Invasive Group A Streptococcal Infections in Children

A Nationwide Survey in Finland

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Background: The incidence of invasive group A streptococcus (iGAS) infections varies in time and geographically for unknown reasons. We performed a nationwide survey to assess the population-based incidence rates and outcomes of children with iGAS infections.

Methods: We collected data on patients from hospital discharge registries and the electronic databases of microbiological laboratories in Finland for the period 1996–2010. We then recorded the enm types or serotypes of the strains. The study physician visited all university clinics and collected the clinical data using the same data entry sheet.

Results: We identified 151 children with iGAS infection. Varicella preceded iGAS infection in 20% of cases and fasciitis infection in 33% of cases. The annual incidence rate of iGAS infection was 0.93 per 100,000 in 1996–2000, 1.80 in 2001–2005 and 2.50 in 2006–2010. The proportion of enm 1.0 or T1M1 strains peaked in 1996–2000 and again in 2006–2010, to 44% and 37% of all typed isolates. The main clinical diagnoses of the patients were severe soft-tissue infection (46%), sepsis (28%), empyema (10%), osteoarticular infection (9%) and primary peritonitis (5%). Severe pain was the most typical symptom for soft-tissue infections. More than half of the patients underwent surgery and received clindamycin. The readmission rate was 7%, and the case fatality rate was 2%.

Conclusions: The incidence rate of pediatric iGAS infections tripled during our study. The increase was not, however, the result of a change in the strain types causing iGAS. Varicella immunization would likely have prevented a significant number of the cases.

Key Words: Streptococcus pyogenes, epidemiology, microbiology, fasciitis, streptococcal M protein, chickenpox, chickenpox vaccine

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during the whole study period independently on the rate of obtaining deep tissue cultures.

The study physician visited all pediatric university clinics and systematically collected the data using the same data entry sheet and IBM SPSS software (IBM, Armonk, NY). A study physician, together with the treating physicians in 5 university hospitals, reviewed the medical records of all possible cases and recorded any underlying conditions, antimicrobial and surgical treatment, intensive care, outcome, recurrences and sequelae.

For our patient series presenting the clinical details and outcome of our patients, all children treated in pediatric university clinics during the study era were included. Pediatric university clinics in Finland treat all children younger than 16 years and occasionally patients of 16–17 years of age. There were 3 patients aged 16–17 years who were treated in pediatric clinics during the study era.

For our population-based calculations, we used the mean annual population of children younger than 15 years during the study period in each hospital district to calculate the population-based incidence rates (per 100,000 children per year). Mean annual population of children in each hospital district in each study year was obtained from Official Statistics of Finland (OSF), which is a comprehensive collection of statistics describing the development and state of society. The basic data of the OSF are available to all users free of charge. The cut-off age of 15 years was chosen as it is used in OSF databases to report the number of children. Thus children older than 15 years and/or referred to the university hospital from other hospital districts (11 cases with any iGAS infection and 3 cases with positive blood culture infection) were excluded from the population-based analyses.

To compare clinical manifestations and incidence rates in different geographical areas within Finland, the data are also presented separately for each hospital. Oulu University Hospital is located 610 km north of Helsinki and Kuopio University Hospital, 390 km northeast of Helsinki; Turku, Tampere and Helsinki University Hospitals are located within 180 km of each other in the southern part of Finland (Fig. 1). The driving times (minutes) from patients’ homes to the nearest university hospital were calculated with a geoinformatics software program (ArcGIS ESRI Inc., Redlands, CA) by using Digiroad database available for this purpose in the Department of Geography, University of Oulu, Finland.

The research plan was accepted in all pediatric university clinics before the study, and the data registry announcement was sent to the national Office of the Data Protection Ombudsman. In accordance with regulations in Finland, no ethical committee review or informed consent is required for registry-based studies conducted by the physicians of institutions that have treated the patients in the study. All medical data reviewed in this study served scientific purposes only and remain confidential.

