Mupirocin Resistance

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With increasing pressure to prevent methicillin-resistant Staphylococcus aureus (MRSA) infection, it is possible that there will be increased use of mupirocin for nasal decolonization of MRSA. Understanding the mechanisms, clinical significance, and epidemiology of mupirocin resistance is important for predicting how changes in mupirocin use may affect bacterial populations and MRSA control. High-level mupirocin resistance in S. aureus is mediated by a plasmid-encoded mupA gene. This gene can be found on conjugative plasmids that carry multiple resistance determinants for other classes of antimicrobial agents. High-level resistance has been associated with decolonization failure, and increased resistance rates have been associated with increased mupirocin use. Low-level mupirocin resistance is mediated via mutation in the native ileS gene, and the clinical significance of this resistance is unclear. Laboratory tests to detect and distinguish between these types of resistance have been described but are not widely available in the United States. Institutions that are considering the implementation of widespread mupirocin use should consider these resistance issues and develop strategies to monitor the impact of mupirocin use.

Mupirocin (pseudomonic acid A) has been widely available for use as a topical antimicrobial agent for many years. It is approved in ointment formulation in the United States for the topical treatment of impetigo and secondary wound infection caused by Staphylococcus aureus and Streptococcus pyogenes. In addition, a nasal formulation is approved by the United States Food and Drug Administration (FDA) for use in eradicating nasal carriage of S. aureus in adult patients and health care personnel, as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of methicillin-resistant S. aureus (MRSA). Eradicating or suppressing S. aureus colonization has remained an attractive strategy for preventing infection and transmission, on the basis of the rationale that S. aureus carriage is a major risk factor for subsequent infection and that most staphylococcal infection is caused by endogenous strains [1]. Although clinical use of mupirocin in the treatment of skin infection has become well established, its use for infection control and other preventive applications in the United States has been limited historically, not only because of insufficient data establishing its efficacy as part of a general S. aureus infection prevention strategy but also because of concern about the emergence of resistance that might be fueled by widespread use. This review focuses on the emergence of mupirocin resistance, its mechanisms, its clinical significance, its relationship to clinical use, and the factors that might lead to increased use and resistance.

MECHANISMS AND EPIDEMIOLOGY OF MUPIROCIN RESISTANCE

Three categories of mupirocin susceptibility have been described for S. aureus (table 1). These categories are mupirocin susceptibility with minimum inhibitory concentrations (MICs) \( \leq 4 \ \mu g/mL \), low-level mupirocin resistance with MICs from 8 to 64 \( \mu g/mL \), and high-level mupirocin resistance with MICs \( \geq 512 \ \mu g/mL \) [2]. Isolates with MICs of 128 or 256 \( \mu g/mL \) are uncommon. Most isolates that demonstrate high-level mupirocin resistance have acquired plasmid-mediated mupA, which encodes a novel isoleucyl RNA synthetase [3, 4]. Isolates with low-level mupirocin resistance usually have acquired base changes in the native isoleucyl RNA synthetase gene, ileS [5].

Studies of mupirocin resistance in S. aureus populations indicate that nearly all S. aureus isolates with high-level mupirocin resistance are mupa positive by polymerase chain reaction (PCR) assay [3, 6, 7]. However, there are some notable excep-
tions to this finding (table 2). Isolates with low-level mupirocin resistance but positive for the mupA gene have been identified. In these isolates, the mupA gene was located on the chromosome rather than on a plasmid [8]. Also, isolates that are mupA positive by PCR but mupirocin susceptible have also been reported. This has been attributed to a frameshift mutation in the mupA gene that inactivates the gene product [9]. Isolates with this frameshift mutation revert to wild-type sequence and have high-level mupirocin resistance at a high frequency (≥10^6). Finally, a few isolates have been identified that demonstrate high-level mupirocin resistance but are mupA negative by PCR despite the use of multiple primer sets (Andrew Simor, personal communication). These isolates may carry a novel mechanism of mupirocin resistance.

