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Author(s): Michael Phillips, MD; Andrew Rosenberg, MD; Bo Shopsin, MD, PhD; Germaine Cuff, RN, PhD; Faith Skeete, RN; Alycia Foti, BA; Kandy Kraemer, RN; Kenneth Inglima, MS; Robert Press, MD, PhD; Joseph Bosco, MD

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ORIGINAL ARTICLE

Preventing Surgical Site Infections: A Randomized, Open-Label Trial of Nasal Mupirocin Ointment and Nasal Povidone-Iodine Solution

Michael Phillips, MD;^{1,2} Andrew Rosenberg, MD;^{1,2} Bo Shopsin, MD, PhD;^{1,2} Germaine Cuff, RN, PhD;²
Faith Skeete, RN;¹ Alycia Foti, BA;¹ Kandy Kraemer, RN;¹ Kenneth Inglima, MS;¹
Robert Press, MD, PhD;^{1,2} Joseph Bosco, MD^{1,2}

BACKGROUND. Treatment of *Staphylococcus aureus* colonization before surgery reduces risk of surgical site infection (SSI). The regimen of nasal mupirocin ointment and topical chlorhexidine gluconate is effective, but cost and patient compliance may be a barrier. Nasal povidone-iodine solution may provide an alternative to mupirocin.

METHODS. We conducted an investigator-initiated, open-label, randomized trial comparing SSI after arthroplasty or spine fusion in patients receiving topical chlorhexidine wipes in combination with either twice daily application of nasal mupirocin ointment during the 5 days before surgery or 2 applications of povidone-iodine solution into each nostril within 2 hours of surgical incision. The primary study end point was deep SSI within the 3 months after surgery.

RESULTS. In the modified intent-to-treat analysis, a deep SSI developed after 14 of 855 surgical procedures in the mupirocin group and 6 of 842 surgical procedures in the povidone-iodine group ($P = .1$); *S. aureus* deep SSI developed after 5 surgical procedures in the mupirocin group and 1 surgical procedure in the povidone-iodine group ($P = .2$). In the per protocol analysis, *S. aureus* deep SSI developed in 5 of 763 surgical procedures in the mupirocin group and 0 of 776 surgical procedures in the povidone-iodine group ($P = .03$).

CONCLUSIONS. Nasal povidone-iodine may be considered as an alternative to mupirocin in a multifaceted approach to reduce SSI.

TRIAL REGISTRATION. ClinicalTrials.gov identifier: NCT01313182.

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An estimated 290,000 surgical site infections (SSIs) occur after a procedure in the United States annually, accounting for 22% of all healthcare-associated infections.¹ Deep SSIs after arthroplasty or spine fusion surgery complicate up to 2% of cases, often resulting in revision surgery and prolonged use of antibiotics.^{2,3} The patient morbidity and healthcare system cost is tremendous; an estimated \$566 million is spent annually in hospital treatment costs for arthroplasty SSI alone.⁴ Prevention of SSI by the application of topical chlorhexidine to the skin and treatment of *Staphylococcus aureus* colonization with intranasal mupirocin has been studied. When nasal mupirocin was combined with use of chlorhexidine soap in a randomized, double-blind, placebo-controlled trial that included 808 *S. aureus*-colonized surgical patients, a significant reduction in deep *S. aureus* SSI was realized.⁵

To reduce the risk of SSI after arthroplasty and spine fusion surgery at our institution, we historically prescribed brand nasal mupirocin ointment for application to the nasal mucosal surfaces twice a day during the 5 days before surgery and provided instructions for the use of chlorhexidine soap on the evening before surgery. After implementation of this

protocol, we conducted an anonymous patient survey to measure compliance. Although 94% of patients used the chlorhexidine soap, only 86% applied the nasal mupirocin ointment, and 8% of patients stated that they found it hard or very hard to purchase the ointment due to cost.⁶ Our survey results, plus reports of emerging mupirocin resistance, led us to search for alternatives.⁷⁻¹¹ Povidone-iodine solution is a broad-spectrum antiseptic suitable for suppression of *S. aureus* in nasal secretions.¹³ Our hypothesis was a one-time application of nasal povidone-iodine just before surgery would be as effective as twice daily application of nasal mupirocin during the 5 days before surgery in preventing SSI and would provide a more convenient option for patients at a lower cost.

