

Distribution of *emm* types in invasive and non-invasive group A and G streptococci

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Abstract Our study describes the *emm* type distributions of invasive and non-invasive group A streptococci (GAS) and group G streptococci (GGS) strains in one of the biggest Health Districts in Finland. A total of 571 GAS or GGS were recovered from patients with invasive or non-invasive infections during a 1-year period in 2008–2009 in Pirkanmaa Health District in Finland. We describe here the *emm* type distributions of GAS and GGS collected from throat ($n=246$), pus ($n=217$), deep tissue ($n=56$) and blood ($n=52$). The most common *emm* types among GAS were *emm77*, *emm1*, *emm28*, *emm89* and *emm12*. Among GGS, the most common *emm* types were stG480, stG643, stG6, stC6979 and stG485. Some *emm* types were found to associate with certain infection focus. In GAS, *emm77* associated with pus isolates, whereas *emm1* and *emm12* were more frequent among throat isolates. In GGS, stG480 was more commonly found from throat isolates.

Introduction

Group A streptococci (GAS; *Streptococcus pyogenes*) are well known human pathogens causing mild superficial infections and a variety of other manifestations, such as cellulitis and erysipelas, but also severe, invasive diseases, such as bacteraemia, streptococcal toxic shock syndrome and necrotising fasciitis [1]. Group G streptococci (GGS; most notably, *Streptococcus dysgalactiae* subsp. *equisimilis*) were previously considered as commensal bacteria, but they have been shown to cause similar diseases to GAS [2–5]. Some countries have recently reported an increasing incidence of invasive GGS [6–8].

Molecular markers associated to the invasiveness of GAS have been studied with various methods (*emm* typing, superantigen gene profiling, random amplified polymorphic DNA [RAPD] and pulsed-field gel electrophoresis [PFGE]), but those of GGS are less well known [4, 9–11]. GAS and GGS share similar virulence factors, such as the M-protein, C5a peptidase, several binding proteins and superantigens, presumably due to horizontal genetic transfer [12–15]. The M-protein is considered to be a major virulence factor in GAS, mainly because of its antiphagocytic activity. Sequence analysis of the hyper-variable 5 end of the *emm* gene, encoding for M-protein, is used for the molecular typing of GAS and GGS. In this study, we characterised GAS and GGS strains isolated from clinical bacterial specimens originating from throat, pus, blood or other deep infections. We compared the *emm* type distributions in GAS and GGS strains to identify possible differences not only between invasive and non-invasive strains, but also depending on the infection site. We aimed at recognising the *emm* types possibly associated with either superficial or invasive diseases.

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Materials and methods

Bacterial strains

GAS and GGS strains from throat, pus (mostly skin infections), deep infections (mostly abscess) and blood were collected from patients with various infectious symptoms during a 1-year period, March 2008 to February 2009, in Pirkanmaa Health District (HD), with 480,000 inhabitants. The Centre for Laboratory Medicine serves for health care centres and hospitals in the HD and all blood and cerebrospinal fluid samples and the majority of other bacteriological samples are studied there in the HD. Each month, approximately ten first clinical throat and pus isolates were selected and collected among all GAS and large colony-forming GGS isolations. Also, all isolations of GAS or GGS from blood, cerebrospinal fluid or deep tissue were collected. The isolates were sent to the reference laboratory at the National Institute for Health and Welfare (THL) for further analysis. The Lancefield serogroups were defined by latex agglutination using the Streptex latex test system (Remel Europe Ltd., Dartford, UK). Isolates were stored at -70°C .

emm typing

emm typing was performed for all isolates according to the protocol of the *emm* sequence database at the Centers for Disease Control and Prevention (CDC; http://www.cdc.gov/ncidod/biotech/strep/protocol_emm-type.htm). When the strain was non-typable with primer1 and primer2, polymerase chain reaction (PCR) was performed using primers MF1/MR1, as previously described [16]. Sequencing of the *emm* gene was performed using primer *emmseq2*.

Data analysis and statistical methods

emm types that were present in $>10\%$ of the isolates were considered to be common *emm* types. The Chi-squared test was used to test for differences between two groups. Statistical analyses were performed using GraphPad InStat version 3.10 for Windows 95 (GraphPad Software, San Diego, CA, USA). A *p*-value below 0.05 was considered to be statistically significant.

