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T. Siljander, O. Lyytikäinen, S. Vähäkuopus, M. Snellman, J. Jalava, et al.. Epidemiology, outcome and types of invasive group A streptococcal infections in Finland. European Journal of Clinical Microbiology and Infectious Diseases, 2010, 29 (10), pp.1229-1235. 10.1007/s10096-010-0989-9 . hal-00601637

HAL Id: hal-00601637

<https://hal.science/hal-00601637>

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Editorial Manager(tm) for European Journal of Clinical Microbiology & Infectious
Diseases
Manuscript Draft

Manuscript Number: EJCMI-D-10-00104R1

Title: Epidemiology, outcome and emm types of invasive group A streptococcal infections in Finland

Article Type: Article

Keywords: group A streptococcus; Streptococcus pyogenes; epidemiology; emm typing; outcome; bacteraemia

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Abstract: Purpose. In 2006, Finnish nationwide surveillance showed an increase of invasive group A streptococcal (iGAS) disease and clinicians were alarmed by severe disease manifestations, prompting investigation of recent trends and outcome for iGAS.

Methods. A case of iGAS was defined as Streptococcus pyogenes isolated from blood or cerebrospinal fluid. Cases during 1998-2007 and isolates during 2004-2007 were included. Case-patients' 7-day outcome was available for 2004-2007. Isolates were emm-typed.

Results. 1318 cases of iGAS were identified. The average annual incidence was 2.5/100,000 population. The rate was higher in males than females in persons aged 45-64 years, but lower in persons aged 25-34 years. The annual incidence was highest in 2007 (3.9/100,000). Occasional peaks occurred during midwinter and midsummer. The most common emm types were 28 (21%), 1 (16%), 84 (10%), 75 (7%) and 89 (6%). During 2004-2007, emm1 replaced emm28 as the most predominant type. The overall case fatality was 8%. Cases with emm1 were associated with high case fatality (14% vs. 8% in other types; $P<0.02$); that of emm28 infections was 2% ($P<0.01$).

Conclusions. Changes in emm-type prevalence influenced incidence and case fatality. Differences in age- and sex-specific incidence and seasonal patterns suggest variation in predisposing factors and underlying conditions.

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Cover letter

[Click here to download Electronic Supplementary Material: Siljander_cover_letter_rev1.doc](#)

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May 20th, 2010

European Journal of Clinical Microbiology & Infectious Diseases

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ABSTRACT

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Key words: group A streptococcus; *Streptococcus pyogenes*; epidemiology; *emm* typing; outcome; bacteraemia

INTRODUCTION

Streptococcus pyogenes (group A streptococcus, GAS) causes a wide array of infections ranging in severity from mild pharyngitis and skin/soft tissue infections to severe invasive infections. In the late 1980s, a change in the epidemiology of severe GAS infections, with an increase in the incidence and severity of disease was documented [20]. The role and increased pathogenic potential of type M1 in epidemics were of specific interest [13, 25]. The incidence of severe GAS disease shows variations over time and geographic region, possibly reflecting the population's susceptibility to particular strains with diverse virulence properties [9, 17, 26]. Dynamic changes in the type distribution of GAS may also influence the case fatality of these infections.

In Finland, the incidence rate of invasive group A streptococcal (iGAS) disease has also shown fluctuations during this and the previous decade, and an increasing trend has been noticed [21]. In 2006, clinicians contacted the National Institute for Health and Welfare and described suddenly encountering more severe disease manifestations with a poor outcome. These events prompted us to investigate the recent trend and outcome of iGAS infections and *emm* type distribution in Finland in more detail.

METHODS

Surveillance. The national healthcare system of Finland (population 5.3 million) is organised into 20 healthcare districts (with catchment populations ranging from 58,000 to 1.5 million), forming five tertiary care districts. Since 1995, all clinical microbiology laboratories have mandatorily notified all isolations of *S. pyogenes* from blood or cerebrospinal fluid (CSF) to the National Infectious Disease Register (NIDR). With each notification, the following information is transmitted (generally electronically) to the NIDR: date and type of specimen, unique national identity code of the patient (since 2004), date of birth, sex, and place of treatment. Within an interval of three months, notifications concerning the same patient are merged into a single case. The corresponding *S. pyogenes* isolates are submitted to the national reference laboratory.

Case definition and outcome. A case of iGAS was defined as *S. pyogenes* isolated from blood or CSF. In this study, iGAS cases from January 1998 to December 2007 and isolates from January 2004 to December 2007 were included. Case-patients' vital status at 7 days of positive blood or CSF culture was obtained for 2004-2007 from the Population Information System through the use of the national identity codes.

