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Epidemiology and Erythromycin Resistance of *Streptococcus pyogenes* in the Last 20 Years

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Serological methods for the epidemiological study of *Streptococcus pyogenes*, such as T-, or M-typing, were replaced by *emm* typing in the 2000s. The frequency of *emm* types may differ according to geographical area and study period. Erythromycin resistance rates and the prevalence of erythromycin-resistant phenotypes in several countries are surveyed, and common *emm* genotypes associated with erythromycin resistance are described for each country. There is no correlation between erythromycin resistance and macrolide use in Korea. *S. pyogenes* is thought to cause severe illness, such as streptococcal toxic shock syndrome (STSS) and necrotizing fasciitis. The mortality rate of STSS is about 50%, and there have been several hundred victims of STSS in Japan in the last 2 decades. The resistance rate to macrolides peaked at 50% in 2002, and currently, <10% of strains exhibit macrolide resistance in Korea. However, the erythromycin resistance rate recently exceeded 90% in China. Considering increases of travel between neighboring countries, a vigilant survey to monitor these highly virulent and antibiotic-resistant strains is necessary. **(Korean J Clin Microbiol 2011;14:119-125)**

Key Words: *Streptococcus pyogenes*, Group A streptococci, *emm*, Epidemiology, Erythromycin resistance

INTRODUCTION

Streptococcus pyogenes, also known as group A streptococci (GAS), is a major pathogen that causes acute bacterial pharyngitis, often resulting in nonsuppurative sequelae, such as rheumatic fever (RF) and post-streptococcal glomerulonephritis (PSGN). While these secondary sequelae were a global threat in the early 20th century, improvement of personal hygiene, better nutrition and the invention of penicillin have made these sequelae rare in developed countries. However, these diseases are still major public health problems in the developing world. Moreover, several outbreaks of RF were reported in the USA during the 1980s [1]. Strains M1, M3, and M18 were more frequently isolated from patients with severe invasive infections as well as strains M3 and M18 from patients with RF than from normal controls [2]. The mucoid type, M3, was a major cause of the resurgence of RF [1]. The most striking diseases caused by GAS are necrotizing fasciitis and streptococcal toxic shock syndrome (STSS), or toxic shock-like syndrome, which was described in the early 1990s in the developed world. The mortality rate of STSS has reached 50%, which is 10 times higher than that of toxic shock syndrome caused by *Staphylococcus aureus* [3]. During the past few decades in Japan, there have been several hundreds of victims of STSS caused by group A, C, or G streptococci [4]. Although STSS cases are rarely reported in Korea, an increased awareness and understanding of this disease should be emphasized. A clinical trial testing a vaccine against the 26-valent serotype of GAS is currently underway [5]. GAS infects only human beings, making it difficult to determine the mechanisms of RF or PSGN, which are currently unknown. Many virulence factors, such as streptococcal pyrogenic exotoxin A (SPE A), have been suggested as a cause of STSS; however, this linkage has not been established, and there are still unknown mechanisms to be discovered [3,4]. Considering the high mortality rate of STSS and the proximity of Korea to Japan, outbreaks of this fatal illness should be closely monitored. The clinical course of STSS is so rapid that sometimes a diagnosis will be incomplete or missed altogether, which is a major problem because most cases of STSS require urgent surgical debridement as part of the treatment regimen [3].

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CARRIER STUDY

A carrier of GAS is defined as a person who has a throat culture positive for GAS but who does not have a sore throat or immunologic response [6]. Carriers may transfer GAS to close contacts, such as classmates or friends and family members. The carrier study is useful to enhance our understanding of the epidemiology of GAS and to conduct a survey of antibiotic resistance in the community. A study demonstrated an association between an increased carriage rate of an invasive streptococcal clone among school children and the outbreak of invasive streptococcal disease [7]. As GAS is common in elementary school children, most carrier studies have been performed using this group. Throat culture results can be completed in a short period of time, even for a large-scale study. Serotypes or the antibiotic resistance of GAS identified in carriers may overlap with those isolated from true infections in the same area. The carrier rate of GAS ranged from 8% to 18% among elementary school children in Korea [8].