Results

In total, we collected 571 GAS and GGS isolates (Table 1). Our collected study material covers 13% (125/993) of GAS throat isolates, 26% (121/467) of GGS throat isolates, 56% (104/185) of GAS pus isolates and 44% (113/258) of GGS

Table 1 Number of group A streptococci (GAS) and group G streptococci (GGS) isolates collected between March 2008 and February 2009

Isolation site	GAS	GGS	Total
Throat	125	121	246
Pus	104	113	217
Deep tissue ^a	27	29	56
Blood	23	29	52
Total	279	292	571

^a E.g. abscess, bursa

pus isolates handled at the Centre for Laboratory Medicine during the study period. In addition, 56 GAS or GGS isolates from deep infections and 52 blood isolates were collected and analysed.

Among 279 GAS isolates, 26 different *emm* types were found (Table 2). Five strains remained non-typable (NT). For GAS, five different *emm* types (*emm77*, *emm1*, *emm28*, *emm89* and *emm12*) were present in $>10\%$ of the isolates and were included in the statistical analysis. *emm77* was significantly associated with skin infections (pus) than with other sample sites (40% (42/104) vs. 13% (22/175), $p < 0.0001$). *emm1* was significantly more commonly found in throat than in other sample sites (27% (34/125) vs. 11% (17/154), $p < 0.001$). The same was true for *emm12* (18% (23/125) vs. 4% (6/154), $p < 0.0001$).

Among the 292 GGS strains studied, we found 26 different *emm* types (Table 3). Fifteen strains remained non-typable. Three *emm* types (stG480, stG643 and stG6) were present in $>10\%$ of the GGS isolates and were included in the statistical analysis. stG480 was significantly associated with throat infections than with other sample sites (32% (39/121) vs. 15% (26/171), $p < 0.01$).

Seasonal occurrence of the five most common *emm* types in GAS and the three most common *emm* types in GGS were studied. Differences in the seasonal occurrence of GAS *emm77* strains were detected (all isolates, regardless of the isolation site). *emm77* isolates were found to be more common between September and February than between March and August (31% (48/157) vs. 13% (16/122), $p < 0.001$) (Fig. 1). In GGS, stG6 was more common between September and February than between March and August (21% (32/158) vs. 8% (11/158), $p < 0.005$) (Fig. 2).

The distribution of strains to common ($>10\%$ of the isolates) and rare ($<10\%$ of the isolates) *emm* types differed in GAS and GGS. The common *emm* types covered 83% of the GAS strains, but only 70% of the GGS strains (231/279 vs. 205/292, $p < 0.001$). *emm* types stG485 and stG643 were present in both GAS and GGS isolates.

Table 2 Number of *emm* types of GAS isolates by isolation site

	Throat (%)	Pus (%)	Deep tissue (%)	Blood (%)	Total
<i>emm77</i>	6 (5)	42(40)	8 (30)	8 (35)	64
<i>emm1</i> ^a	34 (27)	13 (13)	2 (7)	2 (9)	51
<i>emm28</i>	22 (18)	13 (13)	5 (19)	6 (26)	46
<i>emm89</i>	20 (16)	14 (13)	5 (19)	2 (9)	41
<i>emm12</i>	23 (18)	5 (5)		1 (4)	29
<i>emm75</i>	3 (2)	2(2)			5
<i>emm119</i>	2 (2)	3 (3)			5
<i>emm4</i>		3 (3)			3
<i>emm73</i> ^b	2 (2)	1 (1)			3
<i>emm78</i>	2 (2)			1 (4)	3
<i>emm11</i>	1 (1)		1 (4)		2
<i>emm2</i>	2 (2)				2
<i>emm22</i> ^c	2 (2)				2
<i>emm81</i> ^d		1 (1)	1 (4)		2
<i>emm84</i>	1 (1)			1 (4)	2
<i>emm85</i>		2 (2)			2
st75	1 (1)			1 (4)	2
stG485		1 (1)	1 (4)		2
<i>emm27G</i>			1 (4)		1
<i>emm3</i>		1 (1)			1
<i>emm44</i>			1 (4)		1
<i>emm49</i>		1 (1)			1
<i>emm6</i>	1 (1)				1
<i>emm60</i>		1 (1)			1
<i>emm76</i>	1 (1)				1
stG643			1 (4)		1
NT	2 (2)	1 (1)	1 (4)	1 (4)	5
Total	125	104	27	23	279

^aSix subtypes (*emm1.0*, *emm1.10*, *emm1.24*, *emm1.45*, *emm1.49* and *emm1.50*)

^bTwo subtypes (*emm73.0* and *emm73.8*)

^cTwo subtypes (*emm22.0* and *emm22.3*)

