Randomized, Double-Blinded, Placebo-Controlled Trial of Topical Intranasal Mupirocin in Prevention of Staphylococcus aureus Infections in the Intensive Care Unit

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A. Background and Study Purpose

Nosocomoial infections are a major problem in this country, occurring in 5-10% of patients admitted to U.S. hospitals. *Staphylococcus aureus* is the most common cause of nosocomial pneumonia and and the second most common cause of nosocomial blood stream infections. The purpose of this study is to investigate the efficacy of using mupirocin, an antibiotic ointment, administered intranasally to prevent *S. aureus* infections in patients admitted to the intensive care unit (ICU) who are found to have *S. aureus* colonized in their nares.

It has for many years been observed that nasal *S. aureus* carriage is associated with an increased risk of *S. aureus* infections. For instance, one seminal study in 1959 found that among the 35% of inpatients in a unit who were colonized with *S. aureus* in their nares, the infection rate was 37%, compared with 11% in the group with nasal cultures negative for *S. aureus*. Various regimens designed to eradicate nasal carriage, including parenteral vancomycin, topical bacitracin, and oral rifampin in conjunction with bacitracin, have shown no, or only modest, effect in eliminating nasal carriage of *S. aureus*. The advent of the topical agent mupirocin—an antibiotic with a unique mode of action, which was approved in 1987—allowed for the effective elimination of nasal carriage of *S. aureus*. In one study, a five-day course mupirocin eliminated nasal carriage of *S. aureus* in greater then 95% of subjects, with 71% of treated subjects remaining free of *S. aureus* nasal colonization 3 months after being treated.

There have been relatively few trials looking at mupirocin as an intervention to decrease rates of infection in the ICU. One non-blinded prospective study compared two consecutive periods, one in which none of the subjects were given a course of mupirocin intranasally, and one in which all of the subjects were given mupirocin, and found an approximately 75% decrease in the rate of infection during the period the mupirocin was used. This study seeks to conduct a prospective, randomized, double-blinded, placebo-controlled trial to test the hypothesis that mupirocin, given to ICU patients with *S. aureus* nasal colonization, is an effective intervention to decrease the rate of *S. aureus* infections in these patients.

B. Study Design, Procedure, and Statistical Analysis

Subjecs would be patients admitted to the Columbia Presbyterian Medical Center (CPMC) Medical Intensive Care Unit (MICU). Patients who consented to participate would have their nares cultured to look for nasal carriage of *S. aureus*. Patients who had such nasal carriage would be randomized into one of the two arms of the study. Patients in the experimental arm would be given mupirocin (Bactroban Nasal) bid for 5 days. The other, control arm would be given a paraffin base, similar to the vehicle containing the mupirocin, as a placebo. Patients would have their nares re-cultured every five days, and if their nares were found to be colonized with *S. aureus*, they would be re-treated for five days with either the mupirocin or the placebo, consistent with whichever arm they were enrolled in. The primary outcome being measured in the study would be documented *S. aureus* infections in the blood, urine, and sputum. Microbiology data would be followed for all enrolled patients so that any culture-documented infections could be recorded.

Using a chi-square test to compare proportions of documented *S. aureus* infections in the arm treated with mupirocin and the arm treated with placebo, approximately 250 patients would have to be enrolled in each arm, in order to achieve 80% power, testing at P=0.05.

C. Study Drug

The drug to be used in this study is mupirocin calcium ointment 2%. The drug is indicated for the eradication of *S. aureus* colonizing the nares of adults, which is how the drug is to be used in this study. The most commonly seen adverse reactions to the drug are headache (9%), rhinitis (6%), respiratory disorder (5%), pharyngitis (4%), and taste perversion (3%).

D. Other Issues

One issue that has been raised with regards to this study is the risk of resistance to mupirocin. Resistance has been infrequently observed. One series of 7,137 *S. aureus* isolates found a mupirocin resistance rate of 0.3%. Using mupirocin for short courses, in areas known to be colonized with *S. aureus*, in which the drug should be able to fully eradicate the *S. aureus*, should not serve to induce widespread resistance. Given mupirocin's unique mode of action, it is not though to induce resistance to other clinically used antibiotics. Another issue is cost effectiveness. Mupirocin's cost effectiveness has been evaluated in the perioperative context and among hemodialysis patients, and both studies concluded the mupirocin was a cost effective intervention.

