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RESEARCH ARTICLE

Nasal Decolonization to Reduce Surgical Site Infections

Edward J. Septimus

Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute
Boston, Massachusetts, USA

*eseptimus@gmail.com

ABSTRACT

Background: Surgical site infections is one of the most common healthcare-associated infections. *Staphylococcus aureus* remains the most common etiologic agent causing surgical site infections. Studies confirm *Staphylococcus aureus* carriage increases the risk of *Staphylococcus aureus* surgical site infections. The purpose of this paper is to review the strategies to reduce surgical site infections due to *Staphylococcus aureus* focusing on nasal decolonization.

Results: Published studies indicate screening patients for *Staphylococcus aureus* nasal carriage and decolonizing carriers during the preoperative period decreases the risk of *S aureus* surgical site infections in cardiac and orthopedic surgery. Most studies use combined chlorhexidene bathing and mupirocin for patients colonized with *Staphylococcus aureus* since colonization of multiple body sites is common and combination chlorhexidene bathing and intranasal mupirocin has been shown to be more effective at eradicating *Staphylococcus aureus* colonization. Mupirocin remains the best topical agent at eradicating nasal *Staphylococcus aureus.* Mupirocin has been shown to eliminate nasal colonization by over 90% with a five-day course, however, concerns over resistance have led to development of alternative agents. Nasal povidone-iodine, alcohol-based nasal antiseptic, and photodynamic therapy are promising new interventions, but more studies are needed.

Conclusions: Short term nasal mupirocin is still the most studied and effective topical agent in eradicating *Staphylococcus aureus* nasal colonization. However, increasing mupirocin resistance remains an ongoing concern and newer agents are needed.

Keywords: nasal decolonization, surgical site infections, mupirocin, healthcare-associated infections

Introduction

Health care-associated infections (HAIs) continue to pose serious threats to the safety of patients hospitalized in the United States. In a recent publication, the most common HAIs included pneumonia, gastrointestinal infections, and surgical-site infections (SSIs)[1] *Staphylococcus aureus (S aureus)* remains the most common etiologic agent causing SSIs.[2] SSIs due to *S aureus* increase costs and postoperative mortality.[3,4] The purpose of this paper is to review the strategies to reduce SSIs due to *S aureus* focusing on nasal decolonization.

Colonization with *S aureus* is considered the most important factor of subsequent invasive *S aureus* infections. Between 15 and 30% of healthy adults are nasally colonized with methicillin-susceptible S. aureus (MSSA), and 1% to 3% are nasally colonized with methicillin-resistant *S aureus* (MRSA)[5] *S. aureus* colonization at other body sites, including the pharynx, groin, perianal region, or axilla, is also associated with development of *S. aureus* infection. Colonization of multiple body sites is common. Kline et al[6] found extra-nasal *S aureus* colonization in nearly 50% of *S aureus* carriers. One study found that the likelihood of developing an MRSA infection increases as more body sites are MRSA colonized.[7] Among S. aureus nasal carriers, approximately 40% are persistently colonized and 60% are intermittently colonized.[8] Those who are persistently colonized with S. aureus are at a higher risk of infection than intermittent carriers or noncarriers.[9]

Several studies confirm *S aureus* carriage increases the risk of *S. aureus* SSIs.[10-13] There is strong evidence that nasal and skin decolonization prior to cardiac and orthopedic surgery is effective in reducing SSIs caused by MSSA or MRSA. Screening patients for *S. aureus* nasal carriage and decolonizing carriers during the preoperative period decreases the risk of these infections.[11,14] A meta-analysis of 17 randomized control trials (RCTs) or quasi-experimental studies that included cardiac and orthopedic surgery patients evaluated the effectiveness of preoperative decolonization.[15] All but one of the studies included in the meta-analysis used mupirocin ointment for nasal decolonization.[16] The meta-analysis found that decolonization was significantly protective against Gram-positive SSIs, specifically S. aureus SSIs. One of the larger RCTs included in that meta-analysis was performed in the Netherlands.[14] That study used PCR to rapidly identify *S. aureus* carriers and randomized 918 carriers to either placebo or nasal mupirocin and CHG bathing. It found a greater than-2-fold decline in *S. aureus* infections and more than a 4-fold decline in *S. aureus* complex SSIs. In another large, quasi-experimental study prospectively evaluated 992 consecutive open-heart surgery patients who did not receive mupirocin prophylaxis in a 2-year preintervention period. They then began providing open heart surgery patients with intranasal mupirocin and chlorhexidene (CHG) bathing on the night before and morning of surgery, as well as mupirocin twice daily for 5 days postoperatively. This