EPIDEMIOLOGICAL STUDY

1. Serotyping

There are several antigens on the cell wall surface of GAS. The T, OF, and M antigens were commonly used for epidemiological purposes until the 1990s. The T typing test is based on slide agglutination with anti-T sera, which is commercially available. Although the T typing test is convenient to perform, it often causes cross-reactions that resulted in vague interpretations. Certain M proteins do not induce anti-M sera in the rabbit, and these were named opacity factors (OF) because they turned the horse serum opaque. Therefore, the OF antigen is equivalent to M protein such that OF4 is the same as M4. OF antibodies to M4, M2, M75, and M48 were the most common in the USA [9], while antibodies to M4, M28, M22 were more common in Korean children [10]. Instead of rabbit anti-M sera, human sera were used for OF typing in a 96-well microplate opacity method [9]. The M protein is the most important virulence factor of GAS, as it inhibits GAS phagocytosis by neutrophils. Anti-M sera made from rabbit immunizations are difficult to produce and preserve. There have been more than 80 different M proteins discovered. M typing is based on double immunodiffusion on an agarose gel and shows unambiguous results. There are approximately 10 WHO Collaborating Centers for Reference and Research for Streptococci, worldwide. The author sent GAS isolates from Korean carriers to one of these WHO reference centers located in Minnesota in the early 1990s. The M typing results showed a variable distribution of M types by region in Korea. M78 was the most common type in Inje (48%), while M12 was more common in Nonsan, Seoul, and Jinju (24-48%) [8].

2. *emm* genotyping

M typing, once considered the gold standard for the epidemiologic study of GAS, was replaced by *emm* genotyping in the 2000s. The *emm* genotyping method uses PCR and sequencing and is currently available in many laboratories [11]. The *emm* gene encodes the M protein, and this gene has a heterogeneous sequence at 5' terminus. Although the *emm* gene is parallel to the M protein, there are more than 230 different *emm* genes reported. The *emm* genotyping method has been used to show a dynamic change in the distribution of *emm* gene variants within the same regions across time. The *emm* genotyping in Jinju has shown that the most common *emm* genotype, *emm*12, has recently become rare in that region. The prevalence of *emm*12 declined from 34% in 2002 to 7% in 2004, over the period of only two years [12]. Moreover, previously non-existent *emm* type, *emm*44/61 appeared most frequently in 2004 (28%). The *emm*78 type, not detected in the past, was most frequent in 2006 (17%). These results indicate that an influx and expansion of new *emm* types can occur within a community. In another study conducted in Korea, the most prevalent genotypes were *emm*12 and *emm*4 among 615 isolates taken from acute pharyngitis cases from 1998-2003 [13]. An epidemiologic study of invasive *S. pyogenes* isolates from Italy also showed a dynamic change of *emm* types. The *emm*89 epidemic clone decreased from 24% in 1994-1996 to 2% in 2003-2005. The *emm*12 type became rather common with an increase from 1% to 12% during the same time period [14].

ANTIBIOTIC RESISTANCE

1. Treatment regimens

Antibiotic treatment is necessary to reduce unwanted sequelae and to prevent the spreading of these bugs to the other people. However, the use of antibiotics should be restricted to cases of bacterial pharyngitis, and should not be used for cases of viral pharyngitis. Overuse or misuse of antibiotics is a social concern and should be discouraged, as these practices may increase the selective pressure on the bugs resulting in an increase in anti-

biotic resistance. Although penicillin is the drug of choice to eradicate GAS in the throat, oral penicillin V is no longer available in Korea. Moreover, Korean physicians are hesitant to use injectable penicillin due to the risk of shock allergy. Although other oral penicillins or cephalosporins are safe and easy to take, they are not very effective against intracellular organisms. GAS is located in both extra-cellular and intra-cellular compartments. Macrolides are adequate alternative drugs that effectively kill intracellular organisms, and these can be used for patients who are allergic to penicillin. Macrolides are also effective against other etiological agents that cause respiratory tract infections, such as chlamydia and mycoplasma [15]. Long-acting macrolides, such as azithromycin or clarithromycin, have been increasinggly used to treat infections, and these are more likely to induce resistance than erythromycin.

