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Summary of MLS_B Phenotypes in the Asia-Pacific (APAC), Europe (EU), North (NA) and Latin America (LA): Report from the SENTRY Antimicrobial Surveillance Program (1997-2000)

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AMENDED ABSTRACT

Background: The macrolide-lincosamide-streptogramin (MLS_B) group of antimicrobials are widely used in clinical practice, and share several characterized and/or emerging mechanisms of resistance (R). The SENTRY Program has monitored the R rates of drugs in this group since 1997 in 4 geographic regions.

Methods: Erythromycin (ER), clindamycin (CL), quinupristin/dalfopristin (Q/D) and 19 other agents were tested by reference broth microdilution methods and interpreted by NCCLS criteria [2002]. A total of over 39,000 Gram-positive cocci were processed as follows: 22,285 *S. aureus*; 8,495 CoNS; 6,898 *Enterococcus* spp.; and 2,047 invasive streptococcal isolates. All presented isolates were from hospitalized patients (BSI, pneumonias, SSTI).

Results: R rates for ER markedly differed between geographic region. For *S. pneumoniae* the ER-R rates were: EU (40.3%) > APAC (29.4%) > NA (14.6%) > LA (only 7.7%). M-phenotypes were most prevalent in LA and NA (71.2-71.4%) > APAC (65.3) > EU (only 12.9). ER-R rates were always greater than the *S. aureus* oxacillin-R rate in each monitored region; rank order was: APAC (49.9%) > NA (44.2%) > LA (43.3%) > EU (34.9%). In contrast, CoNS ER-R rates were lowest in APAC (55.3%), overall range 55.3-70.7%. M-phenotypes in *S. aureus* and CoNS had identical rank order by region: NA (40.0-43.4%) > EU (33.0-39.7%) > APAC (28.9-30.9%) > LA (25.4-30.4%). ER and CL were not significantly active against enterococci (data not shown). Q/D-R in *S. aureus* varied from nil in the Americas to 0.8% in EU, and all regions reported Q/D-R CoNS (range 0.1-0.3%). Q/D spectrum against streptococci was complete (MIC_{90}, 0.25-1 µg/ml), but only 20.6-32.9% versus all enterococci tested. Conclusions: Long-term and varied use of some MLS_B drugs have established different geographic patterns of R. M-phenotypes are significantly more prevalent in NA, and ER-R was lowest in LA streptococci. Q/D resistance has slowly emerged, especially in EU staphylococci. Continued surveillance on a global scale appears to be justified for this antimicrobial group of drugs (MLS_B).

INTRODUCTION

The macrolide-lincosamide-streptogramin (MLS_B) group of antimicrobials are widely used in clinical practice especially as oral agents in the treatment of commonly-acquired respiratory and SST infections. These agents share several characteristics of spectrum versus key Gram-positive pathogens and risks of emerging resistance by common mechanisms. The rates of resistances mediated by methylases or efflux pumps can vary widely, influenced by geographic differences in MLS_B drug utilization.

The SENTRY Antimicrobial Surveillance Program has monitored MLS_B agents since 1997 in four regions of the world e.g. Asia-Pacific (APAC; 17 medical centers), Europe (EU; 32 medical centers), Latin America (LA; 15 medical centers), and North America (NA; 41 medical centers). The results of this prospective, surveillance program utilizing reference antimicrobial susceptibility test methods are summarized for 1997-2000.

MATERIALS AND METHODS

Isolates in this study were recent clinical strains obtained through the SENTRY Antimicrobial Surveillance Program (1997-2000) which were from blood stream, pneumonia, as well as skin and soft tissue infections only. A total of 30,336 Gram-positive isolates were evaluated which included *S.aureus* and coagulase-negative staphylococci (CoNS; 23,188 strains), *Enterococcus* spp. (5,103 strains), *S.pneumoniae* (1,057 strains), ß-haemolytic streptococcus (633 strains) and viridans-group streptococcus (355 strains).

These strains were tested against a panel of more than 20 antimicrobial agents. These included among others: linezolid, quinupristin/dalfopristin, vancomycin, teicoplanin, oxacillin or ampicillin or penicillin, erythromycin, clindamycin, mupirocin, ciprofloxacin, gatifloxacin, and high-level gentamicin and streptomycin.

All strains were tested by reference broth microdilution methods recommended by the NCCLS using dry form panels supplied by TREK Diagnostics (West Lake, OH). Organisms from pure culture plates were suspended into a Mueller-Hinton broth media to equal a 0.5 McFarland standard and further diluted and inoculated into the antibiotic containing wells to equal approximately $5x10^5$ CFU/ml. Panels were incubated in an ambient or CO2 environment for 24 hours, depending on the species. The panels were read for the lowest drug concentration which visually inhibited growth of the organism which determined the minimum inhibitory concentration (MIC) for each antimicrobial agent. Concomitant processing of ATCC quality control strains including *S.aureus* ATCC 29213, *E.faecalis* ATCC 29212 and *S.pneumoniae* ATCC 49619.