intervention group included 854 consecutive patients was followed prospectively for the intervention period. The rate of sternal wound infections decreased significantly from 2.7% (27 of 992) in the preintervention group to 0.9% (8 of 854) in the intervention group (*P* 0.005).[17]

A recent pragmatic quasi-experimental study implemented an evidence-based bundled in 20 hospitals in order to prevent complex *S. aureus* SSIs after cardiac surgery and hip and knee arthroplasty.[18] [Figure] The bundle included CHG bathing for all patients, screening for MRSA and MSSA nasal colonization, nasal mupirocin decolonization for *S. aureus* carriers, and both vancomycin and cefazolin perioperative prophylaxis for MRSA carriers. The mean rate of complex *S. aureus* SSIs significantly decreased from 36 infections per 10,000 operations during the baseline period to 21 infections per 10,000 operations during the intervention period (rate ratio 0.58; 95% CI, 0.37 to 0.92). This significant decline was also seen when the study was limited to only patients undergoing hip and knee arthroplasty (rate ratio 0.48; 95% CI, 0.29 to 0.80), but it was not statistically significant when the study was limited to only patients undergoing cardiac surgery(rate ratio 0.86; 95%CI, 0.47to 1.57).However, the number of cardiac surgery patients was much smaller than the number of orthopedic surgery patients, so the cardiac analysis may have been underpowered.

