Treatment of *Staphylococcus aureus* Colonization and Prophylaxis for Infection with Topical Intranasal Mupirocin: An Evidence-Based Review

Kevin B. Laupland and John M. Conly

Departments of *Medicine, Critical Care Medicine, and Pathology and Laboratory Medicine, and Centre for Antimicrobial Resistance, University of Calgary and the Calgary Health Region, Calgary, Alberta, Canada

Most *Staphylococcus aureus* infections are endogenously acquired, and treatment of nasal carriage is one potential strategy for prevention. We critically appraised the published evidence regarding the efficacy of intranasal mupirocin for eradication of *S. aureus* nasal carriage and for prophylaxis of infection. Sixteen randomized, controlled trials were appraised; 9 trials assessed eradication of colonization as a primary outcome measure, and 7 assessed the reduction in the rate of infection. Mupirocin was generally highly effective for eradication of nasal carriage in the short term. Prophylactic treatment of patients with intranasal mupirocin in large trials did not lead to a significant reduction in the overall rate of infections. However, subgroup analyses and several small studies revealed lower rates of *S. aureus* infection among selected populations of patients with nasal carriage treated with mupirocin. Although mupirocin is effective at reducing nasal carriage, routine use of topical intranasal mupirocin for infection prophylaxis is not supported by the currently available evidence.

*Staphylococcus aureus* is one of the most important pathogens worldwide and has emerged as a prominent organism infecting critically ill persons [1–4]. The impact of *S. aureus* infection on human health has dramatically increased as a result of its remarkable ability to become resistant to antimicrobials [5–8]. Although asymptomatic nasal colonization with *S. aureus* is common, it appears to be an important factor in the development of most infections due to this organism [2, 9, 10]. As a result, efforts have been made to eliminate *S. aureus* colonization in an attempt to reduce the incidence of infection. Techniques include use of systemic antimicrobials, normal bacterial flora augmentation, antiseptic washes, and topical antimicrobials [10–13]. For a number of potential reasons, including efficacy and minimization of systemic antibiotic use, topical intranasal therapies have been recognized as a preferred method.

Mupirocin has emerged as the topical antibacterial agent of choice for elimination of *S. aureus* nasal carriage [14]. Mupirocin is produced by *Pseudomonas fluorescens* and inhibits bacterial protein synthesis by reversibly binding to bacterial isoleucyl–tRNA-synthetase. It is a novel compound, and many antibiotic-resistant strains of *S. aureus* naive to its use are susceptible [15]. However, with repeated exposure to mupirocin, resistance is known to develop [16–18]. Significant potential exists for mupirocin as an agent to reduce nasal colonization and subsequent systemic *S. aureus* infection. To minimize the risk of excess use and development of resistance, its application should be guided by clinical evidence. Therefore, we critically appraised studies investigating the efficacy of intranasal mupirocin for eradication of *S. aureus* nasal carriage and its role as prophylaxis for infection.

**METHODS**

A structured search of worldwide medical literature was conducted to find clinical trials of intranasal admin-
istration of mupirocin for eradication of nasal colonization and prevention of infection. MEDLINE, Embase, and Cochrane databases were searched for articles from 1966 through November 2002 using the subject term “mupirocin,” and the results were restricted to clinical trials involving humans. The authors’ personal files and bibliographies of selected reports were reviewed in an attempt to identify additional articles. Only prospective investigations with a concurrent control group were considered. Critical appraisal was guided by the principles of Sackett et al. [19]. Studies were assessed for adequacy of randomization and blinding and for completeness of follow-up. Reported outcomes were considered to be statistically significant if P values were <.05.

RESULTS

Intranasal Mupirocin for Eradication of S. aureus Carriage

Nine prospective trials evaluating mupirocin for eradication of nasal colonization with S. aureus fulfilled inclusion criteria [13, 20–27]. Four clinical trials that assessed the development of clinical infection as the primary outcome measure also evaluated clearance of nasal colonization [28–31]. As a result of heterogeneity among study populations and outcomes, quantitative summarization was not performed [32].

