Eur J Clin Microbiol Infect Dis (2001) 20:334–339

Article

Serotyping and Antimicrobial Susceptibility of Group B Streptococcus Over an Eight-Year Period in Southern Taiwan

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Abstract The increase in penicillin resistance among pneumococci and viridans streptococci and the development of serotype-specific conjugate vaccine have increased the need for knowledge of the antimicrobial susceptibility and the capsular serotypes of group B streptococci. Over an 8-year period, 351 group B streptococcal isolates from southern Taiwan were tested for antimicrobial susceptibility and serotype determination. Eighty-seven percent of the isolates were typeable. Types III (28.5%) and V (27.1%) were the most common serotypes. The occurrence of type V isolates increased with age, while that of type III isolates decreased with age, showing a predominance in children less than 1 year of age. Of 118 isolates from cases of invasive infection, types Ia, Ib, II, III, IV, and V accounted for 12.7, 11.9, 0.8, 33, 1.7, and 26.3%, respectively. Using the agar dilution method, all isolates were found to be susceptible to penicillin, cefotaxime, and vancomycin, 99.4% to ofloxacin, 78.1% to chloramphenicol, 63.2% to azithromycin, 62.6% to erythromycin, 57.3% to clindamycin, and 2.8% to tetracycline. Chloramphenicol resistance was associated with type III isolates (59 of 100, 59%) and erythromycin and azithromycin resistance with type Ib isolates (25 of 33 [76%], and 21 of 33 [64%], respectively). Thus, 72% of the isolates from invasive infections were serotype III, V, or Ia, and penicillin remains the drug of choice for treatment or prophylaxis of group B streptococcal infections in southern Taiwan, despite the high prevalence of penicillin resistance among *Streptococcus pneumoniae* and viridans streptococci.

Introduction

Group B streptococcus (GBS, *Streptococcus agalactiae*) is not only one of the primary causes of bacteremia, meningitis in neonates, and infection in pregnant women, it is also an important cause of invasive infections in the elderly and in nonpregnant adults with underlying or chronic diseases [1]. The clinical spectrum of invasive GBS disease in adults includes skin and soft tissue infection, primary bacteremia, urosepsis, pneumonia, osteomyelitis, peritonitis, septic arthritis, meningitis, endocarditis, and intravenous catheter infection [2]. Such diseases usually affect the elderly or those with chronic underlying illness and cause substantial mortality ranging from 4 to 70% [3, 4].

GBS has been classified into different serotypes on the basis of different chain structures of its capsular polysaccharide. There are at least nine recognizable types, i.e. serotypes Ia, Ib, and II-VIII [5]. The presence of serum antibodies to type-specific determinants of capsular polysaccharide has been associated with resistance to GBS infection in infants [6, 7]. The ongoing development of multivalent polysaccharide-protein

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conjugate vaccines for the prevention of GBS disease in neonates and pregnant women and potentially in the elderly will require epidemiological information about serotype distribution.

Penicillin G and ampicillin are the antimicrobial agents most commonly recommended for treatment of serious GBS infections, though the MIC of penicillin has been shown to be higher for GBS than for group A streptococci [2]. The island-wide spread of penicillin-resistant clones of pneumococci [8, 9] and the increasing reports of penicillin resistance among viridans streptococci [10] in Taiwan led us to doubt the antibacterial potency of penicillin against GBS. Thus, the aims of this study were to determine the serotype distribution among clinical isolates of GBS in southern Taiwan and to examine the antimicrobial susceptibility of these isolates in the current era of increasing resistance to penicillin and macrolides among gram-positive cocci.

Materials and Methods

Bacterial Strains. A total of 351 isolates were collected from the microbiology laboratory of a university-affiliated medical center in southern Taiwan between June 1991 and June 1999. This medical center has approximately 900 beds, including 67 intensive-care beds, and serves a population of about 2 million. During the study period, 1,207 isolates of GBS were recovered, some of which were multiple isolates obtained from the same patient. Therefore, the number of clinical isolates included in the current study represented at least one-quarter to one-third of the total group B streptococcal isolates recovered within the 8-year period.

The age and gender of the patients who were the sources of the strains were recorded. Individuals aged 18 years or older were considered adults. A single isolate from each patient was included in the current study, except for two strains with different serotypes that were obtained from the placenta of one pregnant woman. Thus, the medical records of 350 patients were reviewed. Twenty-five (7.1%) patients were less than 1 year of age, 13 (3.7%) were 1–14 years of age, 167 (44.7%) were 15–54 years of age, and 145 (41.4%) were over 55 years of age. Female patients predominated ($n=219$, 62.6%), and 40 women were pregnant or postpartum.