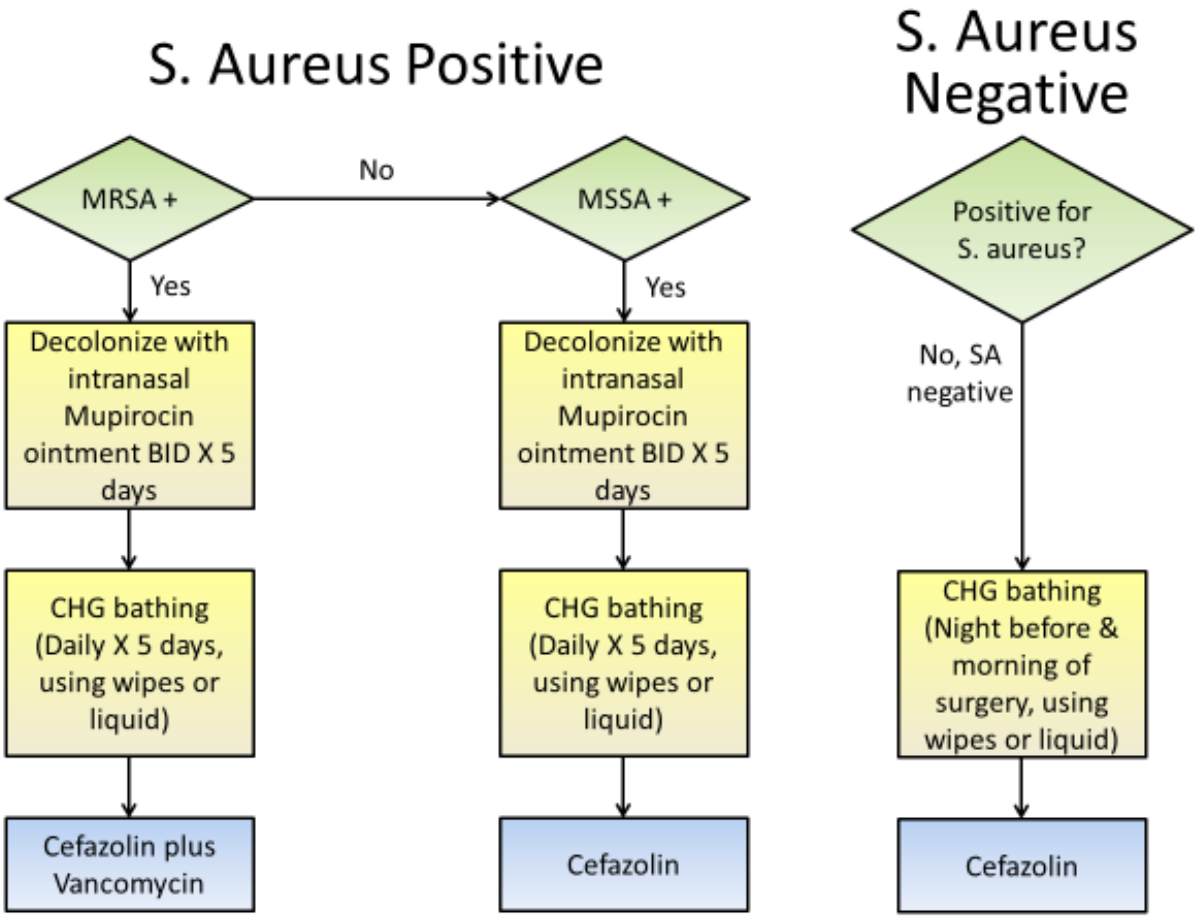

FIGURE-BUNDLE

Lastly a recent publication on the prevalence of health care-associated infections in US hospitals reported a reduction of SSIs. They suggested part of reduction may reflect greater use of decolonization of patients with *S aureus* colonization.[1]

Most studies of *S. aureus* decolonization use combined CHG bathing and nasal mupirocin since colonization of multiple body sites is common and combination CHG bathing and intranasal mupirocin is more effective in eradicating *S aureus* colonization.[6] Several studies suggest nasal decolonization, however, may be the most important component for *S aureus* decolonization.[11,19] Therefore, the rest of this paper will focus on nasal decolonization strategies and alternatives to mupirocin. [Table]

Current Nasal Decolonization Agents

Mupirocin

Povidone-Iodine

Alcohol-based

Photodynamic therapy

TABLE

Mupirocin

Nasal mupirocin is the most widely used topical antibacterial agent. Mupirocin inhibits synthesis of bacterial proteins by reversibly binding to bacterial isoleucyl-tRNA synthetase. It has excellent activity against staphylococci, most streptococci, and some gram-negative organisms, including *Neisseria gonorrhoeae*, *Haemophilus influenzae*, and *Moraxella catarrhalis.*[20] There are two different formulations of mupirocin, depending on the vehicle. The first is a nasal ointment in petrolatum. The second is a generic topical ointment that utilizes a polyethylene glycol vehicle. Both have been used for nasal decolonization; however, the generic topical ointment may be used more frequently due to its lower cost. Side effects are uncommon and are mostly local site reactions such as stuffy nose or burning or stinging of the nose.

A RCT comparing mupirocin against a placebo found that 83% of the mupirocin group were decolonized, compared with only 27% of the placebo group (*P* 0.001). That trial also found that 81% of carriers who received three to five doses of mupirocin were decolonized, compared with 93% of carriers who received six or more doses of mupirocin (*P* 0.001).[11] Currently, mupirocin is recommended to be applied to the anterior nares twice daily for 5 days.

A systematic literature review evaluated 23 clinical trials, including 12 trials that evaluated topically applied antibiotics. The authors concluded that short-term nasal mupirocin was the most effective treatment for MRSA

decolonization, with success rates of 90% at 1 week after treatment and approximately 60% after a longer follow-up time.[21] The effectiveness of mupirocin was similar for both MSSA and MRSA carriers. A Cochrane review aimed to determine whether the use of mupirocin among *S. aureus* carriers reduced *S. aureus* infections. Only RCTs comparing a mupirocin group with a control group that received either no treatment, placebo, or an alternative nasal treatment were included. The authors found that mupirocin was associated with a significant reduction in *S. aureus* infections (relative risk [RR] 0.55; 95% confidence interval [CI], 0.43 to 0.70).[22] Lastly, two systematic literature reviews and meta-analyses of published studies found a protective effect of mupirocin decolonization against surgical site infections (SSIs), especially among nongeneral surgery such as cardiac surgery, orthopedic surgery, and neurosurgery. [15,23]