IRB Proposal

A. Study Purpose

The purpose of this study is to investigate the efficacy of using mupirocin administered intranasally to prevent *S. aureus* infections in patients admitted to the ICU who are found to have *S. aureus* colonized in their nares. A number of studies have shown that nasal carriage of *S. aureus* is a risk factor for later infection with *S. aureus*, and mupirocin has been shown to have sustained effectiveness in eradicating *S. aureus* from the nares. However, there is much less evidence about the effectiveness of mupirocin used prospectively as an intervention to try to decreases the rate of *S. aureus* infections.

B. Background and Rationale

Nosocomial infections occur in 5-10% of patients who are admitted to U.S. hospitals every year.[1] *Staphylococcus aureus* accounts for an increasing number of these infections, with this organism representing the most common cause of nosocomial pneumonia, and the second most common cause of nosocomial blood stream infections.[2]

As far back as the 1950s, nasal carriage of *S. aureus* was recognized as a risk factor for subsequent infectious complications. In a 1959 *New England Journal of Medicine* article, it was found that, in a setting that today would be called a SICU, 35% of patients in the unit had nasal cultures positive for *S. aureus*. Among those with nasal cultures positive for *S. aureus*, the rate of infectious complications was 37%, compared with 11% in the group with nasal cultures negative for *S. aureus*. Of these infectious complications in the group with nasal cultures positive for *S. aureus*, 79% of them were *S. aureus* infections.[3]

Another study performed in 1997 in three 12-bed combined MICU-SICUs found that 22.1% of patients on admission had nasal cultures positive for *S. aureus*. From this group with positive nasal cultures on admission, 22.9% developed *S. aureus* infections in the ICU, compared with a *S. aureus* infection rate of 0.3% among those patients whose nasal cultures remained negative throughout their ICU stay.[4]

In other groups of patients at high risk for infections, in addition to ICU patients, nasal carriage of *S. aureus* has predicted a higher rate of subsequent infectious complications involving *S. aureus*. This

relationship has been found in patients undergoing hemodialysis,[5] peritoneal dialysis,[6] and in HIV patients.[7]

Although nasal colonization with *S. aureus* as a risk factor for later infections has been recognized for many years, initial attempts at trying to eliminate this nasal carriage of *S. aureus* were only modestly successful. Yu, *et al*., during the period 1979-1983, cultured the nares of patients in a VA hemodialysis unit, and assessed the effect on nasal carriage of *S. aureus* of three different antibiotic regiments: parenteral vancomycin, topical bacitracin, or oral rifampin plus topical bacitracin.[5] Neither the parenteral vancomycin nor the topical bactitracin was effective in reducing nasal colonization with *S. aureus*. The regimen of oral rifampin plus topical bacitracin led to an 18% decrease in the incidence of nasal carriage of *S. aureus* as compared to untreated controls. Among those found to have nasal colonization with *S. aureus* at the outset of the study, 2 of 18 patients who received the rifampin-bacitracin regimen developed *S. aureus* infections, as compared with 12 of 26 patients who received no prophylaxis.

The approval of topical mupirocin in 1987 provided a new agent which proved more effective at eradicating nasal carriage of *S. aureus*.

During a MRSA outbreak in 1983-1984, 40 patients were identified as having nasal carriage of *S. aureus* and were treated with five days of intranasal mupirocin. Thirty-nine of these patients had the *S. aureus* cleared from their nares after two days of treatment with the mupirocin. Thirty-six of the patients remained clear of nasal *S. aureus* for the duration that they were followed (mean of two weeks). Also of note, patients who were given the mupirocin showed decreased rates of carriage of *S. aureus* not only in their nares, but also in their perineum, wrists, wounds, and axillae.[8]

