

Multicenter Study of Molecular Epidemiology and Antibiotic Resistance of Group A Streptococci in 2008-2009 in Korea

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Background: Group A *Streptococcus* (GAS) is responsible for a wide spectrum of human diseases. We investigated the distribution of *emm* types and antibiotic resistance rates of GAS from clinical specimens in several Korean medical centers.

Methods: A total of 192 strains of GAS from throat, blood, and other specimens collected in Seoul, Busan, Ulsan, Iksan, and Jeju were studied in 2008-2009. The *emm* genotypes were identified using PCR and sequencing. Antimicrobial susceptibility testing was performed by disk diffusion method. Phenotypes of macrolide resistance were evaluated, and macrolide resistance genes were determined by PCR.

Results: The *emm*89 (33.9%) was most frequently detected, followed by *emm*1 (12.5%), *emm*12 (8.3%), *emm*4 (7.8%), and *emm*75 (7.3%). The distribution of *emm* types did not show a close relation to the type

of specimen and was different for each area. The resistance rates to erythromycin (ERY) and clindamycin (CLI) were 4.6% and 3.7%, respectively. Among the nine ERY-resistant strains, the rate of constitutive resistance was 88.9%, compared with 11.1% for the M phenotype. Five of the ERY-resistant strains were *emm*28.

Conclusion: This multicenter study reveals heterogeneous *emm* genotypes by geographic area. Rates of resistance to ERY and CLI were low, and most of the ERY-resistant strains showed a constitutive macrolide-lincosamide-streptogramin B (cMLS_B) phenotype. (Korean J Clin Microbiol 2011;14:85-90)

Key Words: Group A streptococcus, *Streptococcus pyogenes*, *emm* gene, Erythromycin resistance

INTRODUCTION

Group A streptococcus (GAS) is a common human pathogen responsible for a wide spectrum of diseases, such as tonsillitis, cellulitis, scarlet fever, erysipelas, impetigo, and sepsis. Immunological sequelae, such as rheumatic fever or poststreptococcal glomerulonephritis, have become rare these days as a result of better hygiene and nutritional status. Recently, however, fatal illnesses such as necrotizing fasciitis or toxic shock-like syndrome have been reported in developed countries [1]. As GAS is the most common cause of bacterial pharyngitis, many studies have been performed on these patients. However, studies on the

GAS isolates from the other diseases are rare in Korea.

For epidemiologic study, *emm* genotyping has replaced serotyping, such as T or M typing. The *emm* gene encodes the M protein, which is the most important virulence factor of GAS. The major role of M protein is to inhibit phagocytosis. The M type matches perfectly with the *emm* genotype. There are about 100 M types, but more than 200 *emm* genotypes have been reported as a result of the discovery of new sequences [2]. Although the amplicon size of *emm* is about 500-1,500 bp, it contains hypervariable nucleotide sequences at the 5'-terminus. For *emm* typing, this hypervariable region, about 165 bp long, is sequenced and compared with the database [3].

Although penicillin is the drug of choice to treat GAS infections, macrolides have been used as an alternative, especially when the patient is allergic to penicillin. New macrolides such as azithromycin, clarithromycin, or roxythromycin have been

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used widely during the last decade [4]. These drugs are commonly used because of their minimal side effects, the short duration of treatment, the rapid patient recovery, and their wide coverage of other respiratory tract pathogens such as *Mycoplasma* spp. or *Chlamydia* spp. For invasive GAS infections, clindamycin (CLI) is recommended [4]. Ampicillin, amoxicillin, or a first-generation cephalosporin can be used to treat bacterial tonsillitis. Although penicillin resistance has not been reported in GAS, resistance to erythromycin (ERY), a class drug of the macrolides, is an obstacle to the use of new macrolides for the treatment of GAS infections. Several reports in early 2000s showed a worryingly high rate of resistance to ERY [5-8].

This was a multicenter study, participated in by 9 university-affiliated hospitals in Korea in 2008-2009. The clinical isolates were analyzed for *emm* genotypes as well as antimicrobial susceptibility to understand the epidemiology and status of antimicrobial resistance of GAS in Korea.