Although mupirocin appears to be an effective topical agent, resistance among *S. aureus* has now been identified in multiple studies, especially with widespread use over prolonged periods. [24,25] More importantly, studies have shown that high-level mupirocin-resistant (HL-MR) *S. aureus* results in decolonization failure. The association between low level mupirocin (LL-MR) and failure of mupirocin decolonization is unclear. Walker et al. [26]published a prospective study to determine the efficacy of nasal mupirocin in decolonizing patients with mupirocin-susceptible MRSA (MS MRSA) and mupirocin resistant MRSA, both LL-MR MRSA and HL-MR MRSA. Patients received 2% mupirocin nasally twice daily for 5 days. They were then cultured at day 3 and weeks 1, 2, and 4 after treatment. Nares cultures at day 3 posttreatment were negative for 79% of patients who had MS MRSA, 80% of patients who had LL-MR MRSA, and 28% of patients who had HL-MR MRSA. However, at the follow-up 1 to 4 weeks later, the sustained decolonization for patients with HL-MR MRSA and LL-MR MRSA was low (25% each, compared to 91% in patients colonized with MS MRSA). This result suggests that mupirocin probably temporally suppresses growth of LL-MR MRSA but does not result in sustained decolonization. Posttreatment cultures usually had the same genotype and susceptibility phenotypes as the corresponding baseline cultures. This appears to show endogenous recolonization rather than exogenous acquisition.

In contrast to unrestrictive use, short-term use of nasal mupirocin for perioperative prophylaxis to prevent *S. aureus* SSIs does not appear to be associated with significant increased mupirocin resistance. Perl et al. treated over 2,000 patients with mupirocin, performed mupirocin susceptibility testing, and found that only 6 of the 1,021 isolates (0.6%) were mupirocin resistant.[11] Another study described the results of repeated point-prevalence surveys over 4 years to determine if mupirocin resistance had emerged in surgical units using preoperative prophylaxis with 5 days of nasal mupirocin. They found no evidence of sustained emergence or spread of mupirocin resistance. No HL-MR strains were identified.[27] Finally, a Dutch study evaluated over 20,000 patients who received

mupirocin prophylaxis for major cardiothoracic surgery. No mupirocin resistance emerged.[22] Despite these promising results, all these studies were done a decade ago. More recently Hayden et al[28] evaluated mupirocin susceptibility of MRSA in the REDUCE-MRSA Trial. Isolates from the baseline and intervention periods were collected and tested for susceptibility to mupirocin by Etest. At baseline, 7.1% of MRSA isolates expressed low-level mupirocin resistance, and 7.5% expressed high-level mupirocin resistance. The study found the odds of mupirocin-resistance were no different in the intervention versus baseline periods across arms, but confidence limits were broad and therefore, results should be interpreted with caution. In summary, although mupirocin currently may be the best option for topical *S. aureus* nasal decolonization, the use of mupirocin may lead to mupirocin resistance and treatment failures, specifically with widespread use over long periods of time. Thus, alternatives to mupirocin for eradication of patients colonized with *S aureus* are needed.

Povidone-Iodine

Povidone-iodine (PI) is a complex of polyvinylpyrrolidine and tri-iodine ions that has been widely used as an antiseptic on skin, wounds, and mucous membranes. PI has activity against both gram-positive and gram-negative bacteria. Specifically, PI has activity against both MSSA and MRSA. Hill and Casewell[29] assessed the *in vitro* activity of 5% PI as an alternative to mupirocin for the nasal decolonization of *S. aureus*. In that study, PI was able to eliminate 11 test organisms, including both mupirocin sensitive and mupirocin-resistant MRSA. The results suggested that PI may be a good decolonizing agent for the prevention of infections due to *S. aureus*, including MRSA and mupirocin-resistant strains, however, the addition of nasal secretions *in vitro* reduced the PI activity. This concern was confirmed by Rezapoor et al [30] who published a randomized, placebo-controlled study comparing 10% off-the-shelf PI, 5% PI-based nasal antiseptic (PINA), or saline (placebo) for nasal decolonization. Four hundred and twenty-nine patients undergoing primary or revision total joint arthroplasty, femoroacetabular osteoplasty, pelvic osteotomy, or total shoulder arthroplasty were included. Baseline cultures were taken immediately preoperatively, followed by treatment of both nares twice for 2 minutes with 4 applicators. Reculturing of the right nostril occurred at 4 hours and the left at 24 hours. Ninety-five of the 429 patients (22.1%) had a positive culture result for *S. aureus*. Of these 95, 29 were treated with off-the-shelf PI, 34 with PINA, and 32 with saline swabs. At 4 hours post-treatment, *S. aureus* culture was positive in 52% off-the-shelf PI patients, 21% PINA patients, and 59% saline patients. After 24 hours posttreatment, *S. aureus* culture was positive in 72% off-the-shelf PI patients, 59% PINA patients, and 69% saline group. PINA was significantly more effective at decolonizing *S. aureus* over the 4-hour time interval (P = .003). The authors concluded off the-shelf PI swabs were not as effective at 4 hours as the specifically manufactured