Identification and characterisation of isolates. Isolates were tested for sensitivity to bacitracin, and the Lancefield group A antigen was identified using Streptex latex agglutination (Remel Europe Ltd, U.K.). *emm* typing was performed for all isolates according to guidelines by the Centers of Disease Control and Prevention (http://www.cdc.gov/ncidod/biotech/strep/protocol_emm-type.htm) as previously described [22]. Susceptibility to erythromycin, clindamycin, and tetracycline was determined with agar dilution method for all isolates. Susceptibility was assigned according to interpretative criteria for MIC as recommended by the Clinical and Laboratory Standards Institute [2].

Data analysis and statistics. Data on the cases of iGAS, their outcome, and *emm* typing and antimicrobial susceptibility data (where available) were linked using the national identity code of the case-patient and the date of specimen. Where the national identity code was unavailable, other available information was used for linkage. Average annual incidence rates were calculated for 1998-2007 using the population census at the end of the previous year, as obtained from Statistics Finland. Age- and sex-specific incidence rates and male-to-female ratios with 95% confidence intervals (CI) according to Poisson distribution were calculated. 7-day case fatality was calculated for 2004-2007 and for each *emm* type separately. χ^2 and Kruskal-Wallis tests were applied where appropriate to test for statistical significance between subgroups and distributions. Differences were considered significant when $P < 0.05$. Data were analyzed with Intercooled StataTM 9.1 software for Windows (StataCorp, U.S.) and R statistical software version 2.9.0 (R Development Core Team, Austria).

RESULTS

Incidence rates. From January 1998 to December 2007, 1318 cases of iGAS (range by year, 100-207) were identified (Table 1). The median age of case-patients was 52 years (range, 0-95 years); 55% were males. The average annual incidence rate of iGAS was 2.5 cases per 100,000 population. The rate was

higher in males than in females and in males of adult age groups it increased with age (Table 2). The highest rates were observed among the elderly patients. Males had a significantly higher rate of infection than females especially among persons aged 45-64 years, whereas females had a higher rate than males among persons aged 25-34 years.

The annual incidence rate fluctuated (range by year, 1.9-3.9 cases per 100,000 population) but showed an increasing trend during the study period. Peaks occurred in 2002 (2.9 cases per 100,000) and in 2006-2007 (3.1-3.9). The average annual incidence rate in the five tertiary care districts varied between 1.8-3.1 cases per 100,000. Of all cases, 41% were localized in the tertiary care district around Helsinki, where the annual incidence rate varied within the range of 2.2-4.4 cases per 100,000. Variation in the seasonal activity of iGAS disease could be identified, with occasional peaks of cases occurring during the midwinter (for both sexes) and midsummer (with male cases dominating; Figure 1a and 1b).

***emm* sequence types.** For 602 out of 609 cases during 2004-2007, a corresponding isolate was received. A total of 46 *emm* types were encountered (range by year, 23-28 types). The annual proportion of non-typable isolates varied within 1-5%. The five most common *emm* types were 28, 1, 84, 75 and 89, together accounting for 60% of isolates (Table 3). Type *emm*28 was the most predominant type in 2004, but its proportion declined each year while that of *emm*1 increased, and by 2007, *emm*1 became the most common type. Type *emm*1 isolates were mainly of subtypes 1.0 and 1.10, but sporadic cases of other subtypes were also encountered. A new and uncommon type, *emm*84, emerged in 2005 and became the second most common type by 2007.

Type *emm*28 infections were over-represented in females compared to males (55% vs. 45%, $P<0.01$), and the same was true for *emm*4 infections (73% vs. 27%, respectively, $P<0.05$). Specifically, females of child-bearing age (15-44 years) had a significantly larger proportion of infections by *emm*28 than males of the same age (48% vs. 21% of *emm*28 infections, respectively; $P<0.01$).

Outcome. During 2004-2007, 48/609 case-patients died within 7 days of the positive blood or CSF culture (overall case fatality, 8%). The case fatality did not significantly differ between males and females (9% vs. 6%, $P=0.172$). The case fatality was the lowest in 2004 (3%), increasing to its highest

in 2005 (12%), and then declined by 2006 (10%) and 2007 (7%). The case-patients with fatal outcome were older than those who survived (median age, 60 vs. 54 years; $P<0.01$). No fatalities occurred in patients aged <1 and 15-24 years.

