Trends in Mupirocin Resistance in Europe and USA Among 13,087 Staphylococcal and *S. pyogenes* Isolates (2000 - 2002)

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AMENDED ABSTRACT

Background: Resistance (R) to the topical agent mupirocin (MUP) has been described as increasing in various geographic areas where clinical use is high. Two levels of R (low, MIC > 8 - 256; high, MIC > 256 μg/ml) occur, but routine susceptibility (S) testing has rarely been applied.

Methods: The SENTRY Antimicrobial Surveillance Program monitored for MUP-R from 2000 - 2002 (> 60 medical centers) in Europe (EU) and North America (NA). All S testing was by reference NCCLS methods and results for *S. aureus* (SA; 9,808), coag.-neg. staphylococci (CoNS; 3,006) and *S. pyogenes* (SPYO; 273) were analyzed by region, year and community-acquired (CA) versus nosocomial (NOS) origin. R strains were screened for high-level patterns by Etest (AB BIODISK) strips.

Results: MUP activity against nosocomial isolates (6,484 strains).

		No. tested (% R)		
Region	Year	SPYO	CoNS	SA
EU	2000	10 (0.0)	275 (17.1)	534 (5.2)
	2001	9 (0.0)	482 (22.2)	716 (5.4)
	2002	12 (0.0)	388 (27.3)	865 (6.7)
	Subtotal	31 (0.0)	1,145 (22.7)	2,115 (5.9)
USA	2000	4 (0.0)	246 (39.4)	749 (10.4)
	2001	3 (0.0)	208 (40.4)	719 (8.6)
	2002	2 (0.0)	311 (41.8)	951 (7.7)
	Subtotal	9 (0.0)	765 (40.7)	2,419 (8.8)
Total	-	40 (0.0)	1,910 (29.9)	4,534 (7.5)

MUP-R rates among CA isolates (6,303 strains) were: for EU (CoNS, 16.3%; SA, 2.6%) and for USA (CoNS, 31.2%; SA, 4.7%). MUP-R in SA and CoNS increased in the EU, variable in USA. All SPYO strains were MUP-S. High-level MUP-R was noted in approximately half of all R isolates.

Conclusions: Significant MUP-R was detected in EU and USA in CoNS (16.3 - 40.7%) and SA (2.6 - 8.8%) varying by geography (USA > EU), infection origin (NOS > CA) and year (increasing in EU). A continued stepwise increase in R of staphylococci, especially SA, to MUP may eventually limit its effectiveness as a topical agent. Continued surveillance (SENTRY Program) of topically applied agents should guide selection of those most active.

INTRODUCTION

Mupirocin (pseudomonic acid) is one of a family of aminoacyl-tRNA synthetase inhibitors that interferes with protein synthesis by inhibiting the activity of bacterial isoleucyl-tRNA synthetase (IRS). Two-percent mupirocin ointment was first marketed in Europe in 1985 and in the USA in 1988 for use as a topical agent for eradication of *S. aureus* carriage from nasal passages and prevention of catheter or dialysis exit-site infections. This compound has also been used to treat post-operative and other skin infections, and infections of burn wounds.

Two types of mupirocin resistance have been recognized in different parts of the world, including low-level (MIC, 16-256 μg/ml) resistance produced through spontaneous mutational events in the chromosomally-encoded *ileS-2* (mupA) gene, and high-level (MIC, ≥ 512 μg/ml) resistance primarily mediated by a transferable plasmid containing the *ileS-2* gene encoding an additional IRS enzyme. Increasingly, mupirocin resistance has been documented following both prophylactic and therapeutic use, and concern exists that staphylococcal resistance may seriously limit the usefulness of this valuable compound for hospital and community infection control.

While routine susceptibility testing of topical agents has rarely been applied, the emergence of resistance to mupirocin dictates the need for ongoing surveillance programs to track continued efficacy and, where indicated, identify therapeutic alternatives.

The present study examines the activity of mupirocin against a large collection of contemporary isolates of staphylococci and *S. pyogenes* originating from medical centers in Europe and the USA, and provides a global assessment of emerging resistance patterns to this topical agent. Stratification by region, year, and origin of infection (community or nosocomial) was performed to identify trends in emerging resistance and potential risk factors.

MATERIALS & METHODS

Specimen Collection. A total of 13,087 strains of Gram-positive cocci originating from 60 medical centers in Europe and the USA (2000-2002) were included in the SENTRY Program study and were recovered consecutively from patients hospitalized with bacteremia, pneumonia, skin and soft tissue infections, and urinary tract infections. Isolates were identified by the submitting laboratory and confirmed by the monitoring facility (The JONES Group/JMI Laboratories, North Liberty, IA). The collection consisted of *S. aureus* (9,808 strains), coagulase-negative staphylococci (CoNS; 3,006 strains), and *S. pyogenes* (273 strains).