MATERIALS AND METHODS

1. Bacterial isolates

We studied GAS isolated from throat, blood, and other specimens from June 2008 through May 2009 in the clinical microbiology laboratories in Seoul, Guri, Busan, Ulsan, Iksan, and Jeju. These clinical isolates were sent to Gyeongsang National University Hospital for *emm* genotyping and antimicrobial susceptibility testing. The bacteria were identified by observation of beta-hemolysis on blood agar plates, by inhibition with a bacitracin disk (0.04 U), and by latex agglutination with anti-A serum (Seroiden Strepto Kit, Eiken, Tokyo, Japan).

2. *emm* genotyping

The *emm* genotype was identified by PCR and sequencing. First, amplification of *emm* genes was performed according to the Centers for Disease Control and Prevention protocol [3]. After purification with the AccuPrep Genomic DNA Extraction kit (Bioneer, Cheongwon, Chungbuk), the samples were transferred to Macrogen Co. (Seoul, Korea) for sequencing. The retrieved DNA sequences were compared with the database at the National Center for Biotechnology Information (NCBI) and the BLAST program (<http://ncbi.nlm.nih.gov>). All sequences were longer than 165 bp. When there was greater than 95% compatibility between a sequence and a database entry, that *emm* type was assigned.

3. Antimicrobial resistance

Antimicrobial susceptibility testing was performed using the disk diffusion method against ERY, CLI, tetracycline, ofloxacin, chloramphenicol, and levofloxacin (BBL, Sparks, MD, USA). *Streptococcus pneumoniae* ATCC 49619 was used for quality control. Phenotypes of macrolide resistance were observed with a double disk synergy test for the ERY-resistant strains. The macrolide resistance genes were determined by PCR using the primers reported elsewhere [9]. The amplicons were separated by 2% agarose gel electrophoresis in Tris/boric acid/EDTA (TBE) buffer. The target resistance genes were *erm(A)*, *erm(B)*, and *mef(A)*. Minimal inhibitory concentrations (MIC) of ERY were analyzed by the Etest (AB Biodisk, Solna, Sweden) using Mueller-Hinton blood agar plates.

RESULTS

1. Epidemiology of GAS

The distribution of the 26 *emm* genotypes according to specimen type is shown in Table 1. The *emm89* gene was most common (33.9%) regardless of the specimen type except body fluid. Types *emm1* (12.5%), *emm12* (8.3%), *emm4* (7.8%), *emm75* (7.3%), *emm11* (6.3%), and *emm28* (5.7%) were relatively common. Other *emm* genotypes were observed only once (12 types) or twice (6 types). One isolate from a throat swab did not match any entry in the databases. Although we expected a relation between specimen and *emm* type, especially with invasive infections such as those of the blood, or body fluid, no association was observed. The *emm4* and *emm12* types were more common in throat swabs than in the other specimens, whereas *emm75* was seen only in throat swabs and pus. The *emm1* type was commonly observed in body fluid (5 of 11).

Table 2 shows a distribution of *emm* genotypes according to the geographic region. Data from three hospitals in Seoul were combined. Guri is close to Seoul; the isolates from Seoul and Guri showed a similar distribution. The isolates from Busan and Ulsan in the eastern part of Korea showed quite a different distribution from those from Iksan and Jeju in the western part of Korea. Different distribution in these two areas is understandable, because the areas are far from each other, making transmission of bacteria from one to another rare.

We compared the frequency of *emm* types with data from Jinju during a similar period (Fig. 1). These GAS (n=174) were isolated from acute pharyngitis from September 2008 to

February 2009 in Jinju, whereas the isolates were collected from diverse specimens in each hospital from June 2008 to May 2009 in this study. Compared with the data from Jinju, *emm89*, *emm1*, *emm11*, and *emm12* were significantly more prevalent, whereas *emm4* (7.3%) was less common. The *emm4* type accounted for 28.2% of the isolates in Jinju.