^dTwo subtypes (*emm81.0* and *emm81.1*)

Discussion

This is the first study to describe and compare the *emm* type distributions of invasive and non-invasive GAS and GGS strains during a 1-year period in a defined population in Finland. In both GAS and GGS, 26 different *emm* types were discovered. We observed associations between certain *emm* types and infection foci. Our finding of *emm12* to be common in throat isolates is in line with those previously reported [10, 17, 18]. Our finding of *emm1* strains as a cause for pharyngitis is also commonly known, although *emm1* is often considered to cause especially invasive disease [10, 17–19]. In our study material, *emm77* was found especially in skin and wound swabs, but it was also the most common *emm* type in deep infection and blood isolates. *emm77* seems to have features that enable these strains to cause especially skin infections, rather than pharyngitis, since *emm77* was rare in throat isolates. A recent study in Germany compared *emm* types among invasive and non-invasive isolates (throat and skin) and

found *emm77* to be a predictor of non-invasiveness [9]. It would be essential to study the virulence factors and clonality of these *emm77* strains in more detail.

The *emm* types of invasive GAS have been extensively studied in Finland and Europe [10, 20, 21]. In Finland, the most common *emm* types in 2008 were *emm1*, *emm12*, *emm28* and *emm119* [22]. In our study material, among the 29 GAS blood isolates, the most common *emm* types were *emm77*, *emm1*, *emm28* and *emm89*. The *emm* type distribution of invasive GAS seems to vary geographically in Finland, since the *emm* type distribution of the whole country and Pirkanmaa HD differ. It is noteworthy that *emm3*, which has been shown often to associate with invasive diseases in other Western hemisphere countries, was absent in our study material [21, 23].

Recent studies on GGS have concentrated mainly on invasive strains and their *emm* type distributions also seem to vary geographically [24–26]. The *emm* type distribution of 128 invasive GGS isolates in Pirkanmaa HD has been previously described in a population-based study, and an

Table 3 Number of *emm* types of GGS isolates by isolation site

	Throat (%)	Pus (%)	Deep tissue (%)	Blood (%)	Total
stG480 ^a	39 (32)	17 (15)	4 (14)	5 (17)	65
stG643	15 (12)	23 (20)	9 (31)	4 (14)	51
stG6 ^b	19 (15)	15 (13)	4 (14)	5 (17)	43
stC6979	4 (3)	12 (11)	2 (7)	7 (24)	25
stG485	9 (7)	8 (7)	1 (3)	3 (10)	21
stG10 ^c	5 (4)	8 (7)	1 (3)		14
stG166b	1 (1)	7 (6)	1 (3)	1 (3)	10
stG652 ^d	4 (3)	5 (4)		1 (3)	10
stG245	5 (4)	3 (3)			8
stC74a	3 (2)	1 (1)		1 (3)	5
stG2078 ^e	2 (2)		2 (7)		4
stC1400	1 (1)	1 (1)			2
stG2574			2 (7)		2
stG4222	1 (1)	1 (1)			2
stG5420		2 (2)			2
stG653	2 (2)				2
stG6792 ^f	2 (2)				2
stC36	1 (1)				1
stC5345		1 (1)			1
stG11	1 (1)				1
stG3251	1 (1)				1
stG3343			1 (3)		1
stG4245		1 (1)			1
stG4831		1 (1)			1
stG507		1 (1)			1
stG62647	1 (1)				1
NT	5 (4)	6 (5)	2 (7)	2 (7)	15
Total	121	113	29	29	292

^aTwo subtypes (stG480.0 and stG480.2)

^bFive subtypes (stG6.0, stG6.1, stG6.3, stG6.4 and stG6.6)

^cThree subtypes (stG10.0, stG10.1 and stG10.2)

^dTwo subtypes (stG652.0 and stG652.1)

^eTwo subtypes (stG2078.0 and stG2078.3)

^fTwo subtypes (stG6792.0 and stG6792.3)

association between rare *emm* types and the severity of disease was then discovered [27]. At that time, the most common *emm* types in invasive GGS were stG480, stG6, stG485, stG643 and stC6979 [27]. Similarly, the same five types were the most common *emm* types in our study. Also, among blood isolates, these types covered 83% of the strains (24/29). In Pirkanmaa HD, GGS isolates have also

been studied in patients with acute bacterial non-necrotising cellulitis in 2004–2005 [3]. The most common *emm* types associated with these infections were stG6, stG480 and stG643, which we also found in our study. Based on these findings, we can conclude that stG480, stG6, stG485, stG643 and stC6979 have been the most common *emm*

