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Antimicrobial susceptibility of viridans group streptococci in Taiwan with an emphasis on the high rates of resistance to penicillin and macrolides in *Streptococcus oralis*

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The in-vitro susceptibilities of 13 antimicrobial agents were determined for 207 isolates of viridans group streptococci recovered from patients with significant infections in Taiwan during 1995 and 1997. Variable degrees of susceptibility existed among nine species. High-level penicillin resistance (MIC ≥ 4.0 mg/L) was found most frequently in *Streptococcus oralis* (35%), followed by *Streptococcus mitis* (20%) and *Streptococcus salivarius* (8%). However, *S. salivarius* showed the lowest rate of susceptibility to penicillin (50%). Macrolide resistance also occurred most frequently in *S. oralis* isolates (55%) but in none of *Streptococcus mutans*. Penicillin and macrolides tended to be less active against isolates recovered from non-invasive sites than against those isolated from invasive sites. Imipenem was the most active β-lactam against penicillin-resistant isolates. Ofloxacin, vancomycin and teicoplanin showed good in-vitro activity against all isolates, with MIC_{90}s of 2, 1 and 0.25 mg/L, respectively. None of these isolates displayed high-level resistance to gentamicin and most isolates were susceptible to chloramphenicol. These results indicate the species-related variability of susceptibility, especially to penicillin, macrolides and tetracycline. In addition to *S. mitis*, *S. oralis* also displayed high rates of resistance to penicillin and macrolides. The difference in susceptibilities between species of viridans streptococci indicates the importance of accurate identification and the need for continuing surveillance of antimicrobial resistance.

Introduction

Viridans group streptococci remain the leading cause of infective endocarditis and have also been implicated in serious pyogenic infections. They have traditionally been considered to be uniformly susceptible to penicillin. In Taiwan, we reported in 1987 that all isolates of viridans streptococci from bacteraemia were susceptible to penicillin.[1] However, the emergence of strains intermediately resistant or highly resistant to penicillin is increasingly recognized worldwide,[2–7] and has complicated the antibiotic therapy of infective endocarditis. Erythromycin has been recommended as an alternative treatment for patients who are allergic to penicillin and is widely used in antibiotic prophylaxis of bacterial endocarditis associated with dental procedures. In the past, erythromycin and clindamycin usually showed good activity, but recent studies have shown that macrolide resistance may also be a problem in certain areas.[8]

The taxonomy of the viridans group streptococci has undergone considerable revision in recent years.[9–13] Associations between the newly defined species and diseases was also evaluated recently.[14] *Streptococcus oralis*, *Streptococcus sanguis* and *Streptococcus mitis* have been reported as the leading causes of endocarditis and bacteraemia in neutropenic patients.[14–16] The '*Streptococcus milleri*' group, which includes *Streptococcus constellatus*, *Streptococcus intermedius* and *Streptococcus anginosus*, has been associated with endocarditis and purulent disease of internal organs.[17–19] The heterogeneity in antibiotic susceptibilities among species is evident from earlier reports and penicillin resistance is most prevalent among several species of oral streptococci. For these reasons, we were interested in the current susceptibility patterns of viridans group streptococci and in the differences in susceptibility between species. We identified 207 clinical isolates to species level and determined their susceptibilities to 13 antimicrobial agents.

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Materials and methods

Bacterial isolates

A total of 207 isolates of viridans group streptococci, recovered from patients with clinically significant infections, were collected from the Bacteriology Laboratory of the National Taiwan University Hospital, a 2000-bed teaching hospital in northern Taiwan, during 1995 and 1997. One hundred and sixty-two of the isolates were from invasive sites (including blood, pleural infusion, ascites and abscess aspirate) and 45 were from non-invasive sites, such as pus and urine. The isolates were identified by standard criteria, on the basis of colony morphology, Gram stain, optochin test and catalase reaction. Species identification was initially performed using both the API 20 Strep system (API System, bioMérieux, Marcy-l'Etoile, France) and the AutoMicrobic System (AMS, Vitek, Hazelwood, MO, USA). The identification was also confirmed by conventional biochemical tests.[12,13,20] All isolates were stored at −70°C in trypticase soy broth (BBL Microbiology Systems, Cockeysville, MD, USA) with 15% glycerol until testing.