The mupA gene is typically located on mobile genetic elements, which likely facilitates the dissemination of this resistance mechanism. The mupA gene is typically plasmid mediated, and some of these plasmids are conjugative [10, 11]. Insertion sequences have been identified flanking the mupA gene in plasmids, which might facilitate movement of the mupA gene between plasmids by recombination [11, 12]. A study of clinical mupirocin-resistant Staphylococcus isolates from one hospital demonstrated the presence of mupA on plasmids of different sizes and restriction patterns and the occurrence of identical mupA plasmids in different strains of S. aureus that represented multiple pandemic lineages [13]. In addition, the same mupA conjugative plasmid was identified in strains of S. aureus and Staphylococcus epidermidis from the same institution [14]. These findings suggest both the movement of mupA-mediated mupirocin resistance between plasmids and the transmission of mupA plasmids between bacterial isolates. High-level mupirocin resistance has been identified on conjugative plasmids in the US epidemic MRSA strain USA 300 [15, 16]. These plasmids typically carry resistance determinants to other antimicrobial agents, including macrolides, gentamicin, tetracycline, and trimethoprim [17]. These findings suggest that mupirocin use could select for increased drug resistance in S. aureus.

### LABORATORY DETECTION OF RESISTANCE

Currently, there are no FDA interpretive breakpoints for mupirocin susceptibility testing. This has limited the development of commercial mupirocin susceptibility testing products for use in the United States. In the literature, several laboratory methods to detect mupirocin resistance have been described, including 2 reference MIC methods: broth microdilution and agar dilution. One commercial method has also been developed, Etest (bioMérieux) [18–20]. In a study of 177 staphylococci isolates (167 S. aureus and 10 coagulase-negative staphylococci), good correlation between Etest MICs and agar dilution MICs was reported, with 97% of the MIC values within one doubling dilution difference [18]. Disk diffusion methods have also been developed. A 200-µg mupirocin disk test can be used to distinguish isolates with high-level resistance from isolates that are either susceptible or have low-level resistance [21]. For isolates with high-level resistance, no zone is visible around the disk after overnight incubation, whereas isolates that are low-level resistant or susceptible have a zone of >14 mm. A second disk with 5 µg of mupirocin can be used to distinguish isolates that are susceptible to mupirocin from isolates with either low-level or high-level resistance [21, 22]. With the 5-µg disk, isolates with low-level or high-level resistance will show no zone around the disk, whereas the zone for susceptible isolates is >14 mm. To distinguish between all 3 phenotypic categories, both the 200-µg and the 5-µg disk tests need to be performed (figure 1) [21]. A similar 2-disk strategy for mupirocin susceptibility testing was described in the British Society for Antimicrobial Chemotherapy standardized disk susceptibility testing method. In this procedure, a 5-µg and a 20-µg disk are tested, and the 20-µg disk is used to distinguish low-level resistant isolates from high-level resistant and susceptible isolates [23]. In addition to phenotypic susceptibility testing methods, PCR assays have been described for detection of mupA-mediated high-level mupirocin resistance. In 2 reports, PCR tests demonstrated 100% sensitivity and specificity, compared with Etest MIC ≥512 µg/mL [24].

Guidelines for mupirocin susceptibility testing by agencies that establish standard laboratory methods are limited. As mentioned above, the British Society for Antimicrobial Chemotherapy recommends susceptibility testing of staphylococci by means of a test with both a 5-µg and a 20-µg disk or an MIC method. The Clinical and Laboratory Standards Institute recently recommended a 200-µg disk test to detect high-level mupirocin resistance in S. aureus [25]. Much of the suscepti-

### Table 1. Most Common Phenotypes and Associated Mechanisms for Mupirocin Susceptibility for Staphylococcus aureus

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MIC range</th>
<th>Molecular mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>≤4 µg/mL</td>
<td>Wild type</td>
</tr>
<tr>
<td>Low-level resistance</td>
<td>8–64 µg/mL</td>
<td>Mutations in native tRNA synthetase</td>
</tr>
<tr>
<td>High-level resistance</td>
<td>≥512 µg/mL</td>
<td>Plasmid-mediated mupA (novel tRNA synthetase)</td>
</tr>
</tbody>
</table>

**NOTE.** MIC, minimum inhibitory concentration; tRNA, transfer RNA.
bility testing effort has focused on surveillance studies for emerging resistance when mupirocin use has increased. Clinical laboratories that wish to perform susceptibility testing but do not have access to commercial testing materials can choose to validate in-house prepared assays, such as PCR or disk diffusion assays with in-house prepared disks.