2. Mechanism of macrolide resistance

The macrolides, lincosamides and streptogramin B, also called MLS_B, have similar structures and antibacterial spectra. Erythromycin and clindamycin are class drugs of the macrolides and lincosamides, respectively. The double disk synergy (DDS) of erythromycin and clindamycin is used to classify GAS phenotypes into $cMLS_B$ (constitutive resistance), $iMLS_B$ (inducible resistance), and M. The $cMLS_B$ phenotype is resistant to both erythromycin and clindamycin and its minimal inhibitory concentration (MIC) is very high (>64 μg/mL). It shows a characteristic 'D' shape by DDS in $iMLS_B$. Clindamycin is regarded as resistant in $iMLS_B$ because resistance is induced within 2-3 days of usage. With a microdilution test, an $iMLS_B$ phenotype may be missed. In the case of the M phenotype, clindamycin is susceptible and the MIC of erythromycin is low (4-8 μg/mL). These phenotypes rely upon the macrolide resistance genes: $cMLS_B$ with *erm*(B), $iMLS_B$ with *erm*(A) (previously known as *erm*(TR)), and M with *mef*(A). Most of the macrolide-resistant GAS strains contain only one resistance gene. The antibiotic mechanism of MLS_B phenotype is the methylation of 23S rRNA, whereas the M phenotype is caused by efflux. Resistance due to other mechanisms, e.g., 23S rRNA mutation, is rare.

3. Macrolide resistance rates and phenotype distribution

It is worthwhile to compare the trend of macrolide resistance and its phenotypic distribution by country (Table 1). The emergence of erythromycin resistance (41.3%) was encountered in Seoul, Korea beginning in 1998 [16]. An even higher peak of erythromycin resistance (51%) was observed in Jinju, Korea in 2002 [17]; however, this peak dropped sharply to 9.8% in the same area in just over 2 years [12]. The $cMLS_B$ phenotype was predominant in both of these two studies. The erythromycin resistance rate of GAS strains collected between 1980 and 1992 was 2% [18]. GAS strains isolated between 1990 and 2000 showed resistance rates of 16.1% and 9.8% to erythromycin and clindamycin, respectively in Wonju, Korea [19]. In that report, erythromycin resistance was first observed in 1994. Although the number of isolates tested was low (23 strains), phenotypic

Table 1. Erythromycin resistance rates and predominant phenotypes of *Streptococcus pyogenes* in the last 20 years

Country	Period	N	Erythromycin resistance rates	Predominant phenotypes	References
Korea	2002	98	51.0%	$cMLS_B$ (61.2%)	17
Korea	2004	328	9.8%	$cMLS_B$ (87.5%)	12
Korea	1990-2000	143	16.1%	MLS_B* (65%)	19
Korea	1998-2003	615	20.5%	M (45%), $cMLS_B$ (42%)	13
Korea	1998	92	41.3%	Not specified	16
Korea	1980-1992	59	2.0%	Not specified	18
Korea	1997-2003	222	23.0%	$iMLS_B$ (51%), $cMLS_B$ (31%)	20
Hong Kong	2005-2008	281	25.6%	Not specified	21
China	1993-1994	137	79.7%	$cMLS_B$ (90%)	22
China	2005-2008	319	94.0%	$cMLS_B$ (99%)	22
USA	2002-2003	1,885	6.8%	$iMLS_B$ (47%), M (44%)	24
USA	2002-2003	2,797	6.1%	M (62%)	23
Italy	1994-1996	118	26.5%	$cMLS_B$ (>80%)	14
Spain	1999-2005	17,232	21.3%	M (>80%) before 2003; $cMLS_B$ (~50%) in 2003-2005	26
Spain	2001-2004	146	34.2%	MLS_B (~70%)	25
Spain	2007-2008	108	7.4%	MLS_B (~70%)	25
Greece	2003-2006	1,160	14.9%	M (54%), $iMLS_B$ (40%)	28

*MLS_B includes both constitutive and inducible type.

distribution showed 9, 6, and 8 strains each for the $cMLS_B$, $iMLS_B$, and M phenotypes, respectively [19]. Erythromycin resistance was observed in 23% of clinical isolates collected between 1997 and 2003 in Seoul [20]. Among the 51 erythromycin-resistant strains, the $cMLS_B$ phenotype accounted for 31%, the $iMLS_B$ phenotype for 51%; and the M phenotype for 18% [20]. Another large-scale study in Korea showed that the M (45%) and $cMLS_B$ (42%) phenotypes were rather common among 126 erythromycin-resistant strains in 1998-2003 [13].