Antimicrobial susceptibility testing

MICs were determined by an agar dilution method, using Mueller–Hinton agar (Difco Laboratories, Detroit, MI, USA) supplemented with 5% sheep blood and containing two-fold serial dilutions of the various antimicrobial agents.[21] The plates were inoculated with 10^4 cfu/spot with a multipoint inoculator, and incubated for 18 h in air at 35°C. The following antimicrobial agents were obtained as reference powders of known potency for laboratory use: penicillin, cephalothin, erythromycin, clindamycin, tetracycline, chloramphenicol, gentamicin and vancomycin from Sigma Chemical Co. (St Louis, MO, USA), cefotaxime from Hoechst AG (Frankfurt, Germany); imipenem from Merck Sharp & Dohme (West Point, PA, USA), clarithromycin from Abbott Laboratories (North Chicago, IL, USA), ofloxacin from Daiichi Pharmaceutical Co. Ltd (Tokyo, Japan) and teicoplanin from Marion Merrill Dow (Kansas City, MO, USA). *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were used as control organisms. The susceptibility breakpoint concentrations were in accordance with the interpretive standards for streptococci other than *Streptococcus pneumoniae* recommended by the National Committee for Clinical Laboratory standards (NCCLS).[21] Strains were classified for penicillin susceptibility as follows: susceptible, MIC ⩽ 0.125 mg/L; intermediately resistant, MIC = 0.25–2 mg/L; resistant, MIC ⩾ 4 mg/L. Organisms were considered to lack high-level resistance to gentamicin when the MICs were <2000 mg/L.

Phenotypes of macrolide–lincosamide–streptogramin (MLS) resistance

Conventional double-disc induction tests were performed to determine the phenotypes of MLS resistance. In brief, a bacterial suspension was adjusted to match the turbidity of a 0.5 McFarland standard, and was streaked on to Mueller–Hinton agar supplemented with 5% sheep blood. An erythromycin disc (15 μg) and a clindamycin disc (2 μg) (Becton Dickinson Microbiology Systems, Cockeysville, MD, USA) were placed on the agar surface 15 mm apart. The plate was then incubated for 18 h at 35°C. The interpretation of the inducible resistance or constitutive resistance was according to a previous report.[22]

Results

The MIC_{50}, MIC_{90}, ranges of MICs and percent susceptibility of the 207 isolates of viridans streptococci for the 13 antimicrobial agents are listed in Table I. All *S. mutans* isolates were susceptible to penicillin (Table I), but decreased susceptibility to penicillin was displayed by the remaining species. Overall, 11% of isolates showed high-level resistance to penicillin (MICs ⩾ 4 mg/L), and 14% were intermediately resistant to penicillin (MICs = 0.25–2 mg/L). Although only 50% of isolates of *S. salivarius* were susceptible to penicillin, high-level penicillin resistance was detected in only 8% of isolates of this species (Table II). Among nine species tested, *S. oralis* showed the highest rate of high-level penicillin resistance (35%), followed by *S. mitis* (20%) (Table II). The penicillin-resistant isolates also showed increased resistance to other β-lactam antibiotics, such as cephalothin and cefotaxime. Imipenem showed good activity against all isolates (Table I).

The macrolides, erythromycin and clarithromycin, showed similar activities, though the MICs of erythromycin were generally twice those of clarithromycin (Table I). Resistance to macrolides was found most frequently in *S. oralis* (55%) (Table II). However, no isolates of *S. mutans* showed resistance to macrolides. The double-disc diffusion test revealed that all of the macrolide-resistant isolates were constitutively resistant.

The highest rate of tetracycline resistance was found in *S. mitis* (70%) and the lowest in *S. mutans* (10%). Combined erythromycin and tetracycline resistance was common in most species, and most frequent in *S. oralis* and *S. sanguis* (50%). Most isolates were susceptible to chloramphenicol, although isolates of *S. mitis* and *S. oralis* displayed lower susceptibility (Table I). None of the species displayed high-level resistance to gentamicin (MIC ⩾ 2000 mg/L). Ofloxacin showed good activity against most isolates. Only 12% of isolates of *S. salivarius* were intermediately resistant to ofloxacin. All isolates remained susceptible to vancomycin and teicoplanin.

When the data were analysed with regard to the source of the isolates, differences were detectable for both macrolides and penicillin. These agents had poorer activities against isolates recovered from non-invasive sites than against those recovered from invasive sites (Table III). However, these differences were not statistically significant.

Discussion

The emergence and increase in the frequency of antibiotic resistance in bacteria is of considerable concern, as it limits the available options for the therapy of serious infections. We found that the level of resistance to penicillin and macrolides in viridans group streptococci in Taiwan was higher than previously reported.[1] Species-related variability was significant especially for resistance to penicillin, macrolides and tetracycline.