RESULTS

We identified a total of 151 cases of confirmed or probable iGAS infections in children younger than 18 years between 1996 and 2010 (Table 1). The diagnosis of confirmed cases (n = 123) was based on a positive blood culture (n = 51), a positive deep tissue culture (n = 60) or both (n = 12; Table 2). The diagnosis of probable
The mean age of the patients was 7.0 years (standard deviation, 4.4; range, 2 days to 17.8 years; Table 1; Fig. 2), and 57% (86 cases) were boys. Most children were previously healthy before the iGAS infection and lived within a 1-hour drive from the university hospital (Table 1). Altogether 30 (20%) children had had a recent varicella infection before (<1 month) the invasive GAS infection (Table 1) and in children with fasciitis, 83% of families (10/12) reported a preceding chickenpox infection. In total, 22 (15%) children had had a family member with recent streptococcal pharyngitis. Six (4%) cases had undergone surgery before invasive GAS, and many (49%) families reported that a child had suffered a minor skin trauma, such as a scratch or cut before iGAS, according to medical records.

Almost all the children had a fever before arriving at the hospital. The mean duration of fever was 2.8 days (standard deviation, 2.7) before admittance. Records also contain frequent reports of local pain and skin erythema (Table 1). The main clinical diagnoses of the patients were cellulitis (n = 57), sepsis (n = 42), empyema (n = 15), fasciitis (n = 13), arthritis (n = 10), peritonitis (n = 7), osteomyelitis (n = 3) and a sepsis-like illness without a positive blood culture (n = 4; Table 2). Of the 57 cases with cellulitis, 40 involved a positive deep tissue culture, and 17 cases, a positive skin or throat swab. Severe pain was the most typical symptom of severe iGAS soft-tissue infection (Table 1).

The population-based incidence rate of iGAS infections was 1.60 per 100,000 per year, and the population-based incidence rate of blood culture-positive iGAS infections was 0.67/100,000 per year during the study period. The annual incidence rate of iGAS infections among children younger than 15 years was 0.93 per 100,000 [95% confidence interval (CI): 0.6–1.4] in 1996–2000, 1.76 (95% CI: 1.3–2.3) in 2001–2005 and 2.50 (95% CI: 1.9–3.2) in 2006–2010 (Fig. 3). If only the confirmed cases were included, the incidence rates were 0.71, 1.53 and 1.87, respectively (Fig. 3). The annual incidence rate of blood culture-positive iGAS infections almost tripled from 0.37 per 100,000 (95% CI: 0.2–0.7) in 1996–2000 to 1.16 (95% CI: 0.8–1.6) in 2006–2010 (Fig. 3). The incidence of iGAS infection was highest in December to February.

Serotypes were available from 8 isolates before the emm typing era, and emm types were available from 52 isolates (Fig. 4). The proportion of emm 1.0 or T1M1 strains among the typed isolates was 44% (4/9) in 1996–2000, 15% (2/13) in 2001–2005 and 37% (14/38) in 2006–2010.

The incidence rates in the 2 northernmost hospital districts (Oulu and Kuopio) were the highest (Table 3; Fig. 1). The population-based incidence rate of iGAS infections was 1.60 per 100,000 per year, and the population-based incidence rate of blood culture-positive iGAS infections was 0.67/100,000 per year during the study period. The annual incidence rate of iGAS infections among children younger than 15 years was 0.93 per 100,000 [95% confidence interval (CI): 0.6–1.4] in 1996–2000, 1.76 (95% CI: 1.3–2.3) in 2001–2005 and 2.50 (95% CI: 1.9–3.2) in 2006–2010 (Fig. 3). If only the confirmed cases were included, the incidence rates were 0.71, 1.53 and 1.87, respectively (Fig. 3). The annual incidence rate of blood culture-positive iGAS infections almost tripled from 0.37 per 100,000 (95% CI: 0.2–0.7) in 1996–2000 to 1.16 (95% CI: 0.8–1.6) in 2006–2010 (Fig. 3). The incidence of iGAS infection was highest in December to February. Serotypes were available from 8 isolates before the emm typing era, and emm types were available from 52 isolates (Fig. 4). The proportion of emm 1.0 or T1M1 strains among the typed isolates was 44% (4/9) in 1996–2000, 15% (2/13) in 2001–2005 and 37% (14/38) in 2006–2010.