The overall rate of erythromycin resistance was 25.6% in 281 strains isolated between 2005 and 2008 in Hong Kong [21]. Surprisingly, in China, rates of erythromycin and clindamycin resistance were 79.7% and 75.4%, respectively, in 1993-1994, and these rates increased to 94% and 96.9%, respectively, between 2005 and 2008 [22]. The resistance rate to erythromycin was 6.1% among 2,797 isolates in the USA collected between 2002 and 2003 [23]. In this study, they collected pharyngeal isolates from different locations and at different times, and as a result, they observed variable rates by site (3.0-8.7%) and by month (<2% to >10%). Over 60% of the macrolide-resistant isolates presented with the M phenotype in this study [23]. Another study in the USA during the same time period showed that resistance rates to erythromycin and clindamycin were 6.8% and 0.5%, respectively, among 1,885 isolates [24]. The macrolide-resistance phenotype distribution of strains in this study was as follows: $cMLS_B$ was 9%, $iMLS_B$ was 47%, and the M phenotype was present in 44% of resistant strains. Among the 129 erythromycin-resistant strains, three predominant *emm* types were observed: *emm*75, *emm*12, and *emm*58 [24]. In a long-term study conducted in Spain from 1993 to 2008 [25], the erythromycin resistance trend coincidently overlapped with ours. Erythromycin resistance rates progressively increased from 0% in 1993-1994 to 34.2% in 2001-2004, and then they fell to 7.4% in 2007-2008. Among the 66 erythromycin-resistant isolates studied, the $cMLS_B$, $iMLS_B$, and M phenotypes were 50%, 10.7%, and 39.4%, respectively [25]. Another well-designed study in Spain demonstrated that the erythromycin resistance rate was 21.3% among 17,232 isolates between 1999 and 2005 and most of erythromycin-resistant isolates had the M phenotype prior to 2003 [26]. However, by 2004-2005, 50% of isolates presented with the MLS_B phenotype, suggesting a higher MIC more recently. The $cMLS_B$, $iMLS_B$ and M phenotype rates were 18%, 31% and 50%, respectively, among 167 erythromycin-resistant strains in Italy [27]. Among 1,160 clinical isolates collected between 2003 and 2006, the rates of resistance to erythromycin and clindamycin were 14.9% and 1.4%, respectively, in Greece [28], suggesting that most of these isolates were of the M phenotype.

4. Antimicrobial consumption and antimicrobial resistance

It is well known that erythromycin resistance of GAS in Japan used to be very high (over 60%) in the 1970s, with a substantial decrease in erythromycin resistance since the 1980s [29,30]. The reduction of macrolide usage is postulated as a major reason for the decrease in erythromycin resistance in Japan. Scientists in Finland demonstrated a close association between erythromycin resistance of GAS and the consumption of this drug [31]. The incomparably high resistance rate (>95%) to macrolides in China in the late 2000s is a worrisome trend [21], as well, particularly because most of these strains had the $cMLS_B$ phenotype. As these highly resistant strains are interchangeable between neighboring countries, a vigilant survey should be conducted to monitor these strains.

The resistance rate of erythromycin, class drug of the macrolides, showed a peak (51%) in 2002, which dropped dramatically to 10% in 2004 in Jinju [12], and is currently less than 10%. However, the author has found that the consumption of macrolides, especially new macrolides, such as azithromycin, roxythromycin, and clarithromycin, has recently increased [32]. The author has suggested that the change of distribution of *emm* genotypes may affect the resistance rate more so than reducing the use of antibiotics in Korea [32]. A Spanish group observed a similar phenomenon: the frequency of erythromycin-resistant GAS was altered by the emergence of epidemic clones susceptible to erythromycin [33], and these arose without changes in the use of macrolides.

5. *emm* genotype and antimicrobial resistance

There is a discrepancy in the association between *emm* genotype and erythromycin resistance reported by country (Table 2). The author reported strong associations between *emm*12 and $cMLS_B$, and *emm*18 and *emm*75 with M phenotype in 2002 [17]. While all $iMLS_B$ strains harbored the *emm*12 genotype, nine of 16 $cMLS_B$ had the *emm*28 type observed in Seoul [20]. There was a strong positive association between *emm*12 and the *erm*(B) gene in Korea, where 87.7% of the *emm*12 genotype contained the *erm*(B) gene [13]. The *emm*12 genotype seemed to be the most resistant genotype in Korea [13,17,32]. The *emm*75 genotype seemed to be associated with M phenotype [17,23-25].