The efficacy of mupirocin in eliminating *S. aureus* carriage from the nares has also been demonstrated in more methodologically rigorous studies. In a double-blind, placebo-controlled, randomized study of healthcare workers, subjects who had nasal cultures positive for *S. aureus* received intranasally twice a day for five days either mupirocin or placebo. Mupirocin eliminated nasal carriage of *S. aureus* in greater then 95% of the treatment group, and the mupirocin had a persistent effect, with 71% of the subjects who received muprocin remaining free of *S. aureus* nasal colonization at 3 months, compared with 18% in the control group. The efficacy of intranasal mupirocin in eliminating carriage of *S. aureus* extended to the hands, with 80% of the subjects in the intervention group being free of hand carriage at day 3, as compared to 19% of control subjects.[9]

There have been relatively few trials assessing the efficacy of mupirocin as an intervention designed to decrease infection rates in the ICU setting. One such study that was conducted was a prospective two-step non-placebo-controlled trial in a SICU in which two consecutive periods were analyzed. One was a four month period in which all patients had their nares (and tracheal secretions, and wounds) cultured, and no mupirocin was used.[10] During the second period, lasting two months, after culturing patients, all patients, regardless of culture results, had muprirocin administered intranasally twice a day to each nostril for one week. During the period that mupirocin was used, relative to the prior control period, a decrease in pulmonary tract, blood, surgical, urinary tract, and vascular line infections was seen, with only the decrease in pulmonary tract infections being statistically significant. The data are as follows:

Infections	Control Period (no mupirocin used)	Intervention Period (mupirocin used)	P
Pulmonary tract	13	1	0.032
Bacteremia/Septicemia	6	1	Non-significant
Surgical wound	2	0	Non-significant
Urinary tract	2	1	Non-significant
Surface	1	1	Non-significant
Vascular line	1	0	Non-significant

A total of 157 patients were included in this study. Table adapted from Talon D, Rouget C, Cailleaux V, Bailly P, Thouverez, Barale F, Michel-Briand Y, Nasal carriage a *Staphylococcus aureus* and cross-contamination in a surgical intensive care unit: efficacy of mupirocin ointment. Journal of Hospital Infection 1995; 30: table III, p. 45.

Overall, an approximately 75% reduction in the *S. aureus* infection rate was seen during the period the mupirocin was used, with the infection rate falling from 28 per 100 patients admitted during the period prior to mupirocin use, as compared with an infection rate of 6.8 during the period mupirocin was used for nasal decontamination.

Given that the nasal carriage of *S. aureus* has been demonstrated to be a risk factor for subsequent infection with *S. aureus* and that mupirocin is effective at eliminating such nasal carriage, there is a need for a methodologically rigorous examination of whether mupirocin is a useful intervention to decrease the rate of infection in patients who are intranasally colonized with *S. aureus*. This study is to be conducted in the ICU because ICU patients are at particularly high risk for infection because of the severity of their illnesses and the high rate of indwelling catheters, among other factors.

C. Study Design and Statistical Analysis

The study will take place in the 17-bed medical intensive care unit (MICU) at the Columbia-Presbyterian Medical Center (CPMC). Patients who consented to participate in the study would have nasal cultures taken, and those who were found to have nasal cultures positive for *S. aureus* would be randomized into one of the two arms of the study. In one of the arms, patients would be treated with intranasal mupirocin calcium ointment (Bactroban Nasal) in an effort to eradicate nasal carriage of *S. aureus*. In the other arm, patients would receive a placebo composed of a soft-white paraffin base, similar to the vehicle containing the mupirocin in Bactroban Nasal. Patients would be followed clinically for any signs of infection, as is standard of care in the MICU. Consistent with this standard of care, patients who show signs of infection (e.g., fever, erythema at the site of an indwelling catheter) would be expected to be cultured, thus allowing for collection of information about the incidence of infectious complications and any organism cultured from subjects.

All patients admitted to the MICU would be offered enrolment. The only exclusion criteria are documented ongoing *S. aureus* infection, previous use of mupirocin ointment within the last year, use of other topical antibiotics in or around the nares within the last year, nasal trauma or deformity preventing intranasal administration of mupirocin, and history of hypersensitivity to mupirocin or paraffin.

Data collected on subjects at the time of enrolment would include age, medical diagnosis, presence and number of indwelling catheters, from where the patient was admitted to ICU, whether or not the patient was diabetic, other comorbidities, and previous antibiotic use. Length of stay would also be documented. Microbiology data would be followed for all enrolled patients so that any culture-documented infections could be recorded.