Table 1. Distribution of *emm* genotypes according to specimen type

	Throat	Sputum	Pus	Blood	Body fluid	Other	Total (%)
<i>emm1</i>	9	3	4		5	3	24 (12.5)
<i>emm4</i>	10	1	2		1	1	15 (7.8)
<i>emm6</i>	4	1	3				8 (4.2)
<i>emm9</i>			1				1 (0.5)
<i>emm11</i>	4		4	3	1		12 (6.3)
<i>emm12</i>	9	2	3	1	1		16 (8.3)
<i>emm18</i>			1				1 (0.5)
<i>emm22</i>	1		1				2 (1.0)
<i>emm28</i>	5		1	2	2	1	11 (5.7)
<i>emm44</i>						1	1 (0.5)
<i>emm48</i>			1				1 (0.5)
<i>emm49</i>			1				1 (0.5)
<i>emm50</i>			1				1 (0.5)
<i>emm58</i>				1	1		2 (1.0)
<i>emm63</i>			1				1 (0.5)
<i>emm73</i>		1					1 (0.5)
<i>emm75</i>	8		6				14 (7.3)
<i>emm77</i>			1				1 (0.5)
<i>emm78</i>	2	1					3 (1.6)
<i>emm82</i>	1		1				2 (1.0)
<i>emm85</i>			1				1 (0.5)
<i>emm88</i>	1		1				2 (1.0)
<i>emm89</i>	28	6	23	4		4	65 (33.9)
<i>emm94</i>			1	1			2 (1.0)
<i>emm112</i>	2						2 (1.5)
<i>emm114</i>	1						1 (0.5)
NT	1						1 (0.5)
Total	86	15	58	12	11	10	192

Abbreviation: NT, non-typeable.

Table 3. Minimal inhibitory concentrations (MIC) of erythromycin (ERY) and macrolide-resistant determinants among ERY-resistant group A streptococci

No.	Location	Specimen	<i>emm</i> genotype	ERY	Clindamycin	MIC of ERY (μ g/mL)	Resistant determinant
1	Seoul	Pus	<i>emm28</i>	R	R	256	<i>erm(B)</i>
2	Seoul	Blood	<i>emm28</i>	R	R	256	<i>erm(B)</i>
3	Guri	Throat	<i>emm4</i>	R	S	8	<i>mef(A)</i>
4	Busan	Body fluid	<i>emm28</i>	R	R	256	<i>erm(B)</i>
5	Busan	Throat	<i>emm28</i>	R	R	256	<i>erm(B)</i>
6	Busan	Joint fluid	<i>emm28</i>	R	R	256	<i>erm(B)</i>
7	Iksan	Wound	<i>emm88</i>	R	R	256	<i>erm(B)</i>
8	Jeju	Throat	<i>emm12</i>	R	R	3	<i>erm(B)</i>
9	Jeju	Throat	NT	R	R	3	<i>erm(B)</i>

Abbreviations: NT, non-typeable; R, resistant; S, susceptible.

2. Antibiotic resistance

The resistance rates to ERY and CLI were 4.6% and 3.7%, respectively. Among 9 strains resistant to ERY, constitutive resistance was noted in 8 (88.9%), compared with 1 strain

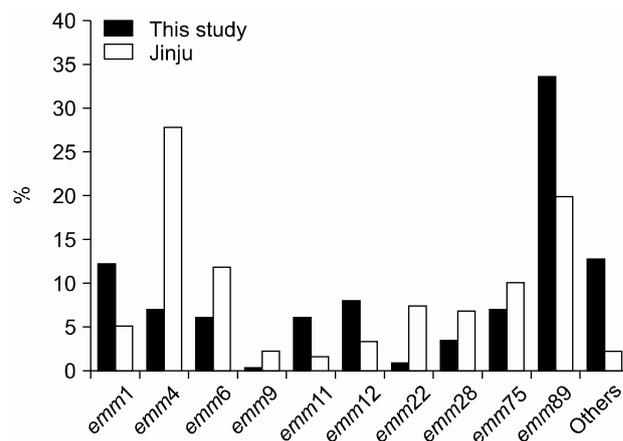


Fig. 1. Frequency of *emm* genotypes in this study and study of acute pharyngitis in Jinju, 2009 [14].

Table 2. Distribution of *emm* genotypes according to geographic region

	Seoul	Guri	Busan & Ulsan	Iksan & Jeju
<i>emm1</i>	12 (14.5)	6 (13.6)	6 (20.7)	0
<i>emm4</i>	5 (6.0)	6 (13.6)	1 (3.4)	3 (8.3)
<i>emm6</i>	2 (2.4)	1 (2.3)	5 (17.2)	0
<i>emm11</i>	5 (6.0)	3 (6.8)	2 (6.9)	2 (5.6)
<i>emm12</i>	8 (9.6)	2 (4.5)	1 (3.4)	5 (13.9)
<i>emm28</i>	6 (7.2)	2 (4.5)	3 (10.3)	0
<i>emm75</i>	1 (1.2)	7 (15.9)	0	5 (13.9)
<i>emm89</i>	31 (37.3)	14 (31.8)	7 (24.1)	13 (36.1)
Others	13 (15.7)	3 (6.8)	4 (13.8)	8 (22.2)
Total	83	44	29	36

