Editorial

Preventing Staphylococcal Infections by Eradicating Nasal Carriage of *Staphylococcus aureus*: Proceeding With Caution

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Staphylococcus aureus is a well-recognized cause of serious community-acquired infections and is a leading cause of nosocomial infections. In addition, it colonizes the anterior nares of 20% to 30% of individuals at any given time. There is a substantial body of evidence that individuals who are asymptomatic nasal carriers of *S aureus* are at increased risk of developing serious staphylococcal infections. Several studies conducted in the 1950s and 1960s demonstrated that the incidence of *S aureus* surgical-wound infections was higher among nasal carriers than among noncarriers.[1] Similarly, a recent case-control study found that preoperative nasal carriage of *S aureus* was significantly more common among cardiothoracic surgery patients who developed *S aureus* wound infections than among controls.[2] In the older studies and in the recent report by Kluytmans et al,[2] phage typing revealed that the nasal and wound isolates frequently were the same phage type.[1]

Similarly, hemodialysis patients who are nasal carriers of *S aureus* are at significantly increased risk of developing staphylococcal infections such as bacteremia or vascular-access infections.[3,4] The article by Boelaert et al[5] in this issue of *Infection Control and Hospital Epidemiology* suggests that this may be due to colonization of the patients' hands with the same strain that is present in the nares. Patients undergoing chronic ambulatory peritoneal dialysis (CAPD) are also much more likely to develop staphylococcal infections if they are nasal carriers of *S aureus*.[6-13] *S aureus* exit-site infections, CAPD-related episodes of peritonitis, and infection-related catheter loss occur more frequently in nasal carriers than among noncarriers.[6,8-10,12,13] In both hemodialysis patients and CAPD patients, phage typing, plasmid analysis, or pulsed-field gel electrophoresis has demonstrated that a majority of isolates recovered from infected sites represented the same strain as that colonizing the patient's nares.[3,6,8-10,14-16]

Other patients with significant underlying diseases or immunosuppression also are at increased risk of staphylococcal infections if they are nasal carriers of *S aureus*. Weinke et al[17] found that patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) were at increased risk of developing *S aureus* septicemia if they were nasal carriers. A few studies have suggested that patients hospitalized in intensive-care units also may experience higher rates of *S aureus* infections if they are nasal carriers.[18-20]

Patients who develop persistent nasal carriage may be colonized on their hands or other areas of intact skin, also, and can disperse the organism into the environment around them. Healthcare workers who have direct contact with persistently colonized patients, or contaminated objects in the immediate environment of such patients, can contaminate their hands and subsequently transmit the organism to other patients. Approximately 20% to 30% of healthcare workers at any given time are also nasal carriers of *S aureus*. A subset of these will remain colonized for prolonged time periods and may spread the

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organism to patients by direct contact transmission.

Because nasal carriage represents an important risk factor for infection in the affected individual, and serves as a source from which the organism can be spread to others, eradicating nasal carriage of *S aureus* has been viewed as a potentially useful control measure for many years. Since the early 1940s, more than 50 different regimens, administered either topically, by nebulization, or orally, have been tested for their ability to eradicate nasal carriage of *S aureus*. Unfortunately, many regimens were not effective, and those that showed promise often were associated with adverse side effects or development of resistance to the agent(s) used.[21]

Mupirocin ointment was introduced in the United Kingdom in the mid-1980s, and subsequently has been demonstrated to be highly effective in eradicating nasal carriage of *S aureus* (both methicillin-susceptible and methicillin-resistant strains), and is well tolerated.[22-24] Many authorities currently consider it to be the agent of choice for eradicating *S aureus* nasal carriage.[25-27] The recent licensure in the United States of a formulation of calcium mupirocin ointment that is approved specifically for intranasal administration (Bactroban Nasal, SmithKline Beecham Pharmaceuticals, Philadelphia, PA) has sparked renewed interest in eradicating nasal carriage as a means of preventing serious staphylococcal infections.

In this issue of *Infection Control and Hospital Epidemiology,* Kluytmans et al[28] report that cardiothoracic surgery patients treated perioperatively with intranasal mupirocin calcium ointment experienced significantly fewer postoperative surgical-site infections (SSI) than historical controls who were not treated. The study must be interpreted with some caution due to its use of historical controls and the fact that patients in the intervention group and controls were not entirely comparable. Nonetheless, the results provide strong suggestive evidence that perioperative eradication of *S aureus* nasal carriage may reduce the incidence of postoperative SSIs in cardiothoracic surgery patients. As pointed out by the authors, confirmatory evidence from a prospective, randomized, placebo-controlled trial is needed before this preventive strategy can be recommended routinely.