The M-phenotypes were defined as strains resistant by NCCLS criteria to erythromycin, but remaining highly susceptible to clindamycin.

Table 1. Antimicrobial potency and spectrum of MLS_B compounds compared to three other agents tested against 23,188 medical center isolates of staphylococci in the SENTRY Antimicrobial Surveillance Program (1997-2000).

	Results of testing by region:[a]							
	APAC		EU		LA		NA	
Organism/antimicrobial agent	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]
S. aureus (n)		(2416)		(3090)		(2248)		(9257)
Erythromycin	1/>8	49.9	0.5/>8	34.9	0.5/>8	43.3	1/>8	44.2
Clindamycin	0.25/>8	35.5	0.12/>8	23.4	0.25/>8	32.3	0.25/>8	26.5
Quinupristin/Dalfopristin	0.25/0.5	<0.1	0.25/0.5	0.8	0.25/0.5	0.0	0.25/0.5	0.0
Oxacillin	1/>8	44.8	0.5/>8	28.0	0.5/>8	35.1	0.5/>8	31.4
Vancomycin	1/1	<0.1[d]	1/1	0.0	1/1	0.0	1/1	0.0
Gatifloxacin	0.12/4	4.6	0.06/4	1.5	0.12/4	1.7	0.12/4	9.2
CoNS[e] (n)		(748)		(1729)		(902)		(2798)
Erythromycin	>8/>8	55.3	>8/>8	62.2	>8/>8	61.6	>8/>8	70.7
Clindamycin	0.12/>8	38.2	0.12/>8	37.5	0.25/>8	42.9	0.25/>8	40.0
Quinupristin/Dalfopristin	0.12/0.5	0.1	0.25/0.5	0.3	0.25/0.5	0.2	0.25/0.5	0.2
Oxacillin	8/>8	78.1	8/>8	74.0	8/>8	76.6	8/>8	74.0
Vancomycin	1/2	0.0	2/2	0.0	2/2	0.0	2/2	0.1
Gatifloxacin	0.12/2	1.9	0.12/2	1.8	0.12/2	0.8	0.25/4	4.0

a. APAC = Asia-Western Pacific; EU = Europe; LA = Latin America; NA = North America; CoNS = coagulase-negative staphylococci.
b. MIC in µg/ml.
c. Percentage resistant (R) using NCCLS [2002] interpretive criteria.
d. One heteroresistant variation of VISA (Hong Kong).

Table 2. Antimicrobial potency and spectrum of the streptogramin combination only compared to four other agents tested against 5,103 medical center isolates of enterococci in the SENTRY Antimicrobial Surveillance Program (1997-2000).

	Results of testing by region (no. tested):[a]							
	APAC (533)		EU (1125)		LA (375)		NA (3070)	
Organism/antimicrobial agent	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]
Quinupristin/Dalfopristin	8/>8	75.8	8/>8	67.1	8/>8	79.4	8/>8	72.0
Ampicillin	1/>16	16.7	1/>16	16.2	1/4	4.5	1/>16	20.8
Vancomycin	1/2	1.3	1/2	3.2	1/2	1.6	1/>16	12.4
Gentamicin[d]	≤500/>1000	32.3	≤500/>1000	30.2	≤500/>1000	20.1	≤500/>1000	30.8
Streptomycin[d]	≤1000/>2000	31.5	≤1000/>2000	44.5	≤1000/>2000	32.5	≤1000/>2000	39.3

a. APAC = Asia-Western Pacific; EU = Europe; LA = Latin America; NA = North America; CoNS = coagulase-negative staphylococci.
b. MIC in µg/ml.
c. Percentage resistant (R) using NCCLS [2002] interpretive criteria.
d. High-level screening for synergy only.

Table 3. Antimicrobial potency and spectrum of linezolid compared to seven other agents tested against 2,045 medical center isolates of streptococci in the SENTRY Antimicrobial Surveillance Program (1997-2000).