(11.1%) with the M phenotype (Table 3). All constitutive macrolide-lincosamide-streptogramin B (cMLS_B) strains harbored *erm(B)*, whereas a strain with the M phenotype showed a *mef(A)* resistance determinant. Neither inducible resistance nor the *erm(A)* gene was detected. Although erythromycin-resistant strains were few, they seemed relatively common in Busan (10.3%) and Iksan and Jeju (8.3%) compared with Seoul (2.4%). The specimen types were diverse, and *emm28* was most common (5 of 9) among erythromycin-resistant GAS. Six strains with cMLS_B showed a high MIC (256 µg/mL) for ERY, whereas a strain with the M phenotype showed a low MIC (8 µg/mL). Interestingly, two strains with cMLS_B isolated from Jeju showed a very low MIC (3 µg/mL).

The resistance rates to tetracycline, ofloxacin, chloramphenicol, and levofloxacin were 6.3%, 1.0%, 0%, and 0%, respectively.

DISCUSSION

Group A *Streptococcus* is the cause of fatal necrotizing fasciitis and toxic shock-like syndrome. The mortality rate of these diseases is as high as 40-50%. Numerous cases of toxic shock-like syndrome have been reported in Japan in the last decade [10], whereas it seems to be rare in Korea, only a few cases having been reported, and those sporadically [11]. The organism can also cause sepsis, pneumonia, cellulitis, and tonsillitis.

There was no significant difference in the distribution of *emm* genotypes between throat swabs and specimens from deep-seated infections, such as sputum, pus, blood, and body fluid (Table 1). The *emm89* type was predominant regardless of the specimen. An epidemiological study in Hong Kong revealed a similar finding; the same prevalent *emm* types in both invasive and non-invasive infections [12]. The *emm22* strains showed a significantly higher ERY resistance rate (86%) in that study. On the other hand, a Japanese study showed a different distribution according to the specimen; *emm12* from mucosa vs. *emm58* and *emm89* from skin. Moreover, those investigators noted that *emm3* strains were dominant in invasive infections [10].

More than 25 *emm* genotypes were identified in this study, which means diverse genotypes are present in our country. The coverage rate of the 26-valent vaccine for GAS [13] was 81.8%. For the development of vaccine, epidemiological data of *emm* genotypes in the country should be preceded.

Although the numbers of strains differed among areas, the distribution of *emm* genotypes was variable (Table 2). Although

the study period was similar between this multicenter study and the study of acute pharyngitis in Jinju, 2009 [14] (Fig. 1), the distributions of *emm* genotypes were quite different. This finding indicates segregation of endemic *emm* genotypes in certain areas.

Although GAS causes rapid and pyogenic inflammation, it is susceptible to penicillin. However, penicillin is not commonly used these days for GAS infections. A macrolide is the first choice for patients allergic to penicillin. There have been many reports on the increase in macrolide or CLI resistance rate in many countries [5-8]. The resistance rates to these antibiotics exceeded 95% in China recently [7]. On the other hand, there were several reports on the decrease of the antibiotic resistance rate lately, including in Korea [14], Spain [15,16], Finland [17], and Japan [18].