The incidence rates in the 2 northernmost hospital districts (Oulu and Kuopio) were the highest (Table 3; Fig. 1). In Oulu University Hospital, the majority of children had severe soft-tissue

*Includes both patients with a positive deep tissue culture or blood culture (n = 40) and patients with a positive skin or throat swab (n = 17).
†Includes 4 patients with sepsis-like illness but a negative blood culture.
‡One child can be included in more than 1 group.
SD indicates standard deviation.

### TABLE 2. Positive Microbiological Findings and the Mean Duration (Days) of Any Antimicrobial Treatment for GAS Among Children With Invasive GAS Infection (n = 151) According to the Treating Physician’s Main Clinical Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
<th>Blood Culture</th>
<th>Deep Tissue Culture</th>
<th>Throat or Skin Swab</th>
<th>Antimicrobials (day, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>57 (16)</td>
<td>9 (16)</td>
<td>34 (60)</td>
<td>17 (30)</td>
<td>15.0 (8.0)</td>
</tr>
<tr>
<td>Sepsis†</td>
<td>46 (100)</td>
<td>42 (100)</td>
<td>1 (2)</td>
<td>5 (11)</td>
<td>13.4 (8.5)</td>
</tr>
<tr>
<td>Empyema</td>
<td>15 (33)</td>
<td>5 (33)</td>
<td>7 (47)</td>
<td>4 (7)</td>
<td>22.6 (8.5)</td>
</tr>
<tr>
<td>Fasciitis</td>
<td>13 (0)</td>
<td>0 (0)</td>
<td>12 (92)</td>
<td>1 (8)</td>
<td>16.4 (4.1)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>10 (50)</td>
<td>5 (50)</td>
<td>9 (90)</td>
<td>0 (0)</td>
<td>21.4 (9.6)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>7 (0)</td>
<td>0 (0)</td>
<td>7 (100)</td>
<td>0 (0)</td>
<td>10.0 (11.5)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>3 (67)</td>
<td>2 (67)</td>
<td>2 (67)</td>
<td>0 (0)</td>
<td>38 (2.5)</td>
</tr>
</tbody>
</table>

* Includes both patients with a positive deep tissue culture or blood culture (n = 40) and patients with a positive skin or throat swab (n = 17).
† Includes 4 patients with sepsis-like illness but a negative blood culture.

**FIGURE 2.** Age distribution of children with invasive GAS infection treated in pediatric university clinics in Finland in 1996–2010. The patients aged 16–17 years are only occasionally treated in pediatric clinics (*).
infection (fasciitis or cellulitis; 24/39, 62%) or empyema (10/39, 26%), whereas in Tampere University Hospital, most children had sepsis (14/22, 64%). *emm* 1.0 strains were present in all university hospitals and in all clinical manifestations. *emm* 28.0 strains caused mainly sepsis (7/9) and were not detected in Oulu.

A total of 29 (19%) children received treatment in an intensive care unit, 17 (11%) patients required ventilator treatment, and 14 (9%) children had hypotension treated with ionotropic drugs. One child received treatment with extracorporeal membrane oxygenation, and 7 children received intravenous (i.v.) immunoglobulin. One child received treatment with extracorporeal membrane oxygenation, and 7 children received intravenous (i.v.) immunoglobulin.

