Infection Control Intervention with Targeted Mupirocin Administration to Prevent S. aureus Infection Using Rapid Diagnosis Techniques in Intensive Care Units

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a. Specific Aims

In this project we plan to examine the impact of the application of mupirocin administered only to ICU patients who are at the highest risk for *S. aureus* nasal infection, those with nasal colonization, diagnosed with rapid PCR.(6)

b. Background and Significance

Infection with *S. aureus* as well as methicillin-resistant *S. aureus,* represents a threat to all hospitalized patients, but represents the greatest threat to those patients who are critically ill.(10) *S. aureus* has been noted by the NNIS to be a major cause of bloodstream infections, as well as a leading cause for ventilator associated pneumonia in medical intensive care units. (9) (11) Amongst all hospitalized patients, nasal colonization is a major risk factor for subsequent *S. aureus* infection. In a two year study, it was found that nasal carriers of *S. aureus* had a RR of 3.0 (CI 2.0-4.7), compared with non-carriers of developing *S. aureus* bacteremia. In addition, it was found by genotyping that 80% of the strains that caused the bacteremia were the same as the ones colonizing the subjects' nares at the time of enrollment. (15) In a 2001 study, 86% patients followed over 5 years who had nasal cultures positive for *S. aureus* had bacteremias caused by *S. aureus* clonally indentical that isolated from their nares. (14) Within the critically ill population, it would seem that nasal colonization represents the greatest risk for *S. aureus* infection. In a study conducted in our intensive care unit in 2002, 208 patients were screened for nasal colonization with *S. aureus*. Forty-six of those patients were found to be colonized, and, compared with non-colonized patients, they had a relative risk of 12.9 of developing a *S. aureus* infection by CDC standards. (6) It is unclear if the difference in the relative risk amongst ICU patients compared with that of general non-surgical patients is attributable to the increased severity of their disease, but it seems that an ICU population is most likely to benefit from an interventional strategy based on eradication of nasal carriage.

Traditional infection control strategies have focused on limiting spread of the pathogen, but data in certain patient populations suggest that eradication of the infection, particularly of the anterior nares, may confer protection against eventual *S. aureus* infection.(1) Research in this subject has not been entirely consistent; recent studies have suggested that mupirocin administration may only delay, or have no impact whatsoever on the rate of infection.(7) These studies, however, differ significantly from the proposed either in patient population, rapidity of diagnosis of *S. aureus* colonization, or study design. In a 2002 randomized control trial mupirocin was compared with placebo for prevention of surgical site infections in all patients undergoing orthopedic surgery over a two year period. There was no significant difference found between the two groups, but in this study, all patients were administered mupirocin regardless of colonization status at the time of admission, and in addition, the patient population undergoing orthopedic surgery is dissimilar from the ICU population. (5) In another randomized controlled trial

the same year of surgical patients, amongst all post-operative infections, no difference was found amongst the placebo and mupirocin groups when all-comers were randomized into the trial. When a subset analysis of only *S. aureus* nasal carriers was done, however, a significant reduction was found OR .49 CI .25-.92, p = .02. (12) In a 2004 randomized control trial mupirocin was compared with placebo in non-surgical patients with nasal swab cultures positive for *S. aureus*. In this study, there was no significant difference noted amongst the two groups, but in this study, the investigators relied upon culture data that took 2-3 days to come back to determine which patients were colonized and therefore eligible for mupirocin. In this study, we would have the advantage of rapid diagnosis, and we would be able to administer mupirocin far earlier in the patient's course, perhaps before a worsening in their condition making the patient more susceptible to infection.(3)

The main purpose of this study is to assess the efficicacy of an eradication-strategy intervention in which mupirocin would be administered to in a targeted fashion, only to colonized patients in the ICU setting. Study patients would be compared to patients admitted prior to the time of the intervention. All patients would have nasal swabs to be tested for MRSA/MSSA by rapid PCR.

c. Study Design and Statistical Analysis

The study will be an observational study of the impact of intranasal mupirocin among medical intensive care unit patients on staphylococcal infection. Previous studies in our medical intensive care unit have suggested that the rate of colonization of patients would be in between 20 and 25%. (6) As this was determined in 2002, a repeat assessment of the rate of colonization amongst MICU/CCU patients would be performed prior to the initiation of the study. Preliminary power analysis based on the previous data would call for a total of 336 subjects. A separate analysis would be performed to determine the rate of MRSA colonization. The rate of infection will be based on cultures taken from blood, sputum wound, urine, catheter tips. The decision to send cultures will be at the discretion of the primary team of physicians caring for the patient.

d. Study Procedure and Data Collection

All of the patients in the study will have cultures of the anterior portion of both nares performed by one of the investigators or ICU nurses upon their admission to a participating ICU. Nasal cultures are painless and without risk. They are currently performed routinely upon patients at admission to medical and intensive care units to assess for nasal colonization by *S. aureus*. The nasal cultures will then be taken to Dr. Lowy's laboratory and will be processed by PCR and culture. The swabs will be directly inoculated onto agar for *S. aureus*, and all positive cultures will be tested with Staphaurex to confirm identification of the isolates as *S. aureus.* The specimens will also be processed using a multiplex polymerase chain reaction (PCR) via a Cepheid RT-PCR machine recently made available to investigators. This instrument is capable of rapidly detecting *S. aureus* (by primers specific for *S. aureus*) as well as methicillin resistance (by primers to detect the mecA gene). The PCR will allow for a more rapid identification of *S. aureus*, and make it possible to begin intervention on the day of nasal culture. To

facilitate this, a study coordinator will collect the results and alert participating intensive care unit staff.