Ninety-one (25.9%) strains were isolated from urine, 76 (21.7%) from the female genital tract, 75 (21.4%) from wound or pus, 63 (17.9%) from blood, and 33 (9.4%) from the respiratory tract. Thirteen isolates were obtained from miscellaneous sources, including semen ($n=4$), ascites ($n=4$), synovial fluid ($n=3$), pleural effusion ($n=1$), and cornea ($n=1$). The sources of pus or wound were diverse and included extremities ($n=44$), trunk ($n=6$), perineum ($n=8$), head and neck ($n=2$), and unknown body sites ($n=15$). Of 91 urinary isolates, 84 (92.3%) strains were obtained from adults, 66 (72.5%) of whom were female; only 1 of these 66 women was pregnant. Of 76 strains obtained from the female genital tract, 74 were obtained from adult patients and 39 from pregnant women. Cases of invasive infection were defined as those from whom GBS was isolated from normally sterile sites or body fluids, such as blood, cerebrospinal fluid, ascites, synovial fluid, or surgically debrided tissue, in conjunction with compatible clinical symptoms and signs. Those isolates obtained from the superficial surface of wounds or from urine of asymptomatic individuals were excluded. At least 118 isolates were obtained from patients with invasive GBS infections, such as primary or secondary bacteremia ($n=63$, including 7 children with meningitis and a woman with puerperal fever and GBS septicemia), soft tissue infection ($n=30$), urinary tract infection ($n=11$), endometritis ($n=4$), respiratory tract infection ($n=4$), septic arthritis ($n=3$), and peritonitis ($n=3$). All cases with meningitis occurred in children aged less than 3 months.

Beta-hemolytic streptococci with a positive CAMP test were tested for the Lancefield group B cell wall antigen by group-specific antiserum (Streptex; Murex Biotech, UK). Those agglutinating with the group B-specific antiserum were identified as GBS. They were stored at –70 °C in Todd-Hewitt medium (Difco Laboratories, USA) with 15% glycerol until further testing.

Serotyping. Serotypes of GBS were determined by the agglutination method. Sera containing six type-specific agglutinins against GBS serotypes Ia, Ib, II, III, IV, and V were purchased from Denka Seiken (Tokyo, Japan); antisera against serotypes VI, VII, and VIII were not used in the current study. The procedures were performed in accordance with the manufacturer's instructions. Todd-Hewitt broth containing the isolate to be tested was incubated at 30 °C overnight and centrifuged. Swine pancreatic extract and phenol-red solution were added to 0.5 ml of sediment. The pH of the mixture was adjusted to 8–8.5, and then the mixture was incubated at 37 °C for 1 h. After centrifugation, 0.5 ml of phosphate-buffered saline (pH 7.2) was added to the sediment and a homogenous suspension was made. The bacterial suspension was heated at 120 °C for 30 min and agglutination tests were performed on a glass slide with antiserum. When a strong agglutination was visible within 1 min, the serotype of the serum was that of the bacterial strain.

Antimicrobial Susceptibility Testing. The procedures for determining in vitro antimicrobial susceptibility with the agar dilution method and MIC breakpoints for susceptibility or resistance followed the National Committee for Clinical Laboratory Standards MIC interpretative standards for *Streptococcus* spp. other than *Streptococcus pneumoniae* [11]. *Streptococcus pneumoniae* ATCC 49619 served as the control strain. Susceptibility to nine antimicrobial agents, including penicillin G, erythromycin, azithromycin, clindamycin, chloramphenicol, tetracycline, cefotaxime, ofloxacin, and vancomycin, was examined. Azithromycin was kindly provided by Pfizer (USA), cefotaxime by Hoechst (Germany), and ofloxacin by Daiichi Pharmaceutical (Japan). All other drugs were purchased from Sigma Chemical (USA). The experimental procedures and the selected ranges of concentrations and sources of antimicrobial agents in each test were as described previously [12]. Mueller-Hinton agar plates with 5% sheep blood and serial twofold dilutions of antibiotics were inoculated with bacterial inocula of $1 \sim 3 \times 10^4$ and incubated at 35 °C in ambient air for 20–24 h. Isolates intermediately susceptible to or fully resistant to at least three antimicrobial agents were defined as being multiply resistant.

Statistical Analysis. The chi-square test or two-tailed Fisher's exact test was employed for categorical variables. A P value of <0.05 was considered statistically significant.

