Mupirocin vs. placebo for reducing Staphylococcus aureus infections in critically ill patients colonized with the bacterium.

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A. Introduction

While twenty percent of the general population are nasal carriers of *Staphylococcus aureus (S. aureus),* the carrier rate is even higher in type 2 diabetics, intravenous drug addicts, hemodialysis patients, and HIV-infected individuals.[1] It is assumed that the carrier rate is elevated in the critically ill, as well. Indeed, *Staphylococcus aureus* is a well-known threat to the critically ill patient; it is an everpresent agent in such conditions as ventilator-associated pneunionias, line sepsis, and wound infections. Myriad studies have linked *S. aureus* infections to endogenous colonization of the nares. Kluytmans et al. demonstrated that cardiothoracic surgery patients with preoperative nasal colonization with *S. aureus* have a tenfold risk of staphylococcal wound infections[2]; von Eiff et al. followed patients with *S. aureus* positive nasal cultures over five years and found that eighty-six percent of bacteremias were caused by the same strain as that previously isolated from the nares.[3] With these data, many attempts to eradicate *S. aureus* colonization have been made. Therapies with systemic antibiotics have evinced varying degrees of success, but have also generated concern regarding toxicity and antimicrobial resistance.

Topical mupirocin appears to be superior in efficacy to other antibiotics such as vancomycin, trimethoprim/sulfamethoxazole, and ciprofloxacin, and does not carry the same toxicity profiles. Indeed, it has been shown to reduce. *S aureus* bloodstream infections in hemodialysis patients by eighty-six percent,[4] wound infections in patients undergoing cardiothoracic surgery by sixty-two percent[5], and ventilator-associated staphylococcal pneumonias by eighty-seven percent.[6] Because of these promising data, some intensive care units have implemented the routine and even empiric use of mupirocin as prophylaxis against staphylococcal infection.

All of the reductions in infection rate cited above, however, were demonstrated in trials that compared treated patients to historical controls; mupirocin's efficacy has yet to be tested in a randomized, placebo-controlled trial. Widespread use of mupirocin is not without cost; its increasing administration has caused concerns and, indeed, reports, of emerging mupirocin resistance. The main purpose of this study is to investigate whether topical mupirocin applied only to those patients known to be colonized with *S. aureus* reduces the risk of *S. aureus* infections in the intensive care unit (ICU). Positive results will validate the practice of diligent surveillance and selective mupirocin prophylaxis. Negative results will call the practice into question.

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[1] Kolmos HJ. Carriers of *Staphylococcus aureus* as a source of nosocomial infections. *Ugeskriftfor Laeger 1999; 161(11): 1580-4*

[2] Klytmans JA, et al. Nasal carriage of *Staphyloccocus aureus* as a major risk factor for wound carriage. *JID 1995; 171: 216-219*

[3] von Eiff C, et al. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. *NEJM 200 1; 344: 11 -16*

[4] Kluytmans J, et al. Elimination of nasal carriage of *Staphylococcus aureus* in hemodialysis patients. *Infection Control and Hospital Epidemiology 1996; 17: 793-7.*

[5] Kluytmans J, et al. Reduction of surgical-site infections in cardiothoracic surgery by elimination of nasal carriage of *Staphylococcus aureus. Infection Control and Hospital Epidemiology 1996; 17: 780-5.*

[6] Rumbak M, et al. Significant reduction in methicillin-resistant *Staphylococcus aureus* ventilatorassociated pneumonia associated with the institution of a prevention protocol. *Critical Care Medicine 1995; 23: 1200-3*

B. Hypothesis

The hypothesis is that topically-applied mupirocin in critically ill patients with *S. aureus* nasal colonization will greatly reduce the incidence of S. aureus bacteremia, pneumonias, and wound infections.

C. Methods

Two primary outcomes will be measured. First, the overall prevalence of *S. aureus* nasal colonization in medical ICU patients will be determined. All patients admitted to the medical ICU will undergo anterior nares swabbing at least three times weekly; specimens will be sent for both polymerase chain reaction (PCR) and culture for *S. aureus*. In addition, all intubated patients will have tracheal aspirates sent for PCR and culture for *S. aureus*.