Heterogeneity in antibiotic susceptibilities among species of viridans group streptococci was evident from the present results, as in other reports.[2] In this report we used a recent scheme to identify species. Our results show that isolates of *S. oralis* were most frequently resistant to both penicillin and macrolides. In accordance with previous reports,[2,4,6] we noted high rates (20%) of high-level resistance to penicillin among *S. mitis* isolates. *S. oralis* is a newly described species and previously may have been called *S. sanguis* II, *S. mitis* or dextran-positive *S. mitior*.[15] *S. oralis* and *S. mitis* are related, but separate from *S. sanguis*, but may easily be misidentified.[23] In 1993, Wilcox and colleagues[24] observed that of nine penicillin-resistant isolates, only two *S. oralis* had high-level resistance (MIC = 4 and 8 mg/L). In agreement with the results described by Wilcox and colleagues, our results show that *S. oralis* was more resistant to penicillin than *S. sanguis*. However, in other reports, the authors used an identification scheme in which *S. oralis* was either not identified separately, or not included.[2,4,6] In the report by Alcaide *et al*.,[2] *S. sanguis* strains accounted for 41.7% of penicillin-resistant viridans streptococci. This inconsistency may be explained by the fact that different identification schemes were used. Consequently interpretation of the correlation between susceptibility and species is very confusing. In the study reported by Doern *et al*.,[4] *S. salivarius* showed a higher rate of penicillin resistance than other species. In contrast, only one strain of *S. salivarius* resistant to penicillin at an MIC of 4 mg/L was detected in our study.

Within the *S. milleri* subgroup, because of the low number of *S. anginosus* (five isolates) collected, the results of susceptibility for *S. anginosus* and *S. constellatus* were pooled (Table I). *S. intermedius* was slightly more resistant to antibiotics than *S. constellatus* or *S. anginosus*. Similar to the results reported by Jacobs & Stobberingh,[25] resistance to penicillin in this group was only intermediate. Our results differ from those published by Bantar *et al*.,[26] who detected two *S. anginosus* strains highly resistant to penicillin at an MIC of 4 mg/L.

It has been proposed that the resistance to penicillin in viridans streptococci results from altered penicillin-binding proteins[27] and the resistance genes may be transferred among viridans streptococci and *Streptococcus pneumoniae*. *S. oralis* and *S. mitis* are closely related and both were more resistant to penicillin than other species in the viridans group.

Our results indicate that *S. mutans* was most susceptible to antimicrobial agents. Penicillin resistance was found in all species except *S. mutans*. It is possible that the heterogeneity of penicillin resistance among species in viridans streptococci may be the result of different efficiencies of transformation and homologous recombination.

We found that imipenem was the most active β-lactam tested, as reported by others.[2] However, imipenem MICs of 1 mg/L were common among strains with high-level penicillin resistance. Resistance to penicillin was also frequently associated with reduced susceptibility to other β-lactam antibiotics. It has been reported that the introduction of penicillin in prophylactic antibiotic treatment has reduced the incidence of infections, but the long-term use of penicillin could be compromised by the emergence of resistant strains.[16]

Macrolides and clindamycin had similar activities against most isolates in our study. The frequencies of resistance to macrolides and clindamycin were greater than those previously reported.[3,6,17,25] In our previous report in 1987, only 9.1% of viridans streptococci were resistant to erythromycin.[1] However, Wu *et al*.[8] recently reported that the frequency of erythromycin resistance was 56.5% in viridans streptococci isolated during 1993 and 1994 in southern Taiwan. Although the overall resistance rate to erythromycin (40%) in northern Taiwan in our study was slightly lower than this, it was still higher than that of other reports.[6,17] Resistance to macrolides was common in most species. However, no isolates of *S. mutans* were resistant to macrolides. Poor activities of erythromycin against *Streptococcus pyogenes* and *S. pneumoniae* were also recently noted in Taiwan and it was reported that the activity of newer macrolides was usually poorer than that of erythromycin in *Streptococcus* spp.[28–30] However, the MICs of clarithromycin were in general half those of erythromycin in this study. Macrolide antibiotics have recently been suggested as an alternative prophylactic approach to prevent viridans streptococcal bacteraemia or endocarditis for penicillin-allergic patients. However, our results suggest that macrolides are unsuitable as prophylactic agents to prevent viridans streptococci infections in Taiwan.