Table 2. Association of *emm* genotypes and erythromycin-resistant phenotypes of *Streptococcus pyogenes*

Country	Period	*emm* genotypes	Associated phenotypes	References
Korea	2002	*emm*12/*emm*18, *emm*75	$cMLS_B$/M	17
Korea	1998-2003	*emm*12	$cMLS_B$	13
Korea	1997-2003	*emm*12/*emm*28	$iMLS_B$/$cMLS_B$	20
China	1993-1994	*emm*1, *emm*12	$cMLS_B$	22
USA	2002-2003	*emm*75/*emm*58, *emm*12	M/$iMLS_B$	24
USA	2002-2003	*emm*75	M	23
Italy	1994-1996	*emm*89	$cMLS_B$	14
Italy	1997	*emm*22/*emm*89/*emm*2, *emm*4	$cMLS_B$/iMLSB/M	27
Spain	1999-2005	*emm*11, *emm*28	$cMLS_B$	26
Spain	1993-2008	*emm*4, *emm*6, *emm*75/*emm*11, *emm*28	M/MLS_B	25
Spain	1996-1999	*emm*4, *emm*75, ST1815	M	34

The most common *emm* genotypes representing erythromycin resistance were *emm*22 (85.7%) in Hong Kong [21], *emm*1 (86.2%) and *emm*12 (91.8%) in China [22], and *emm*77 (17.9%) and *emm*4 (16.8%) in Greece [28]. Almost all strains harboring the *emm*22 gene had the $cMLS_B$ phenotype, and more than 80% of the *emm*89 and *emm*4 positive strains presented with the $iMLS_B$ and M phenotypes, respectively, in Italy [27]. Among the M phenotype isolates, the most frequent genotypes (88.5%) were *emm*4, *emm*6, and *emm*75, while *emm*11, *emm*28, and *emm*25 accounted for 72.5% of MLS_B phenotype isolates in Spain over a period from 1993-2008 [25]. Another study supported the relationship between *emm* types and the MLS_B phenotype reported in Spain. In that study, the most prevalent genotypes were *emm*11 and *emm*28 in isolates collected from 1999 to 2005, and these had the MLS_B phenotype [26]. In the other study in Spain, *emm*4, ST1815, and *emm*75 had been predominantly observed in erythromycin-resistant strains from 1996-1999 [34]; however, the *emm*12 genotype was common both in erythromycin-resistant and susceptible strains. The finding of diverse *emm* types representing erythromycin resistance that varies by country indicates that the M protein does not play a role in the passage of resistance gene clusters (e.g., transposon) through the cell wall. Clonal expansion of resistant strains in a given region is more likely the cause, rather than susceptibility of certain M proteins to resistance genes. However, more studies should be conducted to elucidate the mechanism of macrolide resistance. That no penicillin-resistant GAS strains have been identified, worldwide [35], despite the fact that a very high resistance rate to penicillin occurs in *Streptococcus pneumoniae*, has yet to be fully elucidated.

CONCLUSION

S. pyogenes, or GAS, may cause severe illnesses, such as STSS or necrotizing fasciitis. The mortality rate for STSS is currently 50%. There have been several hundred victims of STSS in Japan. Acute pharyngitis is a very common infection of the upper respiratory tract. Although no strains with resistance to penicillin have been discovered, the macrolides have been the most common treatment used to eradicate this bug. GAS resistance to erythromycin peaked in 2002, but this resistance is currently very low in Korea; however, the macrolide resistance rate exceeded 90% recently in China. Considering the increasing numbers of travelers between neighboring countries, a vigilant survey to monitor these highly virulent and antibiotic-resistant strains is necessary.

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=국문초록=

최근 20년간 *Streptococcus pyogenes*의 역학 및 Erythromycin 내성

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*Streptococcus pyogenes*의 역학조사를 위해서 사용되었던 혈청학적 방법은 2000년 이후에 *emm* 유전자형 검사에 의해 대치되고 있다. 유전자형 분포는 지역이나 연구시기에 따라 다양하게 보고되었다. 이 논문에서는 여러 나라에서 보고된 erythromycin (EM) 내성률과 내성 표현형에 대해 기술하였다. 또한 EM 내성과 *emm* 유전자형의 연관성에 대해서도 살펴보았다. 한국에서는 macrolide계 항균제의 사용량과 EM 내성률과는 무관하였다. *S. pyogenes*는 독성쇼크증후군이나 괴사성 근막염과 같은 치명적인 질환을 일으킨다. *S. pyogenes*에 의한 독성쇼크증후군은 치사율이 50%에 이르며, 일본에서는 이 질환으로 수 백 명이 사망하였다. 한국에서는 2002년 EM 내성률이 50%로서 정점을 보인 후, 현재는 10% 미만으로 매우 낮게 유지되고 있다. 하지만 최근 중국에서는 EM 내성률이 90% 이상으로 보고되고 있다. 근접한 이웃 국가 간에 여행자가 급증하고 있음을 감안하면, 매우 치명률이 높고, 항균제 내성률이 높은 이 균의 유입을 잘 관찰해야 할 것이다.
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