product for *S. aureus* decolonization There are now currently 3 nasal iodophor antiseptics (5% and 10%) with properties which enables better adherence to nasal mucosa.

Phillips et al. [31] performed a prospective, open-label trial of twice-daily nasal mupirocin for 5 days before surgery compared to two applications of a 5% nasal PI solution within 2 hours of surgical incision in patients undergoing arthroplasty or spine fusion surgery. Both groups also received CHG baths, with 2% cloths, the night before and the morning of surgery. A total of 763 surgical procedures were evaluated among patients who received mupirocin and 776 surgical procedures among patients who received PI. In the per-protocol analysis, *S. aureus* deep SSIs developed in five patients (0.66%) who received mupirocin and zero patients (0.00%) among those who received PI (*P* 0.03). In addition, if the preoperative nasal culture was positive for *S. aureus*, another nasal culture was obtained within 1 to 3 days after surgery. The proportion of postoperative negative nasal cultures was 92% (78 of 85 patients) for those assigned to mupirocin versus 54% (45 of 84 patients) for those assigned to PI. The authors commented that this was not unexpected, since mupirocin was intended to eradicate colonization while PI was intended only to suppress *S. aureus* around the perioperative period. This study has several limitations. First it was a single-site study, and the results may not be generalizable. Second, the authors could not perform multivariate analysis due to the small sample size. Third, patients were not followed after discharge to identify late infections.

Bebko and colleagues [32] published a second study using a preoperative decontamination protocol to reduce SSIs in orthopedic patients undergoing elective hardware implantations. This was a quasi-experimental, retrospective, nonrandomized trial comparing a bundled intervention to historical controls. The intervention consisted of application of 2% CHG and oral CHG the night before and morning of surgery plus an intranasal PI solution the morning of surgery. Patients were evaluated for SSI for the 30 days after their surgery date. Rates of SSIs were statistically significantly lower in the intervention group than in the control group (1.1% versus 3.8%; *P* 0.02). However, that study was limited because it was not a randomized trial, patients were only followed for 30 days, and information regarding the MRSA carrier status of patients before and after decontamination was not collected; therefore, the study did not allow for evaluation of the effect of nasal decolonization alone versus other interventions. Nasal PI has not been studied in other clinical settings. Currently nasal PI may be a potential alternative to nasal mupirocin for prevention of SSIs, but more studies are needed.

Alcohol-Based Nasal Antiseptic

Alcohols are antimicrobial by denaturing proteins. Alcohol has bactericidal activity against most gram-positive and gram-negative bacteria, including MDROs. Alcohol concentrations between 60 and 90% are most effective. Most alcohol-based hand antiseptics contain either isopropanol or ethanol.[33] Steed et al. [34] published a double-