In this issue, an accompanying article from the same medical center evaluated the cost-effectiveness of perioperative administration of intranasal mupirocin in patients undergoing cardiothoracic surgery.[29] By taking into account the costs associated with using intranasal mupirocin and the costs attributable to SSIs, the authors estimate that the savings per SSI prevented were $16,633. Additional analysis by the authors suggests that, even if the incidence of SSIs and the costs related to them were lower, perioperative application of mupirocin to all patients having cardiothoracic surgery still would be cost-effective.

Patients undergoing hemodialysis represent another group that may benefit from eradication of *S aureus* nasal carriage. A prospective randomized trial wherein nasal carriers were given either oral rifampin or no treatment revealed that treated patients developed *S aureus* infections significantly less often than control patients.[3] A prospective, placebo-controlled trial by Boelaert et al[14] found that the incidence of *S aureus* carriage and infections were significantly lower in patients who were treated with intranasal mupirocin ointment. A subsequent longitudinal study by Boelaert et al[30] demonstrated that stable nasal carriers who were treated with intranasal mupirocin developed *S aureus* bacteremia significantly less often than historical controls. Holton et al[31] also found that treating nasal carriers with mupirocin significantly reduced the incidence of *S aureus* infections. A longitudinal intervention trial reported in this issue of *Infection Control and Hospital Epidemiology* also found that mupirocin was highly effective in eradicating nasal carriage of *S aureus* in hemodialysis patients and significantly reduced the incidence of *S aureus* bacteremia, when compared to controls.[32] Although the latter study also must be interpreted with some caution, because a historical control group was used, the findings provide additional support for the premise that eradicating nasal carriage of *S aureus* can reduce the incidence of staphylococcal bacteremia substantially in hemodialysis patients. As reported in this issue, the beneficial effect of intranasal mupirocin may be due, in part, to eradicating concomitant hand carriage of *S aureus*.[5] Because of the high costs associated with hemodialysis-related *S aureus* infections, treatment of nasal carriers with mupirocin is likely to be cost-effective, when compared to a policy of no prevention and treatment only of established infection.[33,34]

In CAPD patients, one trial that utilized topical intranasal mupirocin to eradicate *S aureus* nasal carriage reduced the incidence of catheter–exit-site infections and peritonitis.[35] Patients often became recolonized after an initial treatment and required periodic application of mupirocin. A more recent trial studied the effects of either cyclic oral rifampin or daily application of mupirocin to the exit site on the incidence of CAPD-related infections. Patients receiving either regimen experienced fewer exit-site infections, peritonitis, and catheter loss than controls.[36] However, both of the above trials utilized historical controls. A recent randomized trial in children

undergoing peritoneal dialysis found that nasal carriers who received oral rifampin and topical bacitracin suffered fewer dialysis-related *S aureus* infections than those who received no treatment.[11] Finally, long-term oral prophylaxis with trimethoprim-sulfamethoxazole may reduce the incidence of *S aureus* CAPD-related peritonitis.[37] The small sample sizes used in trials of CAPD patients, and the use of historical controls by several investigators, suggests the need for further prospective trials to establish the efficacy of mupirocin or other regimens in prevention of CAPD-related infections. Further studies involving patients with HIV or AIDS, and possibly intravenous drug users or insulin-dependent diabetics, may be indicated to determine if eradication of *S aureus* nasal carriage in these groups can reduce the incidence of serious staphylococcal infections.

Eradicating nasal carriage of *S aureus* also has been used as a means of reducing the chances that the organism will spread from one individual to another. In *S aureus* outbreaks in which there has been convincing epidemiologic evidence that a colonized healthcare worker was the source, eradicating the epidemic strain from the implicated person's nares has controlled the outbreaks.[38-41] In this issue of *Infection Control and Hospital Epidemiology,* Meier et al[42] report that treating three healthcare workers colonized with an epidemic strain of MRSA was associated with termination of an outbreak. Although epidemiologic evidence linking the three healthcare workers to transmission of MRSA was limited (all three worked in the affected burn unit, and all were colonized with the epidemic strain), termination of the outbreak coincided with treatment of the colonized individuals.

In hospitals where MRSA is occurring at epidemic or highly endemic levels, intranasal administration of mupirocin calcium ointment to both patients and personnel colonized with MRSA is considered an appropriate measure, when used in conjunction with other infection control measures.[25,26,43] Routine treatment of all patients and personnel with nasal carriage of MRSA also has been used in some parts of Europe and Australia where the prevalence of MRSA is low, but concern over development of resistance has dissuaded many hospitals in the United States from using mupirocin in this manner.[27] Further studies are warranted to determine if short courses of intranasal mupirocin can be given routinely to MRSA patients in hospitals with low MRSA prevalence rates, without promoting emergence of resistant strains.