Health care workers. A number of placebo-controlled trials evaluating intranasal mupirocin for eradication of S. aureus carriage have been conducted among healthy health care workers. Doebbeling et al. [21] reviewed 6 independent, double-blind, randomized, placebo-controlled clinical trials (DBRPCTs) and subsequently reported data from follow-up studies [22, 23, 33]. On the basis of an intent-to-treat (ITT) analysis, they found that application of mupirocin twice per day to the nares for 5 days led to a significantly lower rate of positive nasal culture results at 48–72 h (22 [13%] of 170 mupirocin recipients vs. 157 [93%] of 169 placebo recipients); the lower rate of carriage persisted at 4-week follow-up (18% vs. 88%). Mupirocin resistance was only identified in 5 (1%) of 339 participants using the disk diffusion method (zone diameter, ≤17 mm), and all isolates were found to be susceptible using the broth dilution method (MIC, ≤0.12 μg/mL). These authors later reported long-term follow-up data for 68 patients [22, 33]. Six months after treatment, rates of nasal positivity were 48% and 72% for mupirocin and placebo recipients, respectively, and at 1 year, the rates were 53% and 76%, respectively.

Fernandez et al. [24] conducted a DBRPCT that was designed similarly to that reported by Doebbeling et al. [21]. Among 68 individuals randomized to receive either mupirocin or placebo, culture positivity rates were 13% and 91% immediately after treatment and 67% and 94% at 6 months after treatment, respectively.

HIV-infected individuals. Martin et al. [20] conducted a DBRPCT that compared mupirocin (twice per day for 5 days) with placebo in 76 HIV-infected patients with stable nasal carriage of S. aureus. At 1-week follow-up, 4 (12%) of 34 mupirocin recipients and 33 (92%) of 36 placebo recipients had positive culture results. This study was limited by incomplete follow-up data, and patients were excluded from further analysis if they missed an appointment. At weeks 2, 6, and 10 after treatment, rates of persistently negative cultures were 34% and 88%, 38% and 77%, and 57% and 69% for mupirocin and placebo recipients, respectively. Of 19 mupirocin-treated patients who became recolonized, 16 (84%) were recolonized with the initial strain, as determined by PFGE. No mupirocin-resistant isolates were identified using the disk diffusion method.

Patients undergoing hemodialysis. Bommer et al. [13] conducted a patient-blinded trial comparing mupirocin (3 times per daily for 10 days) with placebo among 34 patients undergoing long-term hemodialysis. They performed nasal cultures for S. aureus at days 3, 8, 10, 21, 42, 70, and 140 days after commencement of treatment, and they found significantly lower rates of positivity among mupirocin recipients than among placebo recipients on day 10 (8 [24%] of 33 patients vs. 19 [90%] of 21 patients, respectively) and day 140 (19 [58%] of 33 patients vs. ~95% of patients, respectively). They cultured samples from multiple skin sites and found a significantly lower rate of skin colonization on day 10 for mupirocin (33%) than for placebo (75%); this difference remained significantly lower at week 6 of follow-up, with rates of culture positivity of ~40% and 88%, respectively. This study did not include ITT analysis, because 5 patients took the treatment intermittently and were excluded. Furthermore, although nasal eradication did not occur for 24% of mupirocin-treated patients, the investigators did not assess resistance to this agent or the potential impact of horizontal transmission of mupirocin-resistant strains.

Mupirocin versus other active therapies for health care workers and patients. Soto et al. [25] compared intranasal mupirocin and bacitracin in a double-blind, randomized trial involving health care workers and found significantly lower rates of culture positivity among mupirocin recipients (1 [6%] of 16 vs. 10 [56%] of 18 subjects 72–96 h after treatment, and 3 [20%] of 15 vs. 10 [77%] of 13 subjects at 30-day follow-up). ITT analysis was not performed.

Perez-Fontan et al. [26] reported a small study of patients undergoing ambulatory peritoneal dialysis and their assisting partners who were nasal carriers and allocated them to treatment with either mupirocin or neomycin sulphate 3 times per day for 7 days. None of 12 mupirocin-treated patients and 6 of 10 neomycin-treated patients had positive culture results 1 week after treatment; the 3-month follow-up rates were 5 (42%) of 12 and 3 (75%) of 4, respectively. This study was limited by an unclear randomization process, uncertain blinding, unequal
follow-up for small numbers of patients, and inclusion of some patient’s partners as subjects.