Of the 151 patients, 83 (55%) underwent at least 1 surgical procedure (Table 4). Surgical treatment was most common in children with fasciitis, 92% (n = 12/13) of whom underwent fasciotomy. All children with empyema (n = 15) had either a chest tube or underwent thoracotomy. The most typical clinical picture of iGAS soft-tissue infection was unusually severe pain in one or more anatomic regions of the body after a varicella infection that stopped promptly after the incision or fasciotomy. Three children underwent appendectomy because of unusual severe pain from suspected appendicitis. Most children found severe soft-tissue infection to be very painful and had a toxic appearance before surgery, but the necrotizing tissue was rarely observed in surgery.

Ten children were readmitted after the first treatment period (n = 10, 7%), approximately 1 week after the discharge. The diagnoses of the readmitted patients were cellulitis (n = 5), arthritis (n = 2), empyema (n = 1) and sepsis (n = 2). Half of the readmitted patients had received β-lactams without clindamycin (n = 5/10), and rest of them (n = 5/10) received clindamycin alone or combined with β-lactams during their first hospitalization (range, 1–21 days). Five of the readmitted patients had undergone surgical procedure before the discharge and 2 patients after they were readmitted.

At least 1 follow-up visit after the acute treatment was scheduled for 83 children of 148 (56%) discharged patients. One child had restricted joint movements in 1 finger; 1 child had still pleural thickening on chest radiography after empyema but was clinically asymptomatic; 2 children had suspected reactive arthritis on several joints, and one child had Clostridium difficile diarrhea treated with oral metronidazole.

Of the 151 children, 3 (2.0%) died of iGAS infection. One patient admitted to the hospital died there. This 2-year-old girl was previously healthy but deteriorated during the hospital treatment and died of septic shock (caused by serotype T1, *emm* 1.0) on day 3 after receiving i.v. penicillin as a monotherapy for the treatment of pneumonia, empyema and sepsis. The other 2 patients died before reaching the hospital: one of them, an 18-month-old boy, was found dead in bed at home after 1 day of febrile illness; *S. pyogenes* was...
Minodier et al1 1999–2007 Quebec Patient series 68 NR 27 56% 4.4%
Henriet et al2 2000–2007 Paris Patient series 28 NR 25† 61% 3.6%
Laupland et al3 1992–1996 Ontario Prospective surveillance 243 1.9 43† 65% 4.1%
Tapiainen et al (this study)1996–2010 Finland Patient series 151 1.6 47† 42% 2/0.6%‡

The reported incidence and CFRs are not directly comparable because of different study designs and variable case definitions.

§Only necrotizing fasciitis included in the study.
‡Of the 151 children in this study, 3 (2%) died, 2 of whom died before reaching the hospital; 1 (0.6%) of 149 died after admittance.
†Fasciitis and severe soft-tissue infections combined.
*Incidence rate per 100,000 children/year.

TABLE 5. Summary of Main Findings in Clinical Studies of iGAS Infections in Children Including This Study

<table>
<thead>
<tr>
<th>Author</th>
<th>Years</th>
<th>Region</th>
<th>Design</th>
<th>Patients (N)</th>
<th>Incidence*</th>
<th>Fasciitis (%)</th>
<th>Blood culture+</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>iGAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minodier et al1</td>
<td>1999–2007</td>
<td>Quebec</td>
<td>Patient series</td>
<td>68</td>
<td>NR</td>
<td>27</td>
<td>56%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Henriet et al2</td>
<td>2000–2007</td>
<td>Paris</td>
<td>Patient series</td>
<td>28</td>
<td>NR</td>
<td>25†</td>
<td>61%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Laupland et al3</td>
<td>1992–1996</td>
<td>Ontario</td>
<td>Prospective surveillance</td>
<td>243</td>
<td>1.9</td>
<td>43†</td>
<td>65%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Tapiainen et al (this study)</td>
<td>1996–2010</td>
<td>Finland</td>
<td>Patient series</td>
<td>151</td>
<td>1.6</td>
<td>47†</td>
<td>42%</td>
<td>2/0.6%‡</td>
</tr>
</tbody>
</table>