Overall, infections by *emm1* were significantly associated with higher case fatality (14% vs. 8% with all other types; $P<0.02$, Table 3). Cases by *emm75* and 79 were also associated with higher than average case fatality (14% for both). In contrast, *emm28* was associated with lower case fatality (2% vs. all other types, $P<0.01$) along with type 81 (0%, respectively).

Antimicrobial susceptibility. Of the iGAS isolates tested, 1.5% (9/602) were resistant to erythromycin, 0.5% (3/602) to clindamycin and 16% (97/602) to tetracycline. The tetracycline resistant strains were mainly of *emm* types 81 (20 resistant isolates in total; 87% of this type resistant to tetracycline), 27G (19; 100%), 77 (12; 100%) and 85 (9; 100%).

DISCUSSION

This study presents a comprehensive description of the recent epidemiology and outcome of invasive group A streptococcal (*Streptococcus pyogenes*) disease with information on *emm* type prevalence in a well-defined population. The main strength of the study is the nationwide population-based surveillance and the good coverage of isolate collection. We describe how the incidence and case fatality of iGAS infections were influenced by changes in the *emm* type prevalence. Age- and sex-specific differences in the incidence, uncharacteristic seasonal patterns of infections, and aspects of vaccine coverage are also discussed.

The observed incidence rate of 3.9 cases per 100,000 population in 2007 is the highest in Finland since 1995. This study together with our earlier research shows that the incidence of iGAS disease has fluctuated since the 1990s but continued its increasing trend [21, 23]. During 2003-2004, the U.K., Sweden, Denmark and Finland had the highest rates of infection (range 2.5-3.3 per 100,000) in a European study [9]. Since then, indications of an increase in the incidence are seen in Sweden to 4.5 cases per 100,000 by 2007 (<http://www.smittskyddsinstitutet.se/in-english/statistics/beta-hemolytic-group-a-streptococci-gas-invasiv-infection/>) and very recently in the U.K. [11]. In contrast, the incidence of iGAS disease in the U.S.A. has remained relatively stable, at an average of 3.5 cases per

100,000 during 1995-2004, with a moderate increase to 3.8 in 2007

(<http://www.cdc.gov/abcs/survreports.htm>) [17].

The incidence of iGAS disease in Finland generally increased with age as expected, but the rate in the elderly (≥ 65 years) still remained at a lower level than has been reported in Sweden, Denmark, the U.K. or the U.S.A. [4, 10, 12, 17]. Males had a higher incidence of iGAS disease compared to females, which has also been noted by some other studies [9, 17]. Differences could also be identified in the age- and sex-specific rates, with males having significantly more infections than females in the age of 45-64 years. In contrast, females had more infections in the age of 25-34 years than males. A similar clear peak in the incidence of females around the same age has been noticed in earlier studies from Denmark and the U.K. [10, 12].

The characteristic fluctuation in the incidence of iGAS disease is presumably a reflection of changes in the *emm* type distribution and the population's susceptibility towards particular strains, especially of emerging types [4, 16, 17]. The *emm* type distribution in Finland underwent major changes during 2004-2007 when *emm1* replaced *emm28* as the most predominant type. The incidence of iGAS disease increased simultaneously with the increasing prevalence of type *emm1*, as has also been observed by others [25]. However, changes in the prevalence of other types, such as the sudden emergence of *emm84*, also contributed to the increase [23].

The type distribution of iGAS isolates in Finland has common features with that of other countries but also some unique characteristics. *emm* types 1, 28 and 89 are common globally but 75 and 84 are rarer and have not featured among the five most common *emm* types elsewhere [4, 5, 7, 12, 17, 26]. The low prevalence of cases by *emm3* is of interest, as it is a common type in many countries, and often associated with high case fatality [7, 12, 17, 26]. The *emm* types included in the putative 26-valent recombinant vaccine would have covered approximately half of the Finnish isolates in 2004-2007, a notably smaller proportion than has been estimated for the U.S.A. (79%) and Japan (82%) [7, 14, 17].

Within the last 20 years, a periodic fluctuation of peaks and troughs of the two most common genotypes *emm1* and *emm28* has occurred in Finland. Peaks in numbers of M/*emm1* have been observed earlier in 1988-1990 and 1997-1998, and in this study in 2006-2007 [6, 15, 21]. Similarly,

the prevalence of type *emm28* has peaked in 1993-1995 and 2002-2004 [15, 21]. Such a pattern of alternating type prevalence may be a reflection of changes in the general immunity of the population.