Parras et al. [27] compared the use of intranasal mupirocin with the use of a combination of topical fusidic acid and oral trimethoprim-sulfamethoxazole (TMP-SMZ) for eradication of methicillin-resistant S. aureus in an open-label trial involving 11 health care workers and 73 hospitalized patients. Similar rates of nasal culture positivity were observed for recipients of mupirocin and the fusidic acid–TMP-SMZ combination: 0 of 37 and 0 of 36 patients at week 1, one (4%) of 24 and 1 (5%) of 19 patients at week 4, and 3 (21%) of 14 and 2 (29%) of 7 patients at month 3, respectively. No resistance to mupirocin was noted using the agar dilution method. Limitations to this study were the open-label design and inclusion of a heterogeneous group of patients and health care workers.

Intranasal Mupirocin to Prevent Clinical S. aureus Infection

Seven articles were appraised that prospectively compared mupirocin recipients with a control group with clinical infection as the primary outcome [28–31, 34–36]. As a result of heterogeneity among study populations and outcomes, quantitative summarization was not performed.

Surgical site infections. The most recent and largest study investigating mupirocin as preventive therapy was reported by Perl et al. [29]. This DBRPCT included 4030 patients who underwent general, gynecologic, neurologic, and cardiotoracic surgery and assessed the effect of preoperative intranasal administration of mupirocin (twice per day for up to 5 days) on the prevention of the primary outcome of surgical site infection. Clear outcomes were defined a priori, and the duration of follow-up was 30 days. Of 3864 patients in the ITT analysis, 2.3% of mupirocin recipients and 2.4% of placebo recipients developed surgical site infection, but this was not significant. However, in secondary analysis of 891 nasal carriers, significantly fewer mupirocin-treated patients (4%) developed nosocomial S. aureus infection, compared with placebo recipients (7.7%). They observed a low rate of mupirocin resistance (6 [0.6%] of 1021 isolates) using the Etest (AB Biodisk; MIC, >4 μg/mL). Only 83% of patients received ≥3 doses before surgery. Despite this, nasal colonization was cleared in 84% of mupirocin recipients, compared with 27% of placebo recipients. Therefore, the short treatment duration may be of limited significance.

Kalmeyer et al. [30] conducted a DBRPCT in Rotterdam, The Netherlands, involving 614 patients undergoing elective orthopedic surgery who required insertion of implant material. Mupirocin and placebo were applied intranasally twice per day to 315 and 299 patients, respectively, on the day before surgery and the day of surgery. The outcome analyzed was the development of any surgical site infection for 1 month after surgery. The baseline rate of colonization was 30% among mupirocin recipients and 29% among placebo recipients; 15 (16%) of 95 mupirocin recipients tested positive 3–5 days after treatment, compared with 61 (71%) of 86 placebo recipients. No significant difference was observed in the subsequent incidence of surgical site infection between mupirocin and placebo groups (12 [4%] of 315 patients vs. 14 [5%] of 299 patients, respectively). Furthermore, no difference was observed between groups with regard to the incidence of S. aureus surgical site infection. All isolates were mupirocin susceptible. A limitation of this study is that the sample size was based on a high estimated treatment effect of a 75% reduction in the incidence of infection. As a result, this study was underpowered to identify less dramatic but potentially clinically significant treatment effects. They may have underestimated the effectiveness of short-course mupirocin treatment, because a minimum of only 2 doses were required. However, eradication rates of 84% and 22% were observed in the mupirocin and placebo groups, respectively. The short treatment duration may be of limited significance.

Patients undergoing dialysis. The Mupirocin Study Group conducted a study of 267 patients undergoing continuous ambulatory peritoneal dialysis in 9 European health care centers who had nasal cultures persistently positive for S. aureus [31]. Patients were treated with either mupirocin (134 patients) or placebo (133 patients) twice per day for 5 days initially, and then this treatment was repeated monthly. Patients were followed up for 18 months. No overall significant differences in the rates of catheter tunnel or exit site infections or peritonitis were found. They did observe a statistically significant difference in the secondary analysis of exit-site infections due to S. aureus: there were 14 and 44 infections among mupirocin- and placebo-treated patients, respectively. There were no apparent differences observed in the rates of mupirocin resistance.