blinded, placebo controlled RCT testing the effectiveness of an alcohol-based nasal antiseptic in reducing *S. aureus* nasal colonization in colonized health care workers. Health care workers testing positive for nasal *S. aureus* colonization were treated three times during the day with a nasal alcohol-based antiseptic or placebo. The antiseptic formulation contained 70% ethanol combined with natural oil emollients and the preservative benzalkonium chloride. Nasal *S. aureus* and total bacterial colonization levels were determined before and at the end of a 10-hour shift. Antiseptic treatment reduced *S. aureus* colony forming units (CFUs) from baseline by 82% (mean) and 99% (median) (*P* 0.001). Mullen et al [35] published a brief report in 2017 using in an alcohol-based nasal antiseptic decolonization to reduce *Staphylococcus* species surgical site infections. All patients scheduled for spine surgery were included in the study. Records from 1,073 spine surgical patients undergoing inpatient or outpatient procedures (400 and 673 in the baseline and intervention periods, respectively) were part of the study. Investigators combined immediate presurgical application of an alcohol-based nasal antiseptic with existing chlorhexidine bath or wipes in a comprehensive pre and postoperative decolonization protocol After surgery, patients were expected to follow the regular 3 times daily cycle of staff-applied alcohol-based application in the postsurgical units until discharge, at which time the patient and family coach were instructed to continue applications for an additional 5-7 days with the remaining antiseptic. Mean infection rates were significantly decreased by 81% from1.76 to 0.33 per 100 surgeries during the 15-month trial, when compared with the prior 9-month baseline. (P=.036). This is a small, single-center quasi-experimental intervention which needs confirmation.

Photodynamic Therapy (PDT)

The use of a light source, such as a laser, has been suggested as an alternative method to eliminate *S aureus* nasal carriage. Photodynamic therapy (PDT) consists of the combination of a light-activated chemical and UV or infrared wavelengths. This combination creates free radicals that damage bacterial cell walls and membranes. In preliminary human testing, PDT eradicated nasal MRSA, with total treatment times of less than 10 min.[36] In a small cohort study, Bryce et al. [37]found that the colonization rates for MSSA and MRSA were 24.4% and 0.9%, respectively, before PDT therapy. Of those who received PDT (0.1% methylene blue plus laser), 85% had a reduced *S. aureus* burden in the anterior nares as measured by semiquantitative colony counts. In a follow-up study, patients undergoing elective cardiac surgery, orthopedic surgery, spinal surgery, vascular surgery, thoracic surgery, or neurosurgery were asked to bathe with 2% CHG cloths in the 24 h prior to surgery and were given intranasal PDT (0.1% methylene blue plus laser) in the preoperative area. There was a statistically significant decrease in the SSI rate when comparing treated patients to a historical control group (1.6% versus 2.7%; *P* 0.0004; OR 1.73; 95% CI, 1.28 to 2.34). However, the study was limited, since

the benefits of CHG alone compared to PDT alone were not evaluated. PDT is another promising approach for nasal S *aureus* decolonization, but larger clinical trials are needed to evaluate the impact on clinically significant infections.

Conclusion

Short term nasal mupirocin is still the most studied and effective topical agent in eradicating *S aureus* nasal colonization. However, increasing mupirocin resistance remains an ongoing concern. Therefore, alternative nasal strategies are needed. Nasal PI, alcohol-based nasal antiseptic, and PDT are promising new interventions, but more studies are needed. When pre-surgical decolonization is indicated, intranasal mupirocin plus CHG bathing is recommended since other sites are often colonized with *S aureus* in addition to the nares. Finally, a bundle approach [Figure] including CHG bathing, screening for MRSA and MSSA nasal colonization, nasal mupirocin decolonization for *S. aureus* carriers, and both vancomycin and cefazolin perioperative prophylaxis for MRSA carriers is the favored strategy to prevent *S aureus* SSIs in cardiac and orthopedic surgery. Should we expand of these strategies for additional surgical patient populations such as complicated spine, as well as nonsurgical invasive procedures with implants? For example, patients receiving implants such as cardiac implantable electronic devices (CIED) have been associated with significant numbers of postimplant infections, often caused by S aureus.[38] For patients known to be colonized with MRSA or MSSA prior to a CIED procedure, a multigroup British Working Party guideline now recommends the use of nasal and topical antimicrobial agents preprocedure in order to suppress carriage and reduce the risk of infection.[39] Looking to the future we also need to determine if the widespread use of CHG-based products promotes reduced CHG activity. Testing for CHG susceptibility is currently not standardized and the clinical impact of reduced chlorhexidine susceptibility in bacteria is unknown and not yet well-defined.

Corresponding author:
Edward J Septimus, M.D.
Department of Population Medicine
Harvard Pilgrim Health Care Institute
401 Park Drive, Suite 401 East
Boston, MA 02215
Email: eseptimus@gmail.com

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