**CLINICAL SIGNIFICANCE OF MUPIROCIN RESISTANCE**

There are several studies in which high-level mupirocin resistance in *S. aureus* is associated with mupirocin decolonization failure. The association between low-level mupirocin resistance and the outcome of mupirocin decolonization is not clear. In a randomized controlled trial of decolonization with chlorhexidine gluconate washings, mupirocin, rifampin, and doxycycline, colonization with a strain of *S. aureus* with high-level mupirocin resistance was independently associated with decolonization failure [26]. There were not enough patients colonized with strains of *S. aureus* with low-level mupirocin resistance to assess the effects of this association. In another study, a prospective evaluation of mupirocin decolonization, the decolonization rate at 3 days after treatment for patients colonized with high-level resistant strains was low (27.7%), compared with decolonization rates for patients colonized with mupirocin-susceptible strains (78.5%) or with low-level resistant strains (80%) [27]. However, at the 1–4 week follow-up, the sustained negativity for the patients colonized with high-level and low-level resistant isolates was low (25% each), compared with the sustained negativity for the patients colonized with susceptible isolates (91%). Isolates from patients with follow-up cultures positive for *S. aureus* carried strains of the same genotype and susceptibility phenotype as the isolate from the patient’s baseline culture. As in the previous study, these results suggest that high-level mupirocin resistance results in decolonization failure. The results for treatment of low-level mupirocin-resistant isolates suggest that mupirocin might temporarily suppress growth of these isolates but does not result in sustained negativity. Finally, in a double-blind, placebo-controlled trial of mupirocin decolonization, low-level mupirocin resistance increased the risk of persistent MRSA carriage after decolonization but was not independently associated with persistent carriage [28]. Additional studies would be helpful to understand the clinical significance of both high-level and low-level mupirocin resistance.

**RELATIONSHIP BETWEEN CLINICAL USE AND RESISTANCE**

**Treatment and prevention of community-associated infection.** Mupirocin is approved for use in the treatment of superficial skin and soft-tissue infection, and there is some evidence to suggest that widespread use in the community for this purpose can lead to an increase in resistance (table 3). Upton et al [29] describe the experience in New Zealand, where mupirocin became available over the counter in 1991. By 1999, a mean of 28% of *S. aureus* isolates were resistant to mupirocin, with higher rates among community-acquired isolates, compared with rates among hospital-acquired isolates. The authors attributed the emergence of resistance to the widespread community use of mupirocin after it was made available without a prescription. In 1993, mupirocin was used frequently in Western Australia to treat infected skin lesions. As a result, rates of high-level mupirocin resistance among clinical MRSA isolates reached 15%. In response, the Australian health department issued guidance on limiting mupirocin use in the community. Within 4 years, the resistance rate had decreased to 0.3% [45].

Eradication of *S. aureus* carriage with nasal mupirocin has been used in selected communities as part of a strategy to prevent infection, with several reports of success. Mupirocin was most often used in conjunction with other interventions. Therefore, the particular role and contribution of mupirocin use in the termination of community outbreaks is difficult to assess [46–48]. Information with regard to the emergence of mupirocin resistance following its use in control of community outbreaks is scant. A recent study examined the efficacy of a mupirocin-based eradication regimen for preventing community-associated MRSA infection among military trainees, a population in which *S. aureus* skin and soft-tissue infection is highly endemic [30]. Soldiers colonized with MRSA were treated with a single 5-day course of nasal mupirocin and then followed up for 16 weeks to assess infection and colonization rates. No mupirocin resistance was detected in the 199 MRSA isolates tested [30]. A more common use of nasal mupirocin in community settings is eradication of colonization to prevent recurrent infection in individual patients with furunculosis [49].

Table 2. Uncommon Genotypes and Phenotypes of Mupirocin Resistance in *Staphylococcus aureus* Populations

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Explanation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mupA+</td>
<td>Low-level resistance</td>
<td>mupA located on the chromosome</td>
<td>[8]</td>
</tr>
<tr>
<td>mupA+</td>
<td>Susceptibility</td>
<td>Frameshift mutation in mupA</td>
<td>[9]</td>
</tr>
<tr>
<td>mupA−</td>
<td>High-level resistance</td>
<td>Unknown mechanism of resistance</td>
<td>Simor, personal communication</td>
</tr>
</tbody>
</table>

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S. aureus

Mupirocin is often used to eradicate colonization in both patients and health care personnel in response to outbreaks of staphylococcal infection in the health care setting [50–52]. Several reports describe successful control of outbreaks following this approach, but decolonization is often a single component of a multifaceted intervention, and the contribution of the eradication of S. aureus carriage has been difficult to establish with certainty. Reports of mupirocin resistance following use in this way are rare (table 3) [31]. It is possible that use of mupirocin as part of a decolonizing regimen in the inpatient setting for limited periods of time, such as in response to an outbreak, could be less likely to lead to the emergence of resistance [53].