Results

Serotyping. A total of 351 clinical isolates identified as GBS were serotyped. Eighty-seven percent ($n=305$) of the isolates had a visible agglutinating reaction with the corresponding antiserum. The remaining 13% of bacteria did not agglutinate with any antiserum or agglutinated with more than one kind of antisera and were designated as nontypeable isolates. Types III and V accounted for more than half of the isolates, and, similarly, the predominance of types III and V was

Table 1 Serotypes and clinical sources of 351 isolates of group B streptococci

Serotype	No. of isolates						
	Blood	Female genital tract[a]	Pus or wound	Respiratory tract	Urine	Other[b]	Total (%)
Ia	7	12	10	7	14	2	52 (14.8)
Ib	9	7	6	4	6	1	33 (9.4)
II	1	5	3	1	7	0	17 (4.8)
III	27	21	18	4	25	5	100 (28.5)
IV	0	0	4	1	3	0	8 (2.3)
V	13	21	22	8	27	4	95 (27.1)
NT	6	10	12	8	9	1	46 (13.1)
Total	63	76	75	33	91	13	351 (100)

[a] Vagina, cervix, endocervix, placenta, or amniotic fluid
[b] Cornea, sperm, pleural effusion, ascites
NT, nontypeable

noted among isolates from different clinical sources (Table 1). Isolates of serotype III, V, or even IV were recovered over the entire study period, and no clustering of isolation in a specific period was noted. Of 118 isolates obtained from invasive infections, the serotype distribution was similar to that of total 351 isolates: nontypeable, 13.5%; type Ia, 12.7%; Ib, 11.9%; II, 0.8%; III, 33%; IV, 1.7%; and V, 26.3%.

In female adults, the serotype distribution of 74 isolates from the genital tract (Ia, 14.9%; Ib, 9.4%; IV, 5.4%; III, 28.4%; IV, 0%; and V, 28.4%) was similar to that of 66 isolates from urine (Ia, 15.1%; Ib, 4.5%; IV, 4.5%; III, 28.8%; IV, 4.5%; and V, 33.3%). Of 39 isolates from the genital tracts of 38 pregnant women, 5 belonged to serotype Ia, 6 to Ib, 1 to IV, 7 to III, 13 to V, and 7 were nontypeable. Type IV isolates were found only in patients over 16 years of age. Among three age groups, i.e. <1 year of age, 1–15 years of age, and >16 years of age, the proportion of type V isolates increased with age (3.7, 28.8, and 32.9%, respectively), while that of type III isolates decreased with age (85.2, 26, and 23.9%, respectively).

Antimicrobial Susceptibility. The antimicrobial susceptibility of 351 isolates to nine antibiotics was studied by the agar dilution method. All isolates were susceptible to penicillin, cefotaxime, and vancomycin, and all but two isolates were susceptible to ofloxacin. Susceptibility to clindamycin, azithromycin, erythromycin, and chloramphenicol varied, ranging from 57.3 to 78.1% (Table 2). In contrast, the majority of isolates were resistant to tetracycline. Of 118 isolates recovered from invasive infections, 72% were susceptible to chloramphenicol, 66.1% to azithromycin, 62.7% to erythromycin, and 58.4% to clindamycin. Generally, there is a good correlation between susceptibility to erythromycin and azithromycin. Of 222 isolates susceptible to azithromycin, 206 (92.8%) were susceptible to erythromycin, and of 219 isolates susceptible to erythromycin, 206 (94%) were susceptible to azithromycin.

Since the number of strains belonging to certain serotypes was very small, only serotypes represented by more than 20 strains (types Ia, Ib, III, and V) were considered for comparison of antimicrobial susceptibility. Type III isolates had the lowest rate of chloramphenicol susceptibility (41%), while $>90\%$ of type Ia, Ib, and V isolates were susceptible to chloramphenicol ($P<0.0001$). Moreover, type Ib isolates had lower rates of susceptibility to erythromycin and azithromycin than did type Ia, III, or V isolates ($P<0.0001$) (Table 3).

Because the majority of clinical isolates were resistant to tetracycline and susceptible to ofloxacin, and all isolates were susceptible to penicillin, cefotaxime, and vancomycin, the following analysis concerning multiple antimicrobial resistance includes the susceptibilities to three drugs with a preferential binding to the 50S ribosomal subunit, i.e. erythromycin (the macrolide), clindamycin (the lincosamide), and chloramphenicol. Overall, 136 of 351 (38.7%) isolates were susceptible to all three drugs. Such a susceptibility phenotype was noted more often in type Ia (59.6%, 31 of 52 isolates) and type V (53.7%, 51 of 95) than in type III isolates (24%, 24 of 100, $P<0.0001$). One hundred six (30.2%) isolates were intermediately susceptible or resistant to