Susceptibility Testing. All strains were tested for susceptibility to mupirocin according to the NCCLS (2003) reference broth microdilution method using Mueller-Hinton broth (with the addition of 2-5% lysed horse blood for testing of streptococci). Interpretation of quantitative MIC results was in accordance with the manufacturer's and other (Deshpande et al, Diag. Microbiol. Inf. Dis. 2002;42:283-290) recommendations (resistant at ≥ 16 μg/ml). Quality control strains utilized included *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619.

RESULTS

- Mupirocin resistance in *S. aureus* over the three-year period studied was greater in the USA (4.2 to 10.4%) than in Europe (1.9 to 6.7%), and occurred more frequently in nosocomial infections (Europe, 5.2 to 6.7%; USA, 7.7 to 10.4) than in community-acquired infections (Europe, 1.9 to 3.2%; USA, 4.2 to 5.0%).
- While resistance rates remained stable among *S. aureus* in the USA over this time period, an increasing trend in resistance (nosocomial, 5.2 to 6.7%; community-acquired, 1.9 to 3.2%) was documented among European isolates.
- Coagulase-negative staphylococci originating from the USA displayed greater levels of resistance (27.5 to 41.8%) than did European isolates (12.9 to 27.3%), again with those of nosocomial origin (USA, 39.4 to 41.8%; Europe, 17.1 to 27.3%) being more resistant than community-acquired isolates (USA, 27.5 to 39.1%; Europe, 12.9 to 20.0%).
- A trend of increasing resistance was only detected among coagulase-negative staphylococci of nosocomial origin.
- Resistance to mupirocin was not detected among *S. pyogenes* isolates, confirming results from numerous prior studies.

RESULTS

Table 1. Activity of mupirocin against isolates of Gram-positive cocci originating from community-acquired infections (2000 - 2002).

		No. tested (% resistant)[a]		
Region	Year	*S. pyogenes*	CoNS	*S. aureus*
Europe	2000	17(0.0)	155(12.9)	369(1.9)
	2001	29(0.0)	155(20.0)	530(2.3)
	2002	36(0.0)	126(15.9)	594(3.2)
	Subtotal	82(0.0)	436(16.3)	1,493(2.6)
USA	2000	37(0.0)	224(29.9)	1,369(5.0)
	2001	41(0.0)	181(39.1)	966(5.0)
	2002	73(0.0)	255(27.5)	1,446(4.2)
	Subtotal	151(0.0)	660(31.2)	3,781(4.7)
	Total	233(0.0)	1,096(25.3)	5,274(4.1)

a. Breakpoint of ≥ 16 μg/ml (resistant) as recommended by the manufacturer and Deshpande et al. 2002.

Table 2. Activity of mupirocin against isolates of Gram-positive cocci originating from nosocomial infections (2000 - 2002).

		No. tested (% resistant)[a]		
Region	Year	*S. pyogenes*	CoNS	*S. aureus*
Europe	2000	10(0.0)	275(17.1)	534(5.2)
	2001	9(0.0)	482(22.2)	716(5.4)
	2002	12(0.0)	388(27.3)	865(6.7)
	Subtotal	31(0.0)	1,145(22.7)	2,115(5.9)
USA	2000	4(0.0)	246(39.4)	749(10.4)
	2001	3(0.0)	208(40.4)	719(8.6)
	2002	2(0.0)	311(41.8)	951(7.7)
	Subtotal	9(0.0)	765(40.7)	2,419(8.8)
	Total	40(0.0)	1,910(29.9)	4,534(7.5)

a. Breakpoint of ≥ 16 μg/ml (resistant) as recommended by the manufacturer and Deshpande et al. 2002.

CONCLUSIONS

- Significant mupirocin resistance was detected between the years 2000 to 2002 in Europe and the USA for *S. aureus* (2.6-8.8%) and coagulase-negative staphylococci (16.3%-40.7%) varying by geography (USA greater than Europe), infection origin (nosocomial greater than community-acquired infections) and year (increasing through 2002 in Europe).
- A continued stepwise increase in mupirocin resistance of staphylococci, especially *S. aureus*, may eventually limit its effectiveness as a topical agent.
- Local hospital evaluation of *S. aureus* populations for mupirocin susceptibility may now be necessary prior to the incorporation of the compound into or retention within infection control programs.
- Global surveillance for emerging resistance to mupirocin and other topical antimicrobial agents through programs such as the SENTRY Antimicrobial Resistance Surveillance Program appears warranted and should enhance guided selection of those most active topical agents for the particular geographic region.

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