METHODS

Study Treatment

We conducted an investigator-initiated, prospective, open-label, randomized trial of twice daily application of nasal mupirocin ointment (Bactroban Nasal, mupirocin calcium

Affiliations: 1. New York University Hospital Center, New York, New York; 2. New York University School of Medicine, New York, New York.

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TABLE 1. Demographic and Clinical Characteristics of Subjects in the Modified Intention-to-Treat Analysis

Characteristic	Mupirocin group (n = 855)	Povidone-iodine group (n = 842)
Age, years		
Median	62.4	61.8
Range	19.2–93.2	19.1–92.4
Female sex	523 (61)	499 (59)
Race		
White	677 (79)	670 (80)
Black	138 (16)	145 (17)
Asian	23 (2.7)	21 (2.5)
Other ^a	22 (2.6)	7 (0.8)
Ethnic group		
Hispanic	97 (11)	88 (10)
Non-Hispanic	746 (87)	749 (89)
BMI		
Median	29.5	29.5
Range	14.9–58.9	12.0–57.3
Current smoking	104 (12)	114 (13)
Medical comorbidity		
Diabetes mellitus	110 (13)	104 (12)
Rheumatoid arthritis	36 (4.2)	36 (4.3)
Preoperative <i>Staphylococcus aureus</i> colonization		
MSSA	135 (16)	130 (15)
MRSA	24 (2.9)	21 (2.5)
Preoperative serum albumin level, g/dL		
Median	4.2	4.2
Range	2.9–6.9	2.8–5.2
ASA score		
1	35 (4.5)	39 (5.0)
2	486 (62)	524 (68)
3	254 (32)	206 (27) ^b
4	9 (1.1)	4 (0.5)
Receipt of blood products	179 (21)	158 (19)
Postoperative day 1 glucose level \geq 180 mg/dL	40 (4.7)	46 (5.5)
Procedure		
Spine fusion	148 (17)	145 (17)
Spine fusion, revision	12 (1.4)	10 (1.2)
Arthroplasty surgery		
Knee	299 (35)	297 (35)
Knee, revision	24 (2.8)	24 (2.8)
Hip	298 (35)	293 (35)
Hip, revision	35 (4.1)	29 (3.4)
Shoulder	33 (3.9)	42 (5.0)
Shoulder, revision	7 (0.8)	1 (0.1)
Bilateral arthroplasty	49 (6.2)	73 (9.3) ^b
Median operative time, minutes		
Spine fusion	202	205
Spine fusion, revision	256	299
Arthroplasty surgery, unilateral		
Knee	93	87
Knee, revision	137	128
Hip	94	93
Hip, revision	138	123
Shoulder	106	109
Shoulder, revision	122	119

NOTE. Data are no. (%) of patients, unless otherwise indicated. ASA, American Society of Anesthesiologists; BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

^a Other includes Native Hawaiian/Pacific Islander, American Indian/Alaska native, and no race declared.

^b $P < .05$ by χ^2 test.

ointment 2%; GlaxoSmithKline) on the intranasal mucosal surfaces of each nostril during the 5 days before surgery compared with 2 applications of povidone-iodine solution (3M Skin and Nasal Antiseptic, povidone-iodine solution 5% w/

w; 3M) on the intranasal mucosal surfaces of each nostril within 2 hours of surgical incision. The povidone-iodine is applied by dipping a swab into the solution, then rotating the swab over the intranasal mucosal surface for 30 seconds;

this process is performed twice for both nostrils, using a new swab for each of the 4 applications. Both treatments were combined with the application of 6 chlorhexidine wipes (2% Chlorhexidine Gluconate Cloth Patient Preoperative Skin Preparation; Sage Products) on the skin the evening before and again the morning of surgery. One wipe was used for each of the following 6 skin areas: neck, chest, and arms; abdomen and groin; right leg and foot; left leg and foot; and back and buttocks. The patient was instructed to allow the chlorhexidine to air dry on the skin, to not bathe after the wipes were applied, and to avoid use of moisturizers or other lotions. Patients received verbal and written instructions and had access to a 24-hour telephone number in case of study treatment-related questions.