The incidence rate per 100,000 children/year.
Fasciitis and severe soft-tissue infections combined.
§Only necrotizing fasciitis included in the study.
CFR indicates case fatality ratio; NR, not reported.

stantions must take into account local clindamycin resistance.13 In Finland during the study period, the proportion of S. pyogenes strains resistant to clindamycin was low (0%–2%).15 Aggressive surgical debridement of any deep-seated GAS infection is recommended.13 In one earlier patient series among children with suspected necrotizing fasciitis, only those who underwent active surgery within hours of their arrival at the hospital survived.5 Accordingly, our patients underwent active surgery, with 55% undergoing at least 1 surgical procedure. In our patients undergoing soft-tissue surgery, however, clear necrotizing fasciitis was rare.

GAS infections recurred in 10% of our patients even after receiving long antimicrobial treatment. Viable intracellular GAS residing inside macrophages have been present in human biopsies even after prolonged i.v. antimicrobial treatment (i.e., β-lactam and clindamycin) of GAS soft-tissue infections.13 Researchers have previously proposed similar mechanisms to explain the frequent recurrences of streptococcal pharyngitis.11,12 Thus, the relapses of GAS infections in our patients may have derived from an intracellular reservoir after stopping the antimicrobials.

Preceding chickenpox has reportedly increased the risk for GAS infections in children from 50-fold to 60-fold within the first month after the infection.7 The national immunization program for children in Finland has not yet included varicella immunization despite the recommendations of the experts. More than 80% of

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iGAS fasciitis cases and 20% of all iGAS cases in our study were associated with recent chickenpox and could have been prevented with varicella vaccination. The findings of this study further support the use of universal varicella immunization for children.

The most prevalent GAS strain namely emm1/T1M1 accounted for one third of the cases in our study. Streptococcal M protein is located on the surface of \textit{S. pyogenes} and, together with pyrogenic exotoxins, is an important virulence factor and capable of inducing septic shock. 17 The immune response to GAS develops against surface structures, which are thus under selective pressure. \textit{Emm} 1 strains have been associated with the increase of iGAS infections in many countries. 8,18–21 Based on the whole genome sequencing of more than 3600 \textit{emm} 1 strains collected in 8 countries in 1969–2012, the acquisition of specific genetic elements in 1 GAS cell in the early 1980s might be the origin of the iGAS epidemic observed in many countries since the late 1980s. 22 In our study, the relative proportion of \textit{emm} 1 strains showed a typical fluctuation. 7 \textit{Emm} 28.0 strains were not found in Oulu where the occurrence of iGAS infections was the highest.

In our study, the northernmost university hospital district, Oulu (64–70° northern latitude), had the highest annual incidences of iGAS infection, especially severe soft-tissue infections. The strain type distribution did not clearly differ between the university hospitals and did not explain the differences observed. In adult populations, iGAS infections are most common in northern European countries, where the annual incidence rate of iGAS infections has reached 3 per 100,000. 23 In North America, the high incidence rates have been observed in Canada. 3,4 The reasons for the higher risk for iGAS infections in northern countries are not yet understood.

Strengths of this study are its systematic collection of nationwide clinical data on pediatric iGAS infections over a 15-year period. This patient series of iGAS infections in children is one of the largest available (Table 5), and we present the temporal changes in the population-based incidences of iGAS together with the bacterial typing data. The main limitation of the study is that the efficacy of different treatments cannot be analyzed in this study, as our study design was observational. Yet, the active surgery and active use of clindamycin may explain the low case fatality rate in our patients. In addition, the electronic microbiological databases were not available before year 2000, which may partly explain the increasing number of found cases since 2000.

In conclusion, the incidence of pediatric iGAS infections has tripled in Finland over the past 15 years, a rise that cannot be explained only by the rise of \textit{emm} 1.0 (M1T1) strains in the community. Varicella immunization would have prevented a large number of the pediatric iGAS cases observed.

REFERENCES