Using a chi-square test to compare proportions of documented *S. aureus* infections in the arm treated with mupirocin and the arm treated with placebo, approximately 250 patients would have to be enrolled in each arm, in order to achieve 80% power, testing at P=0.05.*

D. Study Procedures

Enrolled patients would have their nares cultured by rotating a rayon-tipped swab in the nares. The specimen would be plated onto mannitol-salt agar plates and incubated. Gram-positive, catalase-positive, and coagulase-positive characteristics would be used to identify *S. aureus* colonies. Disk diffusion methodology would be used to determine the antibiotic susceptibilities of the *S. aureus* colonies. *S. aureus* colonies would then undergo pulsed field gel electrophoresis to further characterize the colony, and allow for later comparison of any documented *S. aureus* infection in the patients with the clone of *S. aureus* that the subject had carried in his or her nose. This procedure of culturing of the nares would be repeated every five days in all patients randomized into one of the arms of the study in order to assess for eradication/persistent colonization rates.

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* This calculation is based on a *S. aureus* infection rate in Columbia Presbyterian's MICU of 8.6%. (This is similar to the 6.8% in Corbella X, Dominguez MA, Pujol M, Ayats J, Sendra M, Pallares R, Ariza J, Gudiol F, *Staphylococcus aureus* nasal carriage as a marker for subsequent staphylococcal infectious in intensive care unit patients. Eur. J. Clin. Micriobiol. Infect. Dis. 1997, 16: 351-357). Given the small number of trials using mupirocin as an intervention to decrease *S. aureus* infections, there is limited data to use in estimating the expected effect of the mupirocin intervention. A study by D. Talon *et al*. (Talon D, Rouget C, Cailleaux V, Bailly P, Thouverez, Barale F, Michel-Briand Y. Nasal carriage a *Staphylococcus aureus* and cross-contamination in a surgical intensive care unit: efficacy of mupirocen ointment. Journal of Hospital Infection 1995: 30: 39-49) found an approximately 75% decrease in *S. aureus* infections after mupirocin was used to eliminate nasal carriage of *S. aureus*.

Component CPMC MICU infection data, kindly supplied by Dr. Adam Keene, covering the period 1/1/00 – 12/31/00:

MRSA infections	
Blood	16
Urine	1
Wound	5
Sputum	36
Cath Tip	3
MSSA infections	
Blood	9
Urine	0
Wound	5
Sputum	32
Cath Tip	1

MICU Beds: 17
MICU admissions in year 2000: 938
MICU patient-days in year 2000: 5,916

Patients randomized into one of the two arms of the study would receive 0.25 grams of either the mupirocin or placebo vehicle per nostril bid for 5 days. Patients who upon reculturing of their nares showed recolonization with *S. aureus* would again be treated with either the mupirocin of placebo. Using data from the microbiology lab, all infections documented from enrolled patients in blood, urine, wounds or sputum would be recorded. *S. aureus* from these documented infections would undergo pulsed field gel electrophoresis so that the strains could be compared to see if it was the same strain that was initially cultured from the nares of the subject upon enrolment in the study.

E. Study Drugs

The drug to be used in this study is mupirocin calcium ointment 2%. The drug, which was approved by the FDA in April 1996,[11] is indicated for the eradication of *S. aureus* colonizing the nares of adult patients in order to control infection, which is how the drug is to be used in this study. The regimen to be used, 0.25 grams to each nostril bid for 5 days is the recommended dosing regimen. The most commonly seen adverse reactions to the drug are headache (9%), rhinitis (6%), respiratory disorder (5%), pharyngitis (4%), and taste perversion (3%).[12] A previous study in which mupirocin and a placebo were used intransally in a manner similar to that in this study had 97% of subjects in both groups rating its use as "acceptable overall."[9]

Mupirocin's mode of action is inhibition bacterial isoleucyl t-RNA synthetase, thereby preventing bacterial protein synthesis. This is a mode of action different from other clinically used antibiotics, and no *in vitro* cross-resistance with other types of antibiotics has been observed.[12]

F. Medical Devices

No medical devices are to be used in this study.