Table 2 Susceptibility of 351 clinical isolates of group B streptococci to nine antimicrobial agents

Antibiotic	MIC (μg/ml)			Percentage of total isolates		
	MIC90	MIC50	Range	S	I	R
Penicillin G	≤0.03	≤0.03	≤0.03–0.09	100	0	0
Cefotaxime	0.12	0.06	≤0.03–0.12	100	0	0
Erythromycin	>256	4	≤0.03–>256	62.6	4.6	33
Azithromycin	>256	0.06	≤0.03–>256	63.2	2.3	34.5
Clindamycin	256	≤0.12	≤0.12–>256	57.3	1.1	41.6
Tetracycline	128	64	≤0.12–256	2.8	0	97.2
Chloramphenicol	16	2	1–32	78.1	5.1	16.8
Ofloxacin	2	1	0.5–4	99.4	0.6	0
Vancomycin	0.5	≤0.5	≤0.5–1	100	0	0

S, susceptible; I, intermediate; R, resistant

Table 3 Rates of antimicrobial susceptibility among different serotypes of 351 isolates of group B streptococci

Antibiotic	No. of susceptible isolates (% of total isolates for each serotype)					
	Ia ($n=52$)	Ib ($n=33$)	IV ($n=17$)	III ($n=100$)	IV ($n=8$)	V ($n=95$)
Penicillin G	52 (100)	33 (100)	17 (100)	100 (100)	8 (100)	95 (100)
Cefotaxime	52 (100)	33 (100)	17 (100)	100 (100)	8 (100)	95 (100)
Erythromycin	38 (73)	8 (24)	13 (76)	56 (56)	2 (25)	74 (78)
Azithromycin	39 (75)	12 (36)	13 (76)	57 (57)	3 (38)	72 (76)
Clindamycin	35 (67)	14 (42)	12 (71)	57 (57)	1 (13)	59 (62)
Tetracycline	2 (4)	0 (0)	0 (0)	4 (4)	1 (13)	2 (2)
Chloramphenicol	48 (92)	31 (94)	15 (88)	41 (41)	6 (75)	93 (98)
Ofloxacin	52 (100)	33 (100)	17 (100)	99 (99)	8 (100)	95 (100)
Vancomycin	52 (100)	33 (100)	17 (100)	100 (100)	8 (100)	95 (100)

one drug, 74 (21.1%) to two drugs, and 35 (10%) to three drugs. Multiple resistance was noted most frequently in type III isolates (23%, 23 of 100) than other serotypes (4.8%, 12 of 251, $P<0.0001$).

Discussion

Earlier studies conducted in the 1970s indicated that the major capsular types of GBS causing neonatal and perinatal infections in the USA were Ia, Ib, IV, and III [13]. However, in metropolitan Atlanta in 1992–1993 [14], types Ia or Ia/c (34%), III (29%), and V (21%) were recovered among all age groups, and type V was the most common serotype isolated from nonpregnant adults. Serotyping data of GBS from the Asian population are scarce. One report from Beijing showed that 29 of 267 (11%) nonpregnant female workers had vaginal colonization [15]. Type III was the most frequent serotype recovered from carriers, but the number of cases was too small to draw any conclusions. Another study from Korea reported that 5.9% of pregnant women and 0.7% of neonates were colonized with GBS, type Ib being the most common serotype [16]. In contrast, serotypes III and V were the most common serotypes in our study. It is worth mentioning that, of 60 isolates serotyped by the same commercial typing antiserum used in our study, no type IV or V isolate was found in the Korean study. The serotype distribution of isolates from invasive infections in this study was similar to that in reports from the USA, where types III, V, and Ia account for 36, 26, and 13%, respectively [5, 14].

The serotype distribution of GBS varied with age. In children less than 1 year of age, the major serotype was type III, and most of the type III isolates were obtained from the bloodstream, whereas the predominant type from persons over 16 years of age was type V (30.7%, 104 of 339 isolates). In two reports from the USA, only 1 of 725 invasive isolates was serotype IV [5, 14]; similarly, none of the 8 type IV isolates in our study caused invasive infection. These common findings suggest that the emergence of serotype V in GBS disease is not only a geographic change in serotype distribution but an international trend and that type IV GBS rarely causes disease in humans. The urinary isolates were collected predominantly from female adults. The serotype distribution of isolates from urine was similar to that of isolates from the genital tract of female adults, suggesting that GBS in the urine of women is the result of contamination from genital secretions. However, it remains possible that the gastrointestinal tract is the reservoir of GBS.

