Surveillance for Mupirocin Resistance Among Methicillin-Resistant *Staphylococcus aureus* Clinical Isolates

To the Editor—Mupirocin is an antimicrobial agent that has a unique mechanism for inhibiting the synthesis of proteins: it selectively binds to bacterial isoleucyl-tRNA synthetase.[1] It has been widely used in an effort to decolonize methicillin-resistant *Staphylococcus aureus* (MRSA) carriers, as a means of controlling the spread of this pathogen. The prevalence of mupirocin resistance among MRSA isolates varies considerably. A significant increase in mupirocin resistance following the widespread use of mupirocin has been reported,[2] and some centers have observed high rates of mupirocin resistance despite low rates of mupirocin use.[3]

In 2007, OSF St. Francis Medical Center, a tertiary care hospital in central Illinois, implemented a comprehensive infection control program that included identifying MRSA colonization among high-risk patients and using topical mupirocin ointment to eradicate MRSA carriage. This program was used in conjunction with other practices, which included patient isolation and cohorting, education, and hand hygiene, to control the spread of multidrug-resistant pathogens. Surveillance for mupirocin resistance was begun in anticipation of the possibility that the emergence of mupirocin-resistant isolates could limit the therapeutic options available for the control and prevention of MRSA infections.

From July through October 2007, a total of 156 nonduplicate MRSA clinical isolates were consecutively collected from the OSF System Laboratory at St. Francis Medical Center. The isolates were screened for mupirocin resistance using a 5-μg and a 20-μg mupirocin disk. The minimum inhibitory concentration (MIC) of mupirocin was measured using Etest strips (AB Biodisk). Isolates were classified as being susceptible (ie, having an MIC of 4 μg/mL or less), having low-level resistance (an MIC of 8–256 μg/mL), or having high-level resistance (an MIC of 512 μg/mL or greater). Multiplex polymerase chain reaction amplification was performed for the simultaneous detection of genes to identify *S. aureus* (*nuc* gene), methicillin resistance (*mecA* gene), and high-level mupirocin resistance (*mupA* gene), as described elsewhere.[4]

Mupirocin resistance was detected in 37 (23.7%) of the 156 MRSA clinical isolates. Of these, 29 isolates (18.6%) exhibited low-level resistance, and 8 isolates (5.1%) exhibited high-level resistance. Mupirocin-resistant isolates were recovered from various clinical specimens, including blood (7), sputum (3), urine (3), skin and soft tissues (18), and specimens from other body sites (6). There were no significant differences between mupirocin-susceptible and mupirocin-resistant isolates with regard to specific sites of isolation. Reduced susceptibility to non–β-lactam antimicrobial agents (erythromycin, clindamycin, levofloxacin, and gatifloxacin) was common among mupirocin-resistant isolates; however, there were no significant differences, compared with mupirocin-susceptible isolates, except with regard to susceptibility to clindamycin (detected in 70.3% of mupirocin-resistant isolates vs 48.7% of mupirocin-susceptible isolates; $P = .02$). Most of the MRSA isolates (more than 95%) were susceptible to gentamicin, trimethoprim-sulfamethoxazole, and tetracycline, regardless of mupirocin susceptibility. A multiplex polymerase chain reaction was performed for 32 MRSA isolates exhibiting mupirocin resistance. The *mupA* gene was detected in all 8 isolates with high-level mupirocin resistance but was not detected in isolates with low-level mupirocin resistance.

Because there are no Clinical and Laboratory Standard Institute guidelines for interpretive criteria for mupirocin, several investigators have proposed interpretive criteria using disks with various concentrations of mupirocin (Table 1). Using a 5-μg mupirocin disk, Finlay et al.[5] found that isolates with a zone-of-inhibition diameter of 14 mm or more were mupirocin susceptible. We found 6 MRSA isolates that were more accurately classified by the Etest as having low-level resistance (16–24 μg/mL). The reliability of using a 5-μg mupirocin disk to detect mupirocin-resistant isolates improved when a larger zone-of-inhibition diameter was applied. Using the breakpoint of 19 mm or more advocated by Creagh and Lucey,[6] we did not observe any very major errors (ie, false-susceptible test results). A 20-μg mupirocin disk was evaluated as a tool to discriminate between low-level and high-level mupirocin resistance. As suggested by the British Society for Antimicrobial Chemotherapy,[7] the breakpoints should be 6 mm or less for high-level resistance and 7–26 mm for low-level resistance. Using these breakpoints, we observed no very major errors. However, we did observe major errors (ie, false-resistant test results) in several isolates that were classified as having low-level mupirocin resistance, on the basis of the

TABLE 1. Disk Diffusion Testing Interpretive Criteria for Mupirocin (Mpc) Susceptibility Proposed by Various Investigators

Study, concentration of Mpc in disk	Zone-of-inhibition diameter, mm, by susceptibility level		
	Susceptible	Low resistance	High resistance
Finlay et al. [5]			
5 μg	$\geqslant$14	$\leqslant$13	$\leqslant$13
Creagh and Lucey [6]			
5 μg	$\geqslant$19	$\leqslant$18	$\leqslant$18
Andrews et al. [7]			
5 μg	$\geqslant$22	$\leqslant$21	$\leqslant$21
20 μg	$\geqslant$27	7–26	$\leqslant$6
Palepou et al. [8]			
25 μg	>26		<10
de Oliveira et al. [9]			
5 μg	$\geqslant$14	$\leqslant$13	$\leqslant$13
200 μg	$\geqslant$14	$\geqslant$14	<14

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zone-of-inhibition diameter, but were also classified as being mupirocin susceptible, on the basis of MICs using the Etest.

Our study demonstrated that there was a high prevalence of mupirocin resistance among MRSA clinical isolates, compared with other surveillance studies that found a geographic variation in the prevalence of mupirocin resistance among MRSA isolates that ranged from 4% to 17%.[10] Although the prevalence of mupirocin resistance prior to this finding was not known, it is plausible that the higher rate could be the consequence of frequent exposure to mupirocin.

The determination of MICs by the Etest is simple, reproducible, and shows a good correlation with agar dilution testing but is relatively expensive. Disk diffusion testing is cheap and easy to perform, but defining breakpoints for mupirocin susceptibility remains problematic. The finding of inconsistent results, which were mainly the result of the different methods used, makes it difficult to judge which interpretive criteria should be applied. We observed the limited usefulness of the disk diffusion method, finding that the susceptibility of the pathogens could not be predicted accurately. Nevertheless, diffusion testing using the 5-μg mupirocin disk has potential as a screening method for prediction of mupirocin resistance. The breakpoint, however, should be 18 mm or less, to increase sensitivity, as proposed by Creagh and Lucey.[6] If the diameter of the inhibition zone is 18 mm or less, an Etest can then be performed to distinguish between high-level and low-level mupirocin resistance.

Although this study was limited by the relatively small number of clinical isolates, the finding of a high rate of mupirocin resistance supports the need to establish effective infection control measures. Further work is required to determine the impact of widely used topical mupirocin and the burden of mupirocin-resistant isolates.

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