In contrast, when mupirocin-based decolonization regimens have been used as a routine and sustained strategy to control endemic S. aureus infection and transmission among general inpatient populations, the emergence of mupirocin resistance has been common, although not universally, observed [13, 35–33]. In particular, resistance seems to emerge readily in health care facilities with unrestricted policies that allow widespread mupirocin use for prolonged periods, especially when application to decubitus ulcers and other skin lesions is allowed [33, 34]. Restricting application to the nares of uninfected patients may limit the emergence of resistance to some degree [1, 26, 54]. Vivoni et al [55] found mupirocin resistance among 65% of isolates recovered from patients with MRSA infection in a hospital 5 years after the initiation of a policy in which patients were actively screened for MRSA carriage and carriers were systematically treated with a regimen that included application of mupirocin to the anterior nares and any skin wounds covering <20% of body surface area. The use of mupirocin was subsequently restricted to only those patients who had no signs of clinical staphylococcal infection and no skin lesions. Five years after this change, despite continuation of the active surveillance and decolonization program, mupirocin resistance had decreased to 15%. Several other studies suggest that mupirocin resistance rates can decline or remain low in the presence of restrictive-use policies, even when mupirocin use for eradicating colonization remains routine [35–37]. During an ongoing program in 3 US hospitals that implemented universal surveillance and mupirocin-based decolonization of all inpatient MRSA carriers, mupirocin resistance remained relatively low but increased substantially, from 4.1% to 7.2% among all MRSA isolates during the 3 years of the program [38].

Colonization with mupirocin-resistant MRSA has also been reported in hospitalized patients in the absence of widespread mupirocin use. In a study of surgical intensive care unit patients, those colonized with mupirocin-resistant MRSA were more likely to have been hospitalized in the same institution within the previous 12 months than those patients colonized with mupirocin-susceptible MRSA [56]. None of the colonized patients had received mupirocin treatment as an inpatient in the previous year.

The use of mupirocin to eradicate or suppress S. aureus carriage among dialysis patients as a strategy for preventing infection has been the subject of numerous studies. Evidence from these trials suggests that decolonization regimens may reduce infection rates, but repeated applications appear necessary, and more study is needed to further elucidate optimal regimens [57]. The risk of mupirocin resistance with prophylactic use in dialysis patients may differ between hemodialysis and peritoneal dialysis patients. In a 2-year study of hemodialysis patients who received regular intranasal mupirocin, Boelaert et al [39] identified a single high-level mupirocin-resistant isolate during 168 patient-years of follow-up. In contrast, the use of mupirocin to prevent infection among peritoneal dialysis patients, particularly when mupirocin is repeatedly applied to

Figure 1. A 2-disk strategy for differentiating between isolates with the 3 different mupirocin susceptibility phenotypes by means of a disk diffusion susceptibility method. A. A mupirocin-susceptible Staphylococcus aureus isolate (minimum inhibitory concentration [MIC], ≤2 μg/mL), 200-μg disk zone size = 32 mm and 50-μg disk zone size = 24 mm. B. S. aureus with low-level mupirocin resistance (MIC, 32 μg/mL), 200-μg disk zone size = 23 mm and 50-μg disk zone size = 6 mm. C. S. aureus with high-level mupirocin resistance (MIC ≥1024 μg/mL), 200-μg disk zone size = 6 mm and 50-μg disk zone size = 6 mm.
the incidence of community-associated skin and soft-tissue infection has apparently increased in the United States in recent years, likely driven by the emergence of community-associated MRSA strains [58]. In an effort to prevent the recurrence of skin and soft-tissue infection often associated with these strains, clinicians may increase use of mupirocin to eradicate MRSA colonization in patients and their families [49, 59–62].

Another factor that may lead to increasing mupirocin use is the growing interest in perioperative eradication of Staphylococcus aureus colonization as a strategy for preventing postsurgical infection [63]. There is an emerging body of evidence that suggests that perioperative eradication of S. aureus colonization can reduce the number of postsurgical staphylococcal infections [54, 64], and this evidence will likely lead to increased use of mupirocin for this purpose.