The rate of ERY resistance among GAS isolated from acute pharyngitis in Korea showed a range of 19-22% in 2000-2002 [6]. The authors reported a change in the antibiotic resistance rate and *emm* genotypes from acute pharyngitis in Jinju over a 7-year period [14]. The peak period of macrolide resistance seemed to have been 2002 in Korea [5,6,14]. It reached 44.8% at that time but dropped to 4.6% in 2009 for the same disease. Because of this drop, we suspected a decrease in macrolide usage. However, the drug production data from pharmaceutical companies witnessed a gradual increase in the availability of new macrolides, such as azithromycin, clarithromycin, and roxythromycin during the same period [14]. It is still unexplained why there was a drop in the ERY and CLI resistance rate in GAS during the last several years in Korea. The mechanism in Korea or Spain [15,16] seems different from that in Finland [17] and Japan [18]. It is suggested that the decline of the ERY and CLI resistance rate might be the result of decreased usage of these drugs in Finland [17] and Japan [18]. However, we did not observe a decrease, nor was one seen in a report from Spain [15]. The resistance rate dropped from between 27 and 39% to 3.7% within a few years in a region of Spain, whereas there was no reduction of consumption of macrolides. Those authors suggested an expansion of two epidemic clones (*emm1* and *emm3*) as the reason for the rapid decrease in macrolide-resistant GAS. Another study showed similar trends in the antibiotic resistance rate; 34% in 2001-2004 and 7.4% in 2007-2008 [16]. Molecular characterization of ERY-resistant strains indicated a close association between *emm* genotypes and the resistance mechanism; *emm4*, *emm6*, and *emm75* having the M phenotype and *emm11*, *emm28*, and *emm25* the cMLS_B

phenotype. The authors suggested a change in the prevalent *emm* genotypes in the community as the reason for the drop in the antibiotic resistance rate, which means expansion of ERY-susceptible strains. However, we need to study this phenomenon more. Most of the bacteria other than GAS have increasing antibiotic resistance rates these days.

This study showed a low resistance rate to ERY and CLI with geographical variation (2.3-10.3%). Although the areas of this study and the numbers of strains are not enough to draw a conclusion, we can assume this pattern might be the same throughout the country. We included a few hospitals in Seoul and Guri, the most densely populated area, as well as hospitals located in eastern and western Korea.

A multicenter surveillance of pharyngeal isolates (n=2,797) of GAS in the USA suggested that rates of macrolide resistance differed by site (3.0-8.7%) and also by month (<2% to >10%). The adjusted overall resistance rate to ERY was 5.2%. The *emm12* and *emm75* were the predominant genotypes among ERY-resistant strains [19]. In contrast, the *emm12* type was closely associated with ERY resistance in Korea [5,6].

The ERY-resistant strains differed by specimen type and location. The *emm28* type seemed rather common among these strains. Two strains from Jeju showed a very low MIC concentration (3 μ g/mL) for ERY, which is unusual considering they have a cMLS_B phenotype. Typically, strains of this phenotype show a high MIC for ERY.

In conclusion, this multicenter study found heterogenous *emm* genotypes according to the specimen and a different distribution by area. Resistance to ERY and CLI was uncommon. Most of the ERY-resistant strains showed a cMLS_B phenotype.

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=국문초록=

2008-2009년 한국에서 분리된 A군 연쇄구균의 분자역학 및 항균제 내성에 관한 다기관 연구

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배경: A군 연쇄구균은 다양한 인체 감염을 일으킨다. 저자들은 우리나라 여러 지역에서 분리된 A군 연쇄구균을 대상으로 *emm* 유전자형과 항균제 내성 검사를 시행하여 분자역학적인 조사를 시행하였다.

방법: 2008-2009년 서울, 부산, 울산, 익산 및 제주 지역에서 총 192균주가 분리되었으며, 검체로는 인두, 혈액 및 기타 검체 등 다양하였다. *emm* 유전자형 검사는 PCR 및 염기서열 분석법으로 시행하였고, 항균제 감수성 검사는 디스크확산법으로 시행하였다. Macrolide 내성 표현형을 살펴 보았고, 내성 유전자는 PCR로 검출하였다.

결과: *emm*89 (33.9%)형이 가장 흔히 분리되었고, 이어서 *emm*1 (12.5%), *emm*12 (8.3%), *emm*4 (7.8%), 그리고 *emm*75 (7.3%) 순이었다. *emm* 유전자형 분포는 검체 종류와는 무관하였고, 지역적으로 서로 다른 분포를 보였다. Erythromycin 내성률은 4.6%, clindamycin 내성률은 3.7%였다. Erythromycin 내성 9균주 중 구성형 내성은 8균주, M형 내성은 1균주 있었다. Erythromycin 내성균 중 5균주는 *emm*28이었다.

결론: 본 다기관 연구에서 *emm* 유전자형 분포는 지역적으로 다양하게 나타났다. Erythromycin 및 clindamycin 내성률은 매우 낮았고, 대부분의 erythromycin 내성균은 구성형이었다. [대한임상미생물학회지 2011;14:85-90]

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