Isolates from non-invasive sites had a higher frequency of resistance to macrolides and penicillin than those from invasive sites in our study. Erythromycin resistance may have evolved in response to differing antibiotic pressure at the community level. The widespread use of erythromycin

Table I. In-vitro susceptibilities of 207 clinical isolates of viridans steptococci

Species	Antimicrobial agent	MIC (mg/L) range	MIC (mg/L) 50%	MIC (mg/L) 90%	Percent susceptible
Streptococcus acidominimus (n =10)[a]	penicillin	≤0.03–1	≤0.03	0.12	90
	cephalothin	0.06–32	0.5	2	NA
	cefotaxime	≤0.03–1	≤0.03	0.25	90
	imipenem	≤0.03–1	≤0.03	0.06	NA
	erythromycin	≤0.03–512	0.06	64	70
	clarithromycin	≤0.03–512	0.06	32	70
	clindamycin	≤0.03–16	0.06	1	70
	tetracycline	≤0.12–32	1	16	60
	chloramphenicol	1–4	2	4	100
	gentamicin	≤0.5–8	4	8	NA
	ofloxacin	≤0.12–2	0.5	2	100
	vancomycin	0.06–1	0.5	1	100
	teicoplanin	0.03–0.25	0.12	0.25	100
S. constellatus (n =20) and *S. anginosus* (n =5)[a]	penicillin	≤0.03–0.25	≤0.03	0.12	92
	cephalothin	0.06–32	0.5	2	NA
	cefotaxime	≤0.03–1	≤0.03	0.5	92
	imipenem	≤0.03–1	≤0.03	0.06	NA
	erythromycin	≤0.03–512	0.06	64	76
	clarithromycin	≤0.03–512	0.06	2	76
	clindamycin	≤0.12–16	0.06	1	80
	tetracycline	≤0.12–32	1	16	68
	chloramphenicol	1–4	2	4	100
	gentamicin	≤0.5–8	4	8	NA
	ofloxacin	≤0.12–2	0.5	2	100
	vancomycin	0.06–1	0.5	1	100
	teicoplanin	≤0.03–0.5	0.06	0.25	100
S. intermedius (n =40)	penicillin	≤0.03–1	≤0.03	0.12	88
	cephalothin	0.06–32	0.5	2	NA
	cefotaxime	≤0.03–1	≤0.03	0.5	88
	imipenem	≤0.03–1	≤0.03	0.06	NA
	erythromycin	≤0.03–512	0.06	64	75
	clarithromycin	≤0.03–512	0.06	32	75
	clindamycin	≤0.12–16	0.06	1	80
	tetracycline	≤0.12–32	2	16	55
	chloramphenicol	1–4	2	4	100
	gentamicin	≤0.5–8	4	8	NA
	ofloxacin	≤0.12–2	0.5	2	100
	vancomycin	0.06–1	0.5	1	100
	teicoplanin	0.03–0.5	0.12	0.25	100
S. mitis (n =40)	penicillin	≤0.03–8	0.06	4	55
	cephalothin	≤0.03–≥32	8	≥32	NA
	cefotaxime	≤0.03–8	0.12	4	80
	imipenem	≤0.03–1	0.06	0.25	NA
	erythromycin	≤0.03–≥512	0.25	≥512	50
	clarithromycin	≤0.03–≥512	0.12	≥512	60
	clindamycin	≤0.03–≥512	0.12	256	60
	tetracycline	≤0.12–64	16	32	30
	chloramphenicol	2–32	4	32	73
	gentamicin	1–16	4	16	NA
	ofloxacin	≤0.12–2	1	1	100
	vancomycin	≤0.06–1	0.25	1	100
	teicoplanin	0.03–0.5	0.12	0.25	100