	Results of testing by region:[a]							
	APAC		EU		LA		NA	
Organism/antimicrobial agent	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]	$MIC_{50/90}$[b]	% R[c]
S. pneumoniae (n)		(245)		(77)		(181)		(554)
Erythromycin	≤0.06/>8	29.4	≤0.06/>8	40.3	≤0.06/≤0.06	7.7	≤0.06/2	14.6
Clindamycin	≤0.06/>8	10.2	≤0.06/>8	35.1	≤0.06/≤0.06	2.2	≤0.06/≤0.06	4.2
Quinupristin/Dalfopristin	0.5/1	0.0	0.25/0.5	0.0	0.5/0.5	0.0	0.25/0.5	0.0
Penicillin	0.03/2	15.1	0.25/2	32.5	≤0.015/2	13.8	≤0.015/1	9.6
Vancomycin	0.5/0.5	0.4[d]	0.25/0.5	0.0	0.5/0.5	0.0	0.25/0.5	0.0
Gatifloxacin	0.25/0.5	1.6	0.25/0.5	0.0	0.25/0.5	0.6	0.25/0.5	0.5
viridans gr. streptococci (n)		(98)		(53)		(42)		(162)
Erythromycin	≤0.06/>8	27.6	≤0.06/>8	41.5	≤0.06/2	32.6	≤0.06/4	36.4
Clindamycin	≤0.06/>2	12.2	≤0.06/>8	12.5	≤0.06/2	14.0	≤0.06/0.12	7.4
Quinupristin/Dalfopristin	1/1	0.0	0.5/1	0.0	0.5/1	0.0	0.5/1	0.0
Penicillin	0.06/1	6.1	0.06/1	5.7	0.06/0.5	2.3	0.06/1	1.2
Vancomycin	1/1	0.0	0.5/1	0.0	0.5/1	0.0	0.5/1	0.0
Gatifloxacin	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.5	2.3	0.25/0.5	3.7
ß-haemolytic streptococci (n)		(185)		(31)		(92)		(325)
Erythromycin	≤0.06/2	10.8	≤0.06/0.25	9.7	≤0.06/≤0.06	2.2	≤0.06/4	23.1
Clindamycin	≤0.06/0.12	3.8	≤0.06/≤0.06	0.0	≤0.06/≤0.06	0.0	≤0.06/0.12	8.0
Quinupristin/Dalfopristin	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.5	0.0
Penicillin	≤0.015/0.06	0.0	0.03/0.06	0.0	≤0.015/0.06	0.0	0.03/0.06	0.0
Vancomycin	0.5/0.5	0.0	0.5/0.5	0.0	0.5/0.5	0.0	0.5/0.5	0.0
Gatifloxacin	0.25/0.25	0.0	0.25/0.5	0.0	0.25/0.5	0.0	0.25/0.25	0.3

a. APAC = Asia-Western Pacific; EU = Europe; LA = Latin America; NA = North America; CoNS = coagulase-negative staphylococci.
b. MIC in µg/ml.
c. Percentage resistant (R) using NCCLS [2002] interpretive criteria.
d. One strain reproducibly having an MIC at 2 µg/ml (1.5 µg/ml by Etest).

RESULTS

- Erythromycin resistance paralleled the oxacillin resistance rates in each region among *S. aureus*, but was always higher (5 - 13%). The oxacillin resistance rates ranked: APAC (44.8%) > LA (35.1%) > NA (31.4%) > EU (28.0%).
- M-phenotypes in staphylococci were more common in NA (40.0 - 43.4%) than in other regions.
- Macrolides and clindamycin were not effective against enterococci and quinupristin/dalfopristin only inhibited 20.6% (Latin America) to 32.9% (Europe) of invasive isolates.
- Erythromycin resistance among *S. pneumoniae* varied widely between the regions: greatest in Europe (40.3%; 12.9% M-phenotypes) to a low rate of only 7.7% in Latin America (71.4% M-phenotypes). The rates of M-phenotypes was very similar within all regions (65.3 - 71.4%) except Europe.
- Viridans streptococci were generally more erythromycin-resistant (27.6 - 41.5%) in all regions compared to ß-haemolytic strains (2.2 - 23.1%). M-phenotypes were the dominant pattern in viridans group species (55.8 - 79.7%), greatest in NA. M-phenotypes in ß-haemolytic streptococci were also most common, with no *erm*-like isolates in the invasive isolates in EU and LA. NA erythromycin resistance (23.1%) among ß-haemolytic species was significantly greater than other regions (2.2 - 10.8%).
- Resistances to quinupristin/dalfopristin have emerged in all geographic regions among staphylococci (0.1 - 0.8%), enterococci including *E. faecium* (data not shown), but not in streptococci.

Table 4. Occurrences of *erm* and M-phenotypes among streptococci tested in the SENTRY Program (1997-2000), indexed by geographic regions.

Organism/region (no. tested)	% M-phenotype[a]	Total macrolide resistance (%)
S. pneumoniae		
Asia-Pacific (245)	65.3	29.4
Europe (77)	12.9	40.3
Latin America (181)	71.4	7.7
North America (554)	71.2	14.6
Viridans group		
Asia-Pacific (98)	55.8	27.6
Europe (53)	69.9	41.5
Latin America (42)	57.1	32.6
North America (162)	79.7	36.4
ß-haemolytic		
Asia-Pacific (185)	64.8	10.8
Europe (31)	100.0	9.7
Latin America (92)	100.0	2.2
North America (325)	65.4	23.1

a. % of all erythromycin-resistant strains from BSI, pneumonia and SSTI.

CONCLUSIONS

- Marked variations in the resistance patterns of MLS_B compounds were noted:
  - Erythromycin resistance in staphylococci highest for APAC; in *S. pneumoniae* for EU; in viridans group streptococci for EU; and in ß-haemolytic streptococci for NA.
  - M-phenotypes were least often noted in EU pneumococci.
- Clindamycin was more active than erythromycin in all regions, but significantly less active than the streptogramin combination.
- The emerging greater resistances to agents in the MLS_B group requires continued surveillance by well structured networks such as the SENTRY Program.

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