Our study had several limitations. First, since the source of GBS isolates was limited to one medical center, these isolates cannot be considered representative of the situation in the general population. Second, the number of isolates from invasive infections was small, and it is likely that the serotype distribution of clinically significant GBS isolates was distorted by the variations in patient age, infectious disease entity, or underlying illness. Third, the percentage of nontypeable isolates among those of invasive infections, 12.5%, was higher than the 2% in one report from the USA [5] but close to the 13% in a report from Canada [17]. This finding is probably related to the inability of the antisera we used to identify capsular polysaccharide serotypes VI, VII, or III or surface protein C or to the geographic diversity in serotype distribution.

For years, penicillin G and ampicillin have been recommended as the drugs of choice in the treatment of GBS infections. In the 1990s, even as penicillin was losing its antibacterial advantage on pneumococci, many reports stated that penicillin [18–21] or ampicillin [18, 19, 22] retained their activity against GBS. Although Betriu et al. [23] have noted decreasing susceptibility of GBS to penicillin in Spain, we did not find any of the clinical isolates collected over an 8-year period to be intermediately susceptible or resistant to penicillin. Until now, penicillin remains the drug of choice for treatment or prophylaxis of GBS infections in southern Taiwan. However, it will not be surprising if GBS isolates become resistant to penicillin in the future following the evolutionary path of pneumococci in antimicrobial resistance. The policy of frequent surveillance for peni-

cillin resistance in clinical GBS isolates is certainly advisable for clinical microbiology laboratories.

Earlier studies indicated that 0 to <10% of GBS isolates were resistant to erythromycin and clindamycin [18, 19, 23, 24]. The rate of erythromycin resistance varies greatly between countries: in Spain it has increased from 8% in 1992 to 18% in 1994 [20] and in the USA from 1% in 1980–1993 to 16–21% over the past 5 years [25–27]. The rate of resistance of GBS to erythromycin is much higher in our isolates (33%), and such resistance confers cross-resistance to a new macrolide, azithromycin. Since the incidence of erythromycin resistance in other β-hemolytic streptococci (groups A, C, F, and G), viridans streptococci [10, 28, 29], and pneumococci [8, 9, 30] is increasing in Taiwan, there is no therapeutic advantage to using erythromycin for streptococcal infections in subjects with penicillin allergy.

In the era of increasing antimicrobial resistance, recent reports indicated that the rate of resistance to clindamycin in clinical GBS isolates was close to [17, 19, 27] or less than [25, 26] that to erythromycin. In contrast, we found resistance to clindamycin (42%) was more common than resistance to erythromycin (33%), and a similar result was also described in Korean women (13% vs. 5%) [16]. The reasons for such a discrepancy in different continents are not clear. Erythromycin resistance mediated by *ermB*, *ermTR*, or *mefA* genes has been demonstrated in *Streptococcus pyogenes* [28], but the molecular mechanisms of macrolide resistance in GBS are not fully elucidated. Recently, a distinct efflux determinant, designated as *mreA* and related to macrolide resistance, has been reported [31] and should be included when surveying the mechanisms of macrolide resistance in GBS isolates.

In Spain, 3% of GBS isolates were resistant to chloramphenicol in 1992 [23], but a higher percentage of our isolates were chloramphenicol resistant (16.8%). Furthermore, there were two unique findings in our study: the negative association of type III isolates with chloramphenicol susceptibility and of type Ib isolates with erythromycin or azithromycin susceptibility. Nagano et al. [32] have found that high sialic acid levels of capsular polysaccharides in isolates of types Ia and Ib were associated with, but did not directly contribute to, susceptibility to tetracycline. This finding suggests that the components of external capsules in GBS will, to some extent, influence antimicrobial susceptibility. Whether the correlation of type III or Ib with certain antimicrobial resistance is an incidental finding or is related to the specific capsular component requires more studies to delineate its significance.

In conclusion, the prevalent serotypes of clinical GBS strains in Taiwan are types III, V, and Ia, which differ from those reported in China and Korea. Resistance to erythromycin, azithromycin, clindamycin, or chloramphenicol was observed in 17–42% of GBS isolates, and tetracycline resistance was noted in almost all isolates. In contrast, penicillin, cefotaxime, and vancomycin remain active against all isolates in Taiwan. However, periodic surveillance of antimicrobial resistance in clinical isolates is essential for the early detection of penicillin-resistant GBS.

Acknowledgements This study was supported by a grant from NCKUH-89–005 from the National Cheng Kung University Hospital, Tainan, Taiwan. We greatly appreciate the help received from the members of Clinical Microbiology Laboratory, National Cheng Kung University Hospital.

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