Table I. *Continued*

Species	Antimicrobial agent	MIC (mg/L) range	50%	90%	Percent susceptible
S. mutans (n = 10)	penicillin	≤0.03–0.06	≤0.03	0.06	100
	cephalothin	0.5–2	1	2	NA
	cefotaxime	≤0.03–0.12	0.06	0.12	100
	imipenem	≤0.03–≤0.03	≤0.03	≤0.03	NA
	erythromycin	≤0.03–0.25	≤0.03	0.25	100
	clarithromycin	≤0.03–0.25	≤0.03	0.25	100
	clindamycin	≤0.12–≤0.12	≤0.12	≤0.12	100
	tetracycline	≤0.12–8	0.25	8	90
	chloramphenicol	2–4	2	4	100
	gentamicin	2–32	8	32	NA
	ofloxacin	0.5–1	0.5	1	100
	vancomycin	0.25–1	0.25	1	100
	teicoplanin	0.03–0.5	0.12	0.25	100
S. oralis (n = 40)	penicillin	≤0.03–8	0.12	4	60
	cephalothin	0.25–≥32	2	≥32	NA
	cefotaxime	≤0.03–8	0.25	4	60
	imipenem	≤0.03–1	0.06	1	NA
	erythromycin	≤0.03–≥512	4	≥512	45
	clarithromycin	≤0.03–≥512	2	≥512	45
	clindamycin	≤0.12–≥512	0.06	256	50
	tetracycline	≤0.12–64	16	64	40
	chloramphenicol	1–8	2	4	90
	gentamicin	≤0.12–32	8	32	NA
	ofloxacin	0.25–2	2	2	100
	vancomycin	≤0.06–1	0.25	1	100
	teicoplanin	0.03–0.5	0.12	0.25	100
S. sanguis (n = 30)	penicillin	≤0.03–1	≤0.03	0.5	80
	cephalothin	0.25–≥32	2	≥32	NA
	cefotaxime	≤0.03–8	0.25	4	80
	imipenem	≤0.03–1	0.06	1	NA
	erythromycin	≤0.03–≥512	2	≥512	47
	clarithromycin	≤0.03–≥512	2	≥512	47
	clindamycin	≤0.12–≥512	0.06	256	60
	tetracycline	≤0.12–64	16	64	33
	chloramphenicol	1–4	2	4	100
	gentamicin	≤0.12–32	8	32	NA
	ofloxacin	0.25–2	2	2	100
	vancomycin	≤0.06–1	0.25	1	100
	teicoplanin	0.03–0.5	0.12	0.25	100
S. salivarius (n = 12)	penicillin	≤0.03–4	0.06	1	50
	cephalothin	0.25–16	2	16	NA
	cefotaxime	≤0.03–4	0.5	4	50
	imipenem	≤0.03–2	0.06	0.12	NA
	erythromycin	≤0.03–512	0.06	512	50
	clarithromycin	≤0.03–512	0.06	512	50
	clindamycin	≤0.03–128	0.06	8	75
	tetracycline	0.5–64	0.5	64	50
	chloramphenicol	1–4	4	4	100
	gentamicin	0.5–8	4	8	NA
	ofloxacin	1–4	2	2	90
	vancomycin	0.25–0.5	0.25	0.5	100
	teicoplanin	0.12–0.25	0.12	0.25	100

NA, Not available
[a]Number of isolates.

Table II. Frequency of resistant isolates in the species of viridans streptococci

Species	No. of isolates	Percentage of resistant isolates[a]				
		penicillin high-level	penicillin intermediate	erythromycin	clindamycin	tetracycline
S. acidominimus	10	0	10	30	30	40
S. constellatus/anginosus	25	0	8	24	20	32
S. intermedius	40	0	13	25	20	45
S. mitis	40	20	25	50	40	70
S. mutans	10	0	0	0	0	10
S. oralis	40	35	5	55	50	60
S. sanguis	30	0	20	50	40	67
S. salivarius	12	8	42	50	25	50

[a]MIC breakpoints were as follows: high-level resistance to penicillin, MIC ⩾4 mg/L; intermediate resistance to penicillin, MIC = 0.25–2 mg/L; erythromycin, MIC ⩾1 mg/L; clindamycin, MIC ⩾1 mg/L; tetracycline, MIC⩾8 mg/L.

Table III. Percentage of isolates resistant to macrolide or penicillin

Antibiotic	Percentage of resistant isolates	
	non-invasive sites (n = 45)	invasive sites (n = 162)
Macrolide	56	35
Penicillin (MIC ⩾4 mg/L)	16	10

in Taiwan may contribute to its poor activity against *S. pyogenes* and *S. pneumoniae*, as well as some species of viridans streptococci.[28,29]

Resistance to tetracycline was found in all species tested. However, we observed high rates of resistance to tetracycline, most frequently in *S. mitis* (70%), followed by *S. sanguis* (67%) and *S. oralis* (60%). A high rate of resistance to tetracycline was also observed in Spain (40% of all isolates) and South Africa (41% of *S. mitis*).[6,17] In Taiwan, a high rate of resistance to tetracycline (71.3%) was also observed in *S. pneumoniae*.[28] As reported in other studies, resistance to macrolides alone was less frequent than resistance to tetracycline alone or combined resistance.[6]

Since the antimicrobial susceptibility patterns of viridans group streptococci differ between species, it is important to identify the individual species accurately. The high frequency of resistance to penicillin and macrolides among some species of viridans streptococci limits the use of these drugs as therapeutic or prophylactic agents for infections caused by these organisms. Our findings clearly indicate that periodic surveillance of antibiotic susceptibility among various species of viridans streptococci should be carried out by clinical microbiology laboratories worldwide. Such studies are particularly important in areas where macrolide and β-lactam antibiotics are frequently prescribed.

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