Development of resistance among *S aureus* isolates was not observed in the trial that used a single 5-day course of mupirocin in cardiothoracic surgery patients.[28] Periodic, short courses of intranasal mupirocin ointment in hemodialysis patients over a period of 5 years at one dialysis center was associated with recovery of mupirocin-resistant *S aureus* in 2 of 235 patients.[44] In contrast, widespread use of mupirocin for the purpose of controlling MRSA has been associated with emergence of mupirocin-resistant strains of *S aureus* in the United Kingdom and, to a lesser extent, in other areas.[45-47] Usage patterns that appear to have promoted the emergence of mupirocin resistance include frequent or continuous application for periods of weeks or months, especially when applied to large wounds or areas of dermatitis, and widespread use within an institution.[47,48] For example, in the article by Miller et al[49] in this issue, intranasal mupirocin was administered daily to *all* patients in one hospital in an attempt to control an MRSA outbreak. All patients received mupirocin for their entire hospital stay. The widespread and indiscriminate use of mupirocin resulted in emergence of mupirocin-resistant *S aureus*. When it became apparent that the outbreak was continuing despite reasonable measures, the hospital should have conducted additional epidemiologic studies and assessed the adequacy of other infection controls, rather than implementing a policy that resulted in excessive use of mupirocin. The article by dos Santos et al[50] also describes rapid emergence of resistance (including high-level resistance) in a hospital where intranasal mupirocin apparently was used frequently in a nursery. In the two previously mentioned articles, genotypic typing of isolates was not performed, and, as a result, it is not clear if rapid emergence of mupirocin resistance was due to development of resistance in multiple strains of MRSA or to nosocomial transmission of one or two resistant clones. Rapid nosocomial spread of a single strain with high-level mupirocin resistance could destroy the usefulness of topical intranasal mupirocin as a measure for controlling MRSA in an institution.

Methicillin-resistant *S aureus* and susceptible strains of *S aureus* continue to pose formidable problems for patients, clinicians, and infection control personnel in the United States. Relying on a single control measure, such as eradication of nasal carriage, to control nosocomial *S aureus* infections is not a viable strategy. More attention needs to be devoted to improving the adherence of healthcare workers to handwashing and hand hygiene measures, and to establishing which barrier precautions are most efficacious. With regard to mupirocin, the major challenge confronting physicians and infection control programs is to identify the clinical indications and

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treatment protocols that take full advantage of the efficacy and safety of mupirocin, while avoiding the emergence of mupirocin resistance. In patients undergoing operative procedures, screening patients for nasal carriage during pre-admission testing, and treatment of only those individuals with nasal carriage rather than administering mupirocin to all patients, should be considered.[29] In populations at continuing risk, screening patients periodically for nasal carriage and treatment of only those who are colonized may be preferable to daily or periodic treatment of all patients at risk. Daily administration of mupirocin to wounds or sites with foreign bodies for long time periods should be avoided. Whenever possible, treatment courses should be limited to 5 days or possibly shorter. Studies designed to evaluate new indications for intranasal mupirocin ointment should include prospective surveillance for mupirocin-resistant *S aureus*. Hopefully, expanded use of intranasal mupirocin ointment utilizing these principles will lead to better prevention of serious staphylococcal infections while preserving the utility of mupirocin.

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VRE in Liver Transplant Recipients

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Investigators at Mount Sinai Medical Center in New York City reported on a study of risk factors for acquisition of, and mortality due to, nosocomial infections with vancomycin-resistant *Enterococcus faecium* (VREF) in orthotopic liver transplant (OLT) recipients. Thirty-two VREF-infected OLT patients (cases) were compared with 33 randomly selected OLT recipients (controls). More antibiotics were administered preoperatively to cases (mean, 4 antibiotics per patient for 474 antibiotic-days) than controls (mean, 1.8 antibiotics per patient for 131 antibiotic-days). Cases were more likely than controls to have received vancomycin therapy preoperatively and to have been hospitalized in the intensive-care unit (ICU) preoperatively. Logistic regression revealed that the risk factors for acquisition of VREF infection were surgical reexploration and a prolonged stay in the surgical ICU postoperatively. In the cases, the risk factors for mortality were admission to the ICU preoperatively and hemodialysis. The mortality rate associated with polymicrobial bloodstream infections was 100% despite appropriate therapy. Sixteen and 18 cases received parenteral chloramphenicol and doxycycline, respectively, for treatment of VREF infection. There were no hematologic adverse effects attributed to chloramphenicol treatment. DNA analysis of selected *E faecium* isolates suggested that infections were due to multiple clones.

The authors concluded that antibiotic usage provides for a selection pressure that probably contributes to VREF colonization and that infection with VREF is a predictor of morbidity and mortality in OLT patients. The authors discourage the use of vancomycin as a perioperative prophylaxis in all institutions that still employ this practice.

FROM: Pananicolaou GA, Meyers BR, Meyers J, et al. Nosocomial infections with vancomycin resistant *Enterococcus faecium* in liver transplant recipients: risk factors for acquisition and mortality. *Clin Infect Dis* 1996;23:760-766.