Types *emm28* and more rarely also *emm4* have been known to associate with postpartum infections and puerperal sepsis [1, 3, 26]. Also in this study, *emm28* infections were found to be specifically concentrated in females of child-bearing age. However, estimations of how many of these cases were pregnancy-related infections are beyond the scope of this study.

The overall erythromycin resistance during 2004-2007 was expectedly low, as the rate has declined during this decade in Finland (http://www.ktl.fi/portal/english/projects/fire/finres/finres__antimicrobial_resistance_statistics_/streptococcus_pyogenes/). The Finnish iGAS strains remain susceptible to clindamycin. Similar low resistance rates have been reported for example in Denmark and the U.S.A. [12, 19]. Tetracycline resistance was associated with certain clones, as has also been found previously, and the resistant strains were mainly of uncommon *emm* types [8].

The overall case fatality of iGAS disease in Finland was relatively low at 8%, compared to those reported by some other European countries and the U.S.A. [4, 5, 10, 17]. A sudden four-fold increase in the case fatality occurred from 3% in 2004 to 12% in 2005. During the study, the proportion of infections by types *emm1* and *emm75* increased, these types being associated with a high case fatality. In parallel, the proportion of *emm28*, associated with a low case fatality, decreased. Having an infection by *emm* type 1 or 3 has been identified as an independent factor associated with death due to iGAS disease [17]. Also in our study, the case fatality by *emm1* was higher than average, however we did not adjust it for age.

Seasonal variation in iGAS disease was observed; in addition to a midwinter peak season, there were also occasional peaks during the midsummer. In the northern hemisphere, peaks of cases are generally observed during the winter and spring [4, 9, 17, 26]. There were also sex-specific differences in the peak seasons, with male cases dominating during the summer. These two peak seasons might be associated with different predisposing factors and underlying conditions. However, the unusual pattern

and irregularity of the seasonality observed in this study may partly arise from natural variation due to a reasonably small study size.

There are some limitations to this study. Firstly, some of the increase in the incidence may be due to more frequent blood culturing activity [24]. It is also possible but less likely that the incidence would have been influenced by changes in the reporting system, which was established in 1995. Secondly, case definitions of iGAS disease differ between countries and complicate comparisons of incidence rates. Exclusion of non-bacteraemic cases with other sterile site isolations and/or toxic shock by the Finnish case definition may partly explain the observed lower incidence rate. Thirdly, differences in blood culture sampling practices between countries may have an effect on the observed incidence [24]. In addition, the observed differences in fatality may arise from the case definition used, the timing of death considered (7/30-day/in-hospital mortality), and the source of information (e.g. population registry vs. hospital records). In this study, the 7-day mortality information obtained from the Population Information System was used. Finally, the surveillance does not include collection of clinical data of disease manifestations, possible risk factors and underlying conditions of patients. These data would be needed to address reasons behind the observed differences in the age- and sex-specific incidence, and such a study has been undertaken within one healthcare district in Finland [18].

In conclusion, dynamic changes in the *emm* type prevalence influenced the incidence and case fatality of iGAS disease in Finland. An unusual seasonal pattern with peaks in the midwinter and midsummer was observed. Differences in age- and sex-specific incidence rates and seasonality suggest variation in predisposing factors and underlying conditions.

225 **ACKNOWLEDGEMENTS**

1
2 226 Laboratory technicians Aila Soininen, Saija Perovuori, Suvi Kavenius, Tuula Randell and Minna
3
4 227 Lamppu are greatly acknowledged for excellent technical assistance. Data Manager Joonas Iivonen is
5
6 228 acknowledged for technical expertise with retrieving and combining data from several database
7
8 229 sources. Clinical microbiology laboratories are acknowledged for submitting notifications and isolates.

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11 230
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13 231 **Previous presentations:** These results have partly been presented at the European Scientific
14
15 232 Conference on Applied Infectious Disease Epidemiology (ESCAIDE), October 2007, Stockholm,
16
17 233 Sweden (poster number B.A.1.28), at the XVII Lancefield International Symposium on Streptococci
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19 234 and Streptococcal Diseases (LISSSD), June 2008, Porto Heli, Greece (abstract number O 4.4), and at
20
21 235 the European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE),
22
23 236 October 2009, Stockholm, Sweden (abstract number 20090261).