At study entry, demographic data on all patients including gender, age, diagnosis on hospital admission, prior days in hospital, prior days intubated, recent surgery, and co-morbid conditions such as diabetes, liver failure, heart failure, COPD, HIV infection, active solid or hematological malignancy and organ transplantation will be recorded. When first found to be nasal culture positive, data including prior days in the ICU, prior days intubated, dialysis in the ICU, and recent administration of vancomycin, penicillins, cephalosporins, aminoglycosides or quinolones will be collected. On discharge from the ICU, demographic data including total days in the ICU, total days intubated, dialysis in the ICU, days of mupirocin received, and recent administration of the above antibiotics will again be collected using a computerized data entry system. Throughout the patient's ICU stay and for one month after ICU discharge or until hospital discharge, the WebCIS system will be queried for any *S. aureus* clinical isolates obtained at the discretion of the patient's primary caretakers.

All nasal cultures that are positive for *S. aureus* will be compared to all clinical isolated positive for *S. aureus* by pulsed field gel electrophoresis in order to determine if the colonization strains are the same as infecting strains. They will also be tested for mupirocin sensitivity in Dr. Lowy's laboratory. This will help to assess for the development of resistance to these antibiotics before and after the intervention period.

d. Study Drugs

Calcium mupirocin is a topical antibiotic that is FDA approved for the eradication of nasal colonization with *S. aurues.* When applied to the anterior nares it has minimal systemic absorption and eradicates *S. aureus* nasal colonization in 90-95% of patients. It has been suggested that such eradication may lead to reductions in *S. aureus* nosocomial infectrion. The treatment dose will be one application twice a day for five days. (12) The study drug has been used in clinical trials, and has been well tolerated. A review of 2186 subjects revealed local symptoms (nasal irritation, sneezing, runny nose or nasal congestion in only 1.46%, abnormal taste in 1.10%, sore throat in 0.82% and headache in .96%. (4) In six double-blind studies which included 339 health care workers, no serious adverse events occurred. Mild to moderate adverse events were limited to rhinitis, as well as local erythema, swelling, burning or stinging, pruritis and dryness. There is one case report of allergic contact dermatitis, which may have been caused by mupirocin ointment.

Once the patients have been screened by PCR of their nasal swab and determined to be colonized with *S. aureus*, they will be part of the study. The mupirocin will be provided to the ICU staff by one of the researchers and applied BID to the nares for a maximum of 5 days or until the patient leaves the ICU.

e. Medical Device

No medical device is being studied, however it will incorporate the use of a mechanized PCR technique, via an "Smart Cycler" instrument, manufactured by Cepheid, Sunnyvale Ca.

f. Study Questionnaires

No questionnaires will be used, but patient information and microbiologic data will be recorded and analyzed using a custom-designed computer data entry system.

g. Study Subjects

Patients will be considered eligible for the study if they are admitted to the medical ICU. Exclusion criteria will include known pregnancy, previous enrollment in the study, known hypersensitivity to mupirocin, active *S. aureus* infection on admission or receipt of mupirocin in the 3 months prior to admission.

h. Recruitment of Subjects

Patients will be recruited from the MICU population, and will be idenitified by a daily survey of the MICU admission logs.
(8)

i. Confidentiality of Study Data

Confidentiality will be protected via the assignment of study identification numbers, which will be used for data processing. A list of the patient identification numbers will be kept in a separate location. All data will be kept in encrypted files on computer. Patient identities will be kept separate from these files.

j. Potential Conflict of Interest

k. Location of Study

CPMC medical ICU.

l. Potential Risks

The potential risks of the study are limited to the minor side effects of mupirocin previously noted. There have been recent reports of low-level mupirocin resistance in patients treated with doses comparable to that of the study doses. (2) High-level mupirocin resistance has only been reported in trials in which mupirocin administration was given at a dose much higher than the study dose, or for much longer than the course in the study protocol. (8, 13)

m. Potential Benefits

The potential benefits include a reduced risk of life-threatening *S. aureus* infections in critically ill patients. In addition, *S. aureus* resistance to oxacillin remains a

persistent problem, in the hospital setting. Reduction in the overall rate of *S. aureus* infections would likely result in a decrease in the rate of resistant infections, and would decrease the need for systemic antibiotics such as vancomycin.

n. Alternative Therapies

Mupirocin is currently the most effective and well-studied topical agent used for eradication of *S. aureus* colonization of the nares. Systemic antibiotics have been used with mixed results, but systemic antibiotics carry a greater risk of toxicity, adverse drug interactions, and are more likely to lead to the selection of resistant organisms.

p. Compensation of Subjects

The subjects will not be compensated for participation in this study

q. Minors as Research Subjects

This study will not involve the participation of minors

r. Radiation or Radioactive Substances

This study will not involve radioactive substances.

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