M1 infection, were male sex, alcohol abuse, infection with no identified focus, and initial leukopenia (table 5). Alcohol abuse and T1M1 infection were significantly associated in the multivariate model as well.

Whether impaired neutrophil (phagocytic) function is directly involved in the pathogenesis of STSS is not known. The M-protein exhibits its main virulence function by antiphagocytic properties [57]. Alcoholism is known to significantly impair neutrophil function [58], and there was a trend in our study of increased risk for STSS in patients treated with cytostatic drugs (table 5). These data point to the importance of phagocytic function in protection against STSS in invasive infections. Alternatively, impaired phagocytic function may allow for increased bacterial load and expression of specific virulence factors involved in the pathogenesis of STSS, notably the streptococcal superantigens [16].

The case fatality rate associated with STSS in our study was 47%, well in agreement with previous studies [16]. Use of a consistent definition of STSS seems important when comparing mortality data, since in one study a case fatality rate of 81% was noted when rapidly fatal cases with incomplete data for STSS definition were included, whereas the rate was 65% in cases fulfilling the consensus definition [13]. Similarly, the inclusion of rapidly fatal cases in the STSS definition increased the mortality figure from 47% to 58% in this study.

The case fatality rate did not show any distinct epidemiological variation and, unlike STSS, was not related to infections with T1M1 strains. This may be due to the limited power of the study. Increasing age and STSS, as well as severe underlying disease affecting immunocompetence, were related to a higher risk of a fatal outcome. Hypotension, even without organ failure, was a significant risk factor for a fatal outcome; this was revealed also in multivariate analysis (data not shown).

In conclusion, T1M1 strains were introduced and widely spread among invasive GAS infections in Stockholm from 1986 onward and carried a higher risk for development of STSS than did invasive infections with non-T1M1 strains. There were temporal increases in incidence of invasive disease but no general increase between 1987 and 1995. The oldest age group had a substantially higher incidence of invasive GAS disease than did the younger age groups throughout the study period. Alcohol abuse and infection with T1M1 strains were identified as independent risk factors for the development of STSS, whereas advanced age, an immunocompromised state, and the development of STSS were identified as independent risk factors affecting fatality.

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