Boellett et al. [28] conducted a DBRPCT in Brugge, Belgium, involving 34 patients undergoing long-term hemodialysis who had documented S. aureus nasal colonization. They allocated 16 patients to receive intranasal mupirocin and 18 to receive placebo 3 times per day for 2 weeks, followed by 3 times per week for 9 months. Cultures were performed during the third week of the study and then bimonthly thereafter. They observed a decrease in the rate of colonization during the follow-up phase of the study (4 [6%] of 66 mupirocin recipients vs. 62 [58%] of 106 placebo recipients). Significantly fewer infections were observed with mupirocin treatment (1 [6%] of 16 patients) than with control treatment (6 [33%] of 18 patients). However, these results may be biased by the shorter duration of follow-up for the mupirocin group than for the placebo group (104 vs. 147 patient-months, respectively). Furthermore, they did not report a strict a priori definition for infection, and the impact of these infections was, therefore, not clear. The blinding process was also not well described. No difference in bacteremia
occurrence was observed. No mupirocin-resistant isolates were identified using the agar dilution method.

**Skin infection.** Raz et al. [35] evaluated the efficacy of maintenance therapy with nasal mupirocin in reducing the number of recurrent skin infections among immunocompetent persons with persistent nasal carriage. All patients were treated with a 5-day course of mupirocin; 17 were then randomized to undergo successive monthly treatments for 1 year, and 17 others were to receive placebo. Cultures and clinical assessments were performed monthly. A significant reduction in the number of clinical skin infections occurred among patients treated with maintenance therapy, compared with placebo (26 vs. 52 infections, respectively). Eight recipients of maintenance mupirocin therapy and 2 placebo recipients remained nasal-culture negative during follow-up. Only 1 of the 10 patients who remained free of colonization had a skin infection, whereas all 24 of those with positive culture results had skin infections. Total duration of use of systemic antibiotics was 142 days in the mupirocin maintenance group and was significantly shorter than the duration for the placebo group (357 days). Mupirocin resistance, as determined by disk diffusion, was observed in 1 (6%) of 17 patients in the maintenance group and in none of the placebo-treated patients. Limitations of the study were the small size and the lack of explicit a priori criteria for establishing infection. Blinding appeared adequate such that this was not likely a major bias.

Manuskiatti et al. [34] attempted to evaluate the use of intranasal mupirocin to prevent skin infections among patients undergoing laser resurfacing. These investigators tested 4 regimens (including oral ciprofloxacin, intranasal mupirocin ointment, oral ketoconazole, and oral fluconazole) in an apparently randomized fashion among 356 consecutive patients over differing time periods. One hundred sixty-four patients were allocated to the mupirocin or "control" arm (not defined). Eleven mupirocin recipients developed infection, compared with none of the control subjects (adequate denominator data provided). However, ciprofloxacin was also given to an undisclosed number of these patients in an unequal distribution, which confounded results. This was a very limited, poorly designed study. Randomization procedures were not specified, the actual number of patients in each group was unclear, treatments overlapped, and blinding procedures and ascertainment of outcome were poorly defined.

**Intensive care unit (ICU)–acquired infections.** Nardi et al. [36] studied the addition of mupirocin or placebo to a topical selective digestive decontamination (SDD) regimen that consisted of tobramycin, polymyxin E, and amphotericin B in a DBRCT involving ICU-infections in Udine, Italy. They randomized 223 patients to receive mupirocin (intranasal and oropharyngeal) or placebo in addition to SDD. A significantly lower rate of pneumonia occurred among patients treated with the mupirocin regimen (9 [8%] of 119 patients), compared with those who received placebo (20 [19%] of 104 patients). This was largely because *S. aureus* was less frequently isolated from mupirocin-treated patients (1 patient) than from placebo-treated patients (9 patients). Inclusion of mupirocin in the SDD protocol was associated with a 36% reduction in overall antibiotic costs (costs were $181 for the mupirocin arm and $283 for the placebo arm). They did not report any difference in overall infection rate among the treatment groups, even though this was suggested to be the primary outcome. The significant difference in pneumonia rates likely represents a secondary analysis. They did not evaluate the incidence of antimicrobial resistance, despite the use of an antimicrobial-intensive regimen.

