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Antimicrobial Susceptibility Patterns and Macrolide Resistance Genes of β-Hemolytic Streptococci in Korea

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In 540 beta-hemolytic streptococci, the rates of resistance to tetracycline, chloramphenicol, erythromycin, and clindamycin were 80.0, 22.8, 20.2, and 19.1%, respectively. Of the erythromycin-resistant isolates, 63.3% had the constitutive macrolide-lincosamide-streptogramin B (MLS_B) resistance phenotype, 23.9% had the M phenotype, and 12.8% had the inducible MLS_B resistance phenotype. The constitutive MLS_B resistance phenotype with the *erm*(B) gene was dominant in Korea.

Current practice guidelines for the management of pharyngitis caused by *Streptococcus pyogenes* include the use of erythromycin as an alternative to penicillin when indicated and clindamycin for persons with multiple recurrent episodes (5). Macrolide or lincosamide therapy is also a recommended treatment option for *S. agalactiae* infection or for prophylaxis when streptococcal colonization among pregnant women is suspected (16). However, recent studies have shown that changes in the susceptibility of beta-hemolytic streptococci (BHS) to erythromycin and clindamycin have been substantial, although differences in rates of resistance to these agents have existed according to geographical location and investigators. The objectives of the present study were to investigate the incidence and possible trends in susceptibility among the BHS isolated from clinical specimens in a Korean hospital and to clarify the phenotypes and genotypes of erythromycin-resistant isolates.

A total of 540 strains of BHS were collected from clinical specimens between January 1990 and December 2000 at Wonju Christian Hospital, a 1,000-bed teaching hospital in South Korea. Multiple isolates from the same patient were avoided. The isolates were identified by standard methods. Beta-hemolytic strains with group F antigens were excluded. Susceptibility to penicillin G, erythromycin, clindamycin, tetracycline, ceftriaxone (Sigma Chemical Co., St. Louis, Mo.), vancomycin (Daewoong Lilly, Seoul, Korea), and chloramphenicol (Chongkundang, Seoul, Korea) was tested by the agar dilution method (14). The resistance phenotypes of erythromycin-resistant (intermediate and resistant) isolates were determined by the double-disk test with erythromycin (15 μg) and clindamycin (2 μg) disks (17). The presence of *erm* and *mef* class genes was determined by PCR amplification with previously described primers (11, 18) specific for *erm*(A) subclasses *erm*(TR), *erm*(B), *erm*(C), and *mef*(A).

The overall resistance rates of BHS were found to be 80.0% for tetracycline, 22.8% for chloramphenicol, 20.2% for erythromycin, and 19.1% for clindamycin, whereas all isolates were susceptible to penicillin G, ceftriaxone, and vancomycin (Table 1). The rates of resistance to erythromycin found in this study were as follows, in order of decreasing rank: *S. agalactiae*, 25.3%; *S. pyogenes*, 16.1%; group C streptococci, 9.1%; group G streptococci, 9.0%. *S. agalactiae* had the highest rate of clindamycin resistance (28.2%), followed by *S. pyogenes* (9.8%), group C streptococci (4.5%), and group G streptococci (1.5%). Of 109 erythromycin-resistant BHS isolates, 63.3% had the $cMLS_B$ phenotype (constitutive resistance to macrolide-lincosamide-streptogramin B [MLS_B]), 23.9% had the M phenotype, and 12.8% had the $iMLS_B$ (inducible resistance to MLS_B) phenotype. With the exception of two isolates, all MLS_B-resistant strains carried the *erm*(B) gene ($cMLS_B$ phenotype), the *erm*(A) subclass *erm*(TR) gene ($iMLS_B$ phenotype), or the *mef*(A) gene (M phenotype).

The erythromycin resistance rate of 20.2% (intermediate, 1.7%; resistant, 18.5%) in this study is similar to that reported in North America (18.6%) but higher than those in the Asia-Pacific region (10.9%), Europe (9.7%), and Latin America (2.7%) (7). The resistance of BHS to clindamycin was significantly higher in this study (19.1%) than in North America (6.8%), the Asia-Pacific region (4.7%), Europe (4.7%), and Latin America (0.9%) (7). Macrolide resistance among *S. pyogenes* isolates is an emerging concern. Erythromycin resistance among *S. pyogenes* isolates has remained variable but generally low in most countries. However, there have been reports from Japan in the 1970s (13) and more recently from Europe (2, 15) and Taiwan (8) of high percentages of isolates that are macrolide resistant. Erythromycin-resistant *S. pyogenes* was isolated for the first time in this study in 1994; after that time, the resistance rate ranged from 14.3 to 23.8% during the period of 1994 to 2000. Although there are far fewer reports of antimicrobial resistance in *S. agalactiae* compared with *S. pyogenes*, the increasing isolation of erythromycin-resistant *S. agalactiae* has also become alarming (3). Studies have documented that the erythromycin resistance rates for invasive *S. agalactiae* isolates during 1997 to 1999 were 14.3 and 25.4% in Canada and the United States, respectively (1). Investigators in Taiwan reported that 46% of *S. agalactiae* isolates were resistant to erythromycin (9). In this study, erythromycin-resistant *S. agalactiae* emerged in 1996; after that time, the resistance rate ranged from 18.7 to 40.0% during the period of 1996 to 2000

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TABLE 1. Antimicrobial susceptibilities of BHS