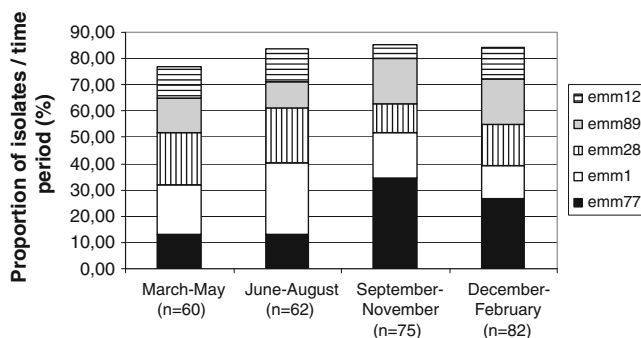


Fig. 1 Seasonal fluctuation of the five most common *emm* types among 279 group A streptococci (GAS) isolates

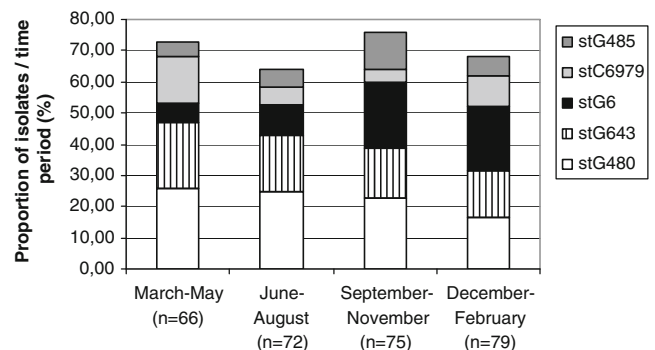


Fig. 2 Seasonal fluctuation of the five most common *emm* types among 292 group G streptococci (GGS) isolates

types among GGS in Pirkanmaa HD in recent years, and they cause both invasive and non-invasive diseases.

Little is known of the association of *emm* types with invasiveness in GGS. In our study, none of the *emm* types presented an association with invasiveness (blood or deep infection). In a Portuguese study, *emm* types stG2078 and stG10 were found to be more common in invasive isolates [4]. These two *emm* types were absent in our blood isolates and, overall, we found these in very small numbers. We found stG480 more often in throat than in other sample sites. No other association was found between *emm* types and infection site in GGS. In a Norwegian study, *emm* types stG6, stG643 and stG485 were the most common *emm* types among GGS and GAS throat and skin isolates, but these types were also found in invasive strains and, therefore, no association of these types to non-invasiveness was found [28]. These types were also common in our throat and pus isolates. In an Australian study, the most common *emm* types among throat and skin GGS isolates were stC1400, stG4831, stG480, stG6792 and stC74a [29]. Apart from stG480, these *emm* types were present in very low numbers in our study material ($n \leq 5$), suggesting that the *emm* distribution in non-invasive GGS varies geographically.

A seasonal difference of genotype distribution was detected in GAS *emm77* and GGS stG6 isolates: both were more common between September and February than between March and August. Our finding of *emm77* being especially prevalent during the winter months has not been reported previously. It is not clear if this is a true sign of seasonal fluctuation. It has been shown that previously unknown or rare *emm* types can rapidly emerge and cause invasive GAS disease [10, 30]. A similar phenomenon may have occurred in Pirkanmaa HD with *emm77* emerging during our study period, which would explain the large number of *emm77* during these winter months, rather than their specific association with the winter season.

emm types StG485 and stG643 were found in both GAS and GGS, although they were more common in GGS. Lateral genetic transfer has been shown to occur between GAS and GGS, and it may be one interpretative factor for these shared *emm* types [31]. It is also possible that GAS strains that harbour *emm* types typical to GGS belong to *Streptococcus dysgalactiae* subsp. *equisimilis* species and not *Streptococcus pyogenes*. GAS bearing *Streptococcus dysgalactiae* subsp. *equisimilis* strains have been reported previously [32].

Limitations of our study are that no patient data were collected and that species identification was not performed for the strains.

We conclude that *emm77* associates to skin and invasive infections in GAS, but is rare in throat isolates. More detailed studies of the clonality of *emm77* strains would be

of interest. The over-representation of *emm12* and *emm1* among throat isolates is in congruence with findings from previous studies. In GGS, stG480 was associated with throat isolates. *emm* typing is a useful tool in epidemiological surveys on GAS and GGS, but a more detailed study of several virulence factors and clonality would be essential in order to further investigate the invasiveness of the isolates.

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