One other study reported in the Italian literature fulfilled search criteria, but only the English-language abstract was reviewed [37]. In this DBRCT conducted in Florence, Italy, 48 consecutive patients in the intensive care unit who were undergoing ventilation were randomized to receive intranasal mupirocin or placebo 3 times per day for 3 days. Ventilator-acquired pneumonia occurred at comparable rates among study patients. Critical appraisal of this study was not performed.

**DISCUSSION**

Several studies conducted with varied populations demonstrated that mupirocin was highly effective in eradicating nasal colonization with *S. aureus* when compared with placebo in the short term. The efficacy of mupirocin was also comparable to a systemic regimen and superior to other topical antibiotics in a few small trials. However, 2–14-day therapeutic courses of mupirocin did not typically result in long-term clearance of *S. aureus* colonization. This is not surprising, because *S. aureus* carrier status is known to be dynamic over time, and certain individuals are at increased risk for chronic colonization [10]. Repeated application of mupirocin is a potential option for reducing colonization in the long term, but the evolution of resistance is a risk. Several of the studies included in this review described resistance associated with mupirocin therapy, but the rates were typically low. However, the long-term effect on resistance development is not known because no studies included several years of follow-up. In addition, the techniques used varied between studies, and, in some studies, no assessment of mupirocin resistance was conducted. It is reasonable to expect that prolonged use among patients at risk for colonization will result in resistance, although the time frame for this event is poorly defined. For these patients, therapies such as normal flora augmentation may be preferred [11].

Ultimately, the most important goal of intranasal mupirocin application is to reduce subsequent clinical infection. The body of literature currently does not support routine administration of prophylactic intranasal mupirocin to patients in an attempt
to decrease the rate of clinical infection. There may be a role in some selected cases, such as those involving patients or personnel who have been epidemiologically implicated in the transmission of Staphylococcus aureus to others. Although subgroup analyses have suggested some effect in reducing infection, when applied to highly selected patients, the benefits observed appear to be minimal. Clinically important outcomes may include reduction in overall infection incidence or in some other measure, such as length of hospital stay, overall cost, consumption of antimicrobials, or mortality. A reduction in the overall incidence of infection is more meaningful than a reduction in the number of Staphylococcus aureus infections specifically because of the possibility of organism replacement, where Staphylococcus aureus colonization and infection is reduced only to allow infection with a different, potentially more virulent organism. In the single study to have evaluated nasal mupirocin to reduce infections in patients undergoing peritoneal dialysis, no overall difference in infection occurrence was seen [31]. Although the proportion of peritonitis in patients treated with mupirocin as compared with placebo demonstrated a trend toward fewer Staphylococcus aureus infections (18 [25%] of 72 vs. 24 [40%] of 60; P = .09), a significantly higher rate of infections due to gram-negative or mixed organisms (20 [28%] of 72 vs. 7 [12%] of 60; P = .03, by Fisher’s exact test) was observed [31]. The potential cost or clinical outcome difference associated with organism replacement is not known. The cost associated with use of mupirocin is significant and may exceed the benefit if the incidence and costs of treatment of infectious complications are low. One study involving patients undergoing peritoneal dialysis suggested that mupirocin use was not cost-effective [38].

Although the available literature does not support routine use of topical intranasal mupirocin to prevent subsequent infections, there may be yet-identified patient populations that could benefit. For a significant effect to be seen, one may speculate as to the characteristics of patients who would benefit the most. Ideally, mupirocin should be used for patients when the period of risk for infection is acute. Chronic infection risk, such as with dialysis patients, has demonstrated minimal clinical benefit but increased risk for resistance. Examples of patients with acute disease who may be candidates for prophylactic mupirocin treatment include patients who have undergone cardiac surgery, patients with multiple trauma (especially those with head injuries), and, possibly, other selected critically ill patients [38–41]. The selection of patients with high rates of nasal colonization or documented carriers is also important for mupirocin therapy to be effective. Clinical prediction of nasal carriage is not sufficiently discriminating; culture data are needed. The requirement for incubation of cultures before mupirocin therapy is started can result in delays that may lessen its effectiveness. The development of rapid diagnostic techniques to identify Staphylococcus aureus nasal carriage may be a requisite advance before mupirocin therapy can used as prophylaxis.

References