24
25 237
26
27 238 **Funding sources:** Funding was received from The Ministry of Social Affairs and Health, the Paulo
28
29 239 Foundation, the Sigrid Jusélius Foundation, the University of Helsinki, the Finnish Cultural
30
31 240 Foundation and the Alfred Kordelin Foundation.

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33 241
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35 242 **Conflict of interest:** The authors declare that they have no conflict of interest.

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323 **FIGURE LEGENDS**

1
2 324 **Fig. 1a** Cases of invasive group A streptococcal disease during 1998-2007 in Finland. Thin line,
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4 325 number of cases; bold line, number of cases (12-week moving average)
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7 326 **Fig. 1b** Monthly cases of iGAS during 1998-2007 in Finland (all years combined) in males and
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329 **TABLES**

330 **Table 1** Annual incidence of invasive group A streptococcal disease and the number of cases and
331 isolates studied, Finland, 1998-2007

Year	Rate ^a of invasive disease	Number of cases (isolates)
1998	2.1	105
1999	2.2	116
2000	2.2	116
2001	1.9	100
2002	2.9	153
2003	2.3	119
2004	2.5	130 (128)
2005	2.1	110 (110)
2006	3.1	162 (161)
2007	3.9	207 (203)
All	2.5	1318 (602)

^a Average annual incidence (cases per 100,000 population)

Table 2 Age- and sex-specific incidence of invasive group A streptococcal disease, Finland, 1998-

2007

Age group (years)	Rate ^a of invasive disease (no. of cases)						Rate ratio (RR) ^b	95% CI ^c of RR
	Male		Female		Total			
<1	2.7	(8)	2.2	(6)	2.5	(14)	1.3	0.4-3.9
1-14	1.2	(51)	0.9	(38)	1.0	(89)	1.3	0.8-2.0
15-24	0.8	(26)	1.2	(39)	1.0	(65)	0.6	0.4-1.0
25-34	1.2	(40)	2.7	(86)	1.9	(126)	0.4	0.3-0.6*
35-44	3.0	(112)	2.7	(97)	2.8	(209)	1.1	0.9-1.5
45-54	4.2	(168)	1.8	(69)	3.0	(237)	2.4	1.8-3.2*
55-64	4.8	(151)	2.4	(79)	3.6	(230)	2.0	1.5-2.6*
≥65	5.1	(163)	3.8	(185)	4.3	(348)	1.4	1.1-1.7*
All	2.8	(719)	2.2	(599)	2.5	(1318)	1.3	1.1-1.4*

^a Average incidence (cases per 100,000 population)

^b male-to-female incidence rate ratio

^c CI, confidence interval. Statistical significance (P<0.05) is indicated with an asterisk (*).

Table 3 The number and proportion (% of total number) of most common *emm* types encountered in the order of overall prevalence, and case fatality (%) by *emm* type, 2004-2007, Finland.

<i>emm</i> type	Number of isolates (%)					Fatal cases (%)
	2004 (N=128)	2005 (N=110)	2006 (N=161)	2007 (N=203)	2004-2007 (N=602)	2004-2007 (N=48)
28	46 (35.9)	22 (20.0)	32 (19.9)	25 (12.3)	125 (20.8)	3 (2)
1	6 (4.7)	9 (8.2)	26 (16.1)	57 (28.1)	98 (16.3)	14 (14)
84	0 (0.0)	1 (0.9)	24 (14.9)	32 (15.8)	57 (9.5)	4 (7)
75	10 (7.8)	17 (15.5)	12 (7.5)	4 (2.0)	43 (7.1)	6 (14)
89	10 (7.8)	4 (3.6)	11 (6.8)	12 (5.9)	37 (6.1)	2 (5)
79	10 (7.8)	12 (10.9)	4 (2.5)	2 (1.0)	28 (4.7)	4 (14)
12	2 (1.6)	6 (5.5)	6 (3.7)	12 (5.9)	26 (4.3)	2 (8)
81	7 (5.5)	3 (2.7)	5 (3.1)	8 (3.9)	23 (3.8)	0 (0)
27G	3 (2.3)	1 (0.9)	4 (2.5)	11 (5.4)	19 (3.2)	2 (11)
other ^a	34 (26.6)	35 (31.8)	37 (23.0)	40 (19.7)	146 (24.2)	11 ^b (7)

^a Including isolates from a total of 37 other *emm* types and nontypable isolates.

^b Other types causing poor outcome: *emm*4 and *emm*110 (2 cases each); *emm*22, *emm*59, *emm*60, *emm*77, *emm*85, *emm*87 and *emm*112 (1 case each).

Figure

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b