Serogroup (no. of isolates tested)	$MIC_{50/90}$ (%R)[a]			
	Erythromycin	Clindamycin	Tetracycline	Chloramphenicol
A (143)	0.06/4 (16.1)	0.06/0.12 (9.8)	16/64 (55.2)	2/8 (12.6)
B (308)	0.06/256 (25.3)	0.06/256 (28.2)	64/64 (95.8)	4/8 (23.4)
C (22)	0.06/0.12 (9.1)	0.03/0.06 (4.5)	2/64 (50.0)	4/4 (18.2)
G (67)	0.03/0.25 (9.0)	0.06/0.12 (1.5)	32/64 (70.1)	4/8 (43.3)
Total (540)	0.06/64 (20.2)	0.06/64 (19.1)	32/64 (80.0)	4/8 (22.8)

[a] $MIC_{50/90}$ MIC (micrograms per milliliter) for 50 and 90% of strains tested. %R, percent resistance (intermediate and resistant).

(Table 2). Most studies reported rates of resistance to erythromycin higher than those of clindamycin (1, 3, 4, 6, 7, 19). In contrast, the rate of resistance to clindamycin in our *S. agalactiae* isolates was higher than the rate of resistance to erythromycin. Among the BHS, *S. agalactiae* exhibited the highest rates of resistance to erythromycin, clindamycin, and tetracycline. Although the susceptibility data for group C and G BHS were sparse, our studies showed that all isolates were susceptible to penicillin G, ceftriaxone, and vancomycin and ≥90% of the isolates were susceptible to erythromycin and clindamycin. The rates of resistance to tetracycline and chloramphenicol were high for both group C and G streptococci.

It was noted that the prevalent phenotype of MLS_B resistance of BHS is serogroup dependent. A study conducted in North America found that rates of the M phenotype of group A and B streptococci were 91.4 and 59.1%, respectively (4). In Europe, the distribution of frequencies of MLS_B resistance phenotypes and genotypes of *S. pyogenes* are quite different according to geographical location; e.g., in Spain, 89.5% of *S. pyogenes* isolates had the M phenotype (15); in Italy, 47.4% of *S. pyogenes* isolates had the $cMLS_B$ phenotype (20); and in central and Eastern European countries, 60.5% of *S. pyogenes* isolates had the $cMLS_B$ phenotype (12). In Taiwan, 80.2% of erythromycin-resistant *S. pyogenes* isolates exhibited the M phenotype (8). The predominant MLS_B resistance phenotype of *S. agalactiae* was $cMLS_B$ in Spain (3) and Taiwan (9), whereas the M phenotype was prevalent in North America (4). Kataja et al. (10) reported that nearly all (95%) of the erythromycin-resistant group C streptococcus isolates had the M phenotype, whereas 91% of the erythromycin-resistant group G streptococcus isolates had the $iMLS_B$ phenotype. In our study, *S. pyogenes* isolates showed a nearly equal distribution of MLS_B resistance phenotypes (Table 3). The prevalence rate of the $cMLS_B$ resistance phenotype in *S. agalactiae* was much higher than in streptococci of other serogroups, and the M phenotype was more prevalent in group G streptococci.

We found that erythromycin and clindamycin resistance was relatively common, particularly among *S. agalactiae*; that the $cMLS_B$ resistance phenotype was dominant among erythromycin-resistant BHS; and that rates of *S. agalactiae* resistance to erythromycin and clindamycin showed an increasing trend in Korea.

TABLE 2. Trend in antimicrobial susceptibilities of 143 *S. pyogenes* and 308 *S. agalactiae* isolates by year

Serogroup and antimicrobial	Resistance (intermediate and resistant) rate (%)							
	1990–1993	1994	1995	1996	1997	1998	1999	2000
A								
Tetracycline	61.1	71.4	57.1	35.0	57.1	64.3	61.9	50.0
Chloramphenicol	16.7	0	0	0	0	14.3	0	46.4
Erythromycin	0	14.3	23.8	15.0	21.4	21.4	19.0	14.3
Clindamycin	0	0	14.3	0	14.3	21.4	14.3	10.7
B								
Tetracycline	96.2	100	100	98.0	91.7	100	91.2	97.0
Chloramphenicol	7.7	0	0	8.0	2.1	20.0	12.3	74.6
Erythromycin	0	0	0	26.0	18.7	40.0	29.8	34.6
Clindamycin	0	23.1	28.6	22.0	25.0	32.5	36.8	37.3

TABLE 3. Distribution of MLS_B resistance phenotypes and genotypes among 109 isolates of erythromycin-resistant BHS[a]

Serogroup (no. of isolates tested)	Phenotype (no. of isolates)	Genotype (no. of isolates)
A (23)	CR (9)	*erm*(B) (9)
	M (8)	*mef*(A) (7), ND (1)
	IR (6)	*erm*(A) (6)
B (78)	CR (58)	*erm*(B) (58)
	M (14)	*mef*(A) (14)
	IR (6)	*erm*(A) (6)
C (2)	CR (1)	*erm*(B) (1)
	IR (1)	ND (1)
G (6)	CR (1)	*erm*(B) (1)
	M (4)	*mef*(A) (4)
	IR (1)	*erm*(A) (1)

[a] Abbreviations: CR, constitutive resistance; M, M phenotype; IR, inducible resistance; ND, not detected.

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