G. Study Questionnaires

No questionnaires are to be used in this study.

H. Study Subjects

Inclusion criteria for this study are:
- admission to the MICU for at least four days

Exclusion criteria for this study are:
- documented ongoing *S. aureus* infection
- previous use of mupirocin within the last year
- previous use of other topical antibiotic in or around the nares within the last year
- nasal trauma or deformity preventing intranasal administration of medicine
- history of hypersensitivity to mupirocin or paraffin

I. Recruitment of Subjects

Patients admitted to the MICU would be recruited to participate in the study, and informed consent would be obtained. In accordance with CPMC policy, the patient's primary physician would be contacted regarding the patient's suitability for the study.

J. Confidentiality of Study Data

Data from patients enrolled in the study will be coded using unique identifying numbers to safeguard the confidentiality of the patients. Data will be kept in a secure location, accessible only to investigators.

K. Potential Conflict of Interest

None of the investigators has a proprietary interest in mupirocin or stands to benefit financially from sales of mupirocin.

L. Location of the Study

The study will be conducted in the MICU at CPMC. Patients enrolled may continue to be followed once they leave the MICU for other clinical areas in the hospital.

M. Potential Risks

The only potential risks to the patient include adverse reactions associated with the topical, intranasal administration of mupirocin. As discussed above, these risks are minor and rare, and include, most commonly, headache and rhinitis. Topical administration of mupirocin has been shown to not result in measurable systemic absorption.[12] The use of mupirocin in this study represents a new intervention designed to prevent *S. aureus* infections in patients thought to be at high-risk for infection, and is not being used in place of any standard-of-care intervention.

N. Potential Benefits

Potential benefits include a decreased risk of *S. aureus* infection.

O. Alternative Therapies

Alternative therapies include systemic antibiotics (e.g., rifampin) and other topical agents (e.g., neomycin, chlorohexidine) designed to reduce nasal carriage of *S. aureus*. The current standard of care is not to use any medication to prevent *S. aureus* infections in patients who may be colonized with *S. aureus*.

P. Compensation

Subjects would not be compensated for their participation in the study.

Q. Costs to Subjects

Participation in the study does not incur and addition monetary costs to the enrollees.

R. Minors as Research Subjects

It is not anticipated that minors will participate in the study.

S. Radiation or Radioactive substances.

No radiation or radioactive substance are to be used in the study.

T. Other Issues

Among the other issues raised by the use of mupirocin intransally to eliminate nasal carriage of *S. aureus* is that of mupirocin resistance.[13] Clinically, resistance to mupirocin has not commonly been observed.[14] In one series, 7,137 *S. aureus* isolates were tested for mupirocin resistance. Only 23 of these 7,137 isolates (0.3%) were found to be mupirocin resistant.[15] Mupirocin resistance that has been observed has often happened in the context of the treatment of dermatologic conditions, in which mupirocin has been administered to large areas of skin over extended periods of time, often intermittently.[15] Avoiding the use of mupirocin in areas in which there is a low likelihood of it eliminating *S. aureus*, such as in large infected areas of skin, large decubitus ulcers, and around indwelling devices such as PEG tubes is one way to try to minimize the development of resistance to mupirocin.[13] Mupirocin use in this study is to a defined area (the nares) in which mupirocin has repeatedly been demonstrated to achieve rapid, effective eradication of *S. aureus*.[16]

Another issue is the cost-effectiveness of mupirocin administered to the nares to try to prevent *S. aureus* infection. One study which examined this issue used intranasal mupirocin twice per day beginning the day before cardiothoracic surgery and continuing for 5 days. Historical controls were used for comparison. During the intervention period in which mupirocin was used, the rate of surgical site infections was 2.8%, as compared to 7.3% in the control group. The estimated cost per surgical site infection was $16,876, with mupirocin costing $11 per patient. The estimated savings per surgical site infection prevented with mupirocin was $16,633, with the authors concluding that mupirocin used in this manner was a highly cost-effective intervention.[17] Intranasal mupirocin also proved cost-effective in a study examining its use to prevent infections in hemodialysis patients.[18]

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