The second outcome will measure the reduction, if any, in *S. aureus* infections in those who are known to harbor intranasal *S. aureus*. If patients' nasal swab proves positive for *S. aureus* at any time during their ICU stay, they will be randomized to five days of nasal mupirocin ointment or placebo. All patients who harbor methillicinresistant *S. aureus* will be placed in contact isolation, in keeping with the current infection control policy.

Upon entering the study, each patient's demographic data, including sex and age, diagnosis on hospital admission, diagnosis on ICU admission, prior days in hospital, prior days intubated, recent surgery, and comorbid conditions, such as diabetes, HIV infection, cancer, renal failure, and organ transplantation, will be recorded. When a patient is first found to be colonized with *S. aureus*, further data will be collected, including prior number of days in the ICU, prior number of days intubated, dialysis in the ICU, and recent administration of vancomycin, penicillins, cephalosporins, aminoglycosides, or quinolones. Patients will be randomized to mupirocin or control groups accordingly. Throughout the patients' ICU stay and for one month after ICU or hospital discharge (whichever is first), the WebCIS system will be queried for any *S. aureus* clinical isolates, specifically blood, sputum, wound, urine, and catheter tip cultures, which will have been obtained at the discretion of the patients' primary physicians, and processed uniformly in the microbiology lab at CPMC.

This study will be a prospective, randomized, double-blinded, placebo-controlled trial of intranasal mupirocin. Approximately 400 patients in the medical ICU will be followed prospectively over a six-month period. Of these 400, it is estimated that approximately 120 will be colonized with *S. aureus.* The Chi square test will be used to analyze collected data.

D. Subjects Selection

The only criterion needed to be eligible for the study will be admission to the medical ICU. Exclusion criteria will include previous enrollment in the study, known hypersensitivity to mupirocin, receipt of mupirocin in the prior three months, and active *S. aureus* infection upon admission to the ICU.

The ICU at CPMC is something of a cross-section of the population in regard to demography, with the exception of age. There is no preponderance of gender, and minorities and whites are admitted in similar numbers. There is, however, a prevalence of elderly in any adult ICU, and particularly in a medical ICU.

Unfortunately, the critically ill patients who are at most risk for *S. aureus* infections are also the most unlikely to be able to provide informed consent. Many patients are sedated while on mechanical ventilators, and many are in a comatose state. Exemption from the informed consent requirement would then be requested, under the "minimal risk" classification. It is felt that this study should qualify for such an exemption because (1) it involves a procedure for which written consent is not normally required outside the research context (nasal cultures are continually being performed on ICU patients for infection control), (2) the cardiothoracic ICU already applies intranasal mupirocin to all patients prior to surgery

and ICU admission as a standard procedure, and (3) intranasal mupirocin has no known severe side effects.

E. Study Drugs

Calcium mupirocin ointment is a topical antibiotic that is FDA-approved for the eradication of nasal colonization with *S. aureus.* When applied to the nares twice daily for three to five days, it has minimal systemic absorption and eradicated *S. aureus* nasal colonization in 90-95% of patients. Intranasal mupirocin has been very well tolerated in clinical trials. A review of 2186 subjects revealed localized 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 0.96%.[7]

Both mupirocin and mupirocin placebo (the base of inactive ingredients used in calcium mupirocin ointment), made available by Glaxo-SmithKline, will be applied to the nares of control patients by medical ICU nurses.

F. Potential Risks to Patients

The potential risks to patients are limited to the few, minor side effects of mupirocin described above. There is a theoretical risk of the development of resistance to mupirocin in *S. aureus* isolates; however, this has been described only in trials in which multiple or much longer than recommended courses of mupirocin were administered.

G. Potential Benefits

The potential benefits include a reduced risk of *S. aureus* infections in the treated patients. With the use of topical mupirocin, the use of systemic antibiotics such as vancomycin, with its attendant toxicity profile, should be reduced. In addition, a decrease in the use of antiobiotics such as vancomycin should in turn cause a decline in the selective pressure, which has led to high rates of infection with organisms such as vancomycin-resistant enteroccocus.

H. Compensation and Costs to Subjects

The study subjects will not be compensated for participation in this study, nor will they incur any additional costs as a result of their participation in this study.

[7] Hudson IR, et al. The efficacy of intrnasal mupirocin in the prevention of staphylococcal infections: a review of recent experience. Journal of Hospital *infection 1994; 27: 81-98.*