A third factor that could influence mupirocin use is the fact that many US hospitals, in an effort to control health care–associated MRSA infection and transmission, now routinely screen patients for asymptomatic MRSA colonization. Although routine use of decolonization therapy for MRSA carriers is not currently recommended by the guidelines of the Healthcare Infection Control Practices Advisory Committee [65], some US hospitals currently employ this strategy [49]. A recent multicenter study involving 3 US hospitals that showed a reduction in the rate of MRSA infection that was associated with this practice could further influence the use of mupirocin for preventing MRSA among general hospital populations, despite caution from the authors that their findings should be confirmed by additional studies [66].

If the clinical use of mupirocin increases as anticipated in the United States, an increase in the prevalence of mupirocin resistance will likely follow. The emergence of resistance could be limited if several steps are taken in the near future. First, we need additional studies to quantify the efficacy, effectiveness, and unintended consequences of mupirocin use as a prevention strategy. Second, a strategy for monitoring the prevalence of resistance should be developed and implemented whenever mupirocin is to be routinely used. The monitoring plan not only should focus on mupirocin resistance itself but also should

### Table 3. Relationship between Mupirocin Use and the Emergence of Mupirocin Resistance in Staphylococcus aureus Isolates

<table>
<thead>
<tr>
<th>Mupirocin use</th>
<th>Occurrence of resistance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over-the-counter availability of mupirocin</td>
<td>Common</td>
<td>[29]</td>
</tr>
<tr>
<td>Limited use for controlling outbreaks</td>
<td>Rare</td>
<td>[30, 31]</td>
</tr>
<tr>
<td>Limited use to prevent recurring infection</td>
<td>Rare</td>
<td>[32]</td>
</tr>
<tr>
<td>Widespread use in the general patient population (nasal and skin lesions)</td>
<td>Common</td>
<td>[33, 34]</td>
</tr>
<tr>
<td>Routine but restricted use in the general patient population (nasal only)</td>
<td>Moderate</td>
<td>[35–38]</td>
</tr>
<tr>
<td>Routine use in hemodialysis patients (nasal only)</td>
<td>Rare</td>
<td>[39]</td>
</tr>
<tr>
<td>Routine use in peritoneal dialysis patients (nasal and exit site)</td>
<td>Common</td>
<td>[40, 41]</td>
</tr>
<tr>
<td>Short-term use for perioperative prophylaxis (nasal only)</td>
<td>Rare</td>
<td>[42–44]</td>
</tr>
</tbody>
</table>

**WILL MUPIROCIN RESISTANCE BECOME MORE PREVALENT IN THE UNITED STATES?**

The confluence of several current clinical and epidemiologic trends is likely contributing to increases in mupirocin use in both community and health care settings and could portend an increase in mupirocin resistance in the United States. First, the incidence of community-associated skin and soft-tissue infection has been associated with the emergence of resistant strains, and patients who carry resistant strains could have an increased risk for exit-site infection [40, 41].

Perioperative treatment of surgical patients with staphylococcal decolonization regimens has been studied as a strategy for preventing postoperative infection. In the randomized controlled trial that examined the effect of preoperative mupirocin, Perl et al [42] treated 2012 patients from 1995 through 1998. Mupirocin susceptibility testing was performed on 1021 S. aureus isolates (150 from patients with surgical-site infection and 871 from nares of uninfected patients), and only 6 isolates (0.6%) were resistant [42]. Similarly, Fawley et al [43] studied the emergence of resistance for 4 years after initiation of perioperative prophylaxis with nasal mupirocin for patients who were undergoing orthopedic or vascular surgical procedures. Before starting the program and every 6 months thereafter, point-prevalence surveillance for nasal S. aureus carriage was performed for all patients on 5 orthopedic surgery wards and 1 vascular surgery ward. The overall prevalence of low-level mupirocin resistance among S. aureus isolates recovered from patients in study units was 7%, with no trend towards increasing prevalence during the 4-year study period. No high-level resistant strains were isolated [43]. In a Dutch hospital where more than 20,000 patients who were undergoing major cardiothoracic surgery have been routinely treated with mupirocin perioperatively since 1993, no mupirocin resistance has emerged [44]. These data suggest that short-term use of intranasal mupirocin as part of a perioperative prophylactic regimen is not strongly associated with the emergence of mupirocin resistance.
help determine whether mupirocin use might amplify the spread of multidrug resistance via its linkage to other resistance determinants. Unfortunately, as noted above, there are currently no commercially available test methods or FDA interpretative breakpoints for mupirocin susceptibility testing. Even when testing methods become more widely available, additional information will be needed to inform clinicians and health care facilities of how best to use these methods to guide therapeutic and prophylactic use of mupirocin.

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