Subjects

From March 2011 through March 2012, we recruited subjects at least 18 years of age who presented to the presurgical assessment clinic before primary or revision arthroplasty and spine fusion surgery. Exclusion criteria included pregnancy, breastfeeding, allergy to mupirocin or povidone-iodine, interval from presurgical assessment clinic visit to surgery of less than 7 days, and an infectious indication for surgery. The need for nasal intubation (typically for cervical spine surgery) was added as an exclusion criterion shortly after study initiation. All subjects underwent the routine preoperative evaluation appropriate for their planned surgical procedure, including pregnancy testing, tobacco cessation education, nasal culture for *S. aureus*, and collection of blood samples for hematology and serum chemistry testing.

Randomization, Perioperative Surgical Prophylaxis, and Evaluation of *S. aureus* Isolates

Subjects were stratified by arthroplasty or spine fusion surgery and then randomized 50 : 50 to either mupirocin or povidone-iodine treatment groups in blocks of 100. Research personnel evaluated subjects in the preoperative holding area to determine chlorhexidine compliance and to either apply povidone-iodine or assess compliance with mupirocin.

Subjects received routine antimicrobial prophylaxis, surgical site preparation, and surgical draping. Primary antimicrobial prophylaxis was cefazolin (1 g); subjects with reported β -lactam allergy received clindamycin (600 mg), and those colonized with methicillin-resistant *S. aureus* (MRSA) received vancomycin (1 g). Antibiotic infusion was started within 1 hour of incision (2 hours for vancomycin) and was readministered per accepted guidelines. Weight-based dosing was employed at the discretion of the anesthesiologist. Standard preoperative surgical site skin preparation consisted of a 2% chlorhexidine gluconate/70% isopropyl alcohol solution. If needed, electrical clippers were used for hair removal at the surgical site, and patients were actively warmed in the intraoperative and postoperative period.

Subjects were reassessed within 1 to 3 days after surgery

to record adverse events related to study treatment. If the preoperative nasal culture grew *S. aureus*, a second nasal culture was ordered to determine rate of clearance. If the postoperative culture had positive results, relatedness of preoperative and postoperative isolates was characterized by *spa* typing.¹⁴⁻¹⁶ Identification of MRSA was based on routine criteria, including the coagulase tube test and the automated Vitek 2 system (bioMérieux), and mupirocin susceptibility testing was performed by E-test. Isolates with a mupirocin minimum inhibitory concentration of 8 μ g/mL or greater were considered to be mupirocin resistant.^{11,17}

End Points

The primary study end point was onset of a deep SSI within the 3 months after surgery. Potential SSIs were identified by review of microbiology reports, hospital readmissions, reports received from other healthcare facilities (as mandated by New York State Department of Health regulations), and during infection prevention and control (IPC) rounds on inpatient units. Patient records were reviewed, and the SSI was classified using the Centers for Disease Control and Prevention's National Healthcare Safety Network case definitions. IPC practitioners reviewing the records were blinded to study participation and receipt of study treatment; potential cases were discussed at a group meeting to ensure consistent application of the SSI case definition. Infections in subjects were retrieved from the IPC database maintained for routine SSI surveillance.

Statistical Analysis

We expected no difference in SSI between treatment groups. Our baseline combined arthroplasty and spine fusion deep SSI rate was 1.5 cases per 100 procedures, with *S. aureus* as the infecting pathogen in 37% of cases. During the baseline period, all patients received a prescription for mupirocin ointment with instructions to apply to the nares twice a day for the 5 days before surgery and were provided chlorhexidine wipes for use on the evening before and morning of surgery. We assumed that a doubling of SSI rate in the povidone-iodine group would be clinically relevant and calculated that a sample size of 3,000 subjects would provide a power of 80% to detect a doubling of SSI rate to 3.0 cases per 100 procedures with an α level of 0.05 and a 2-sided Fisher exact test. Analysis was conducted using SAS version 9.1 (SAS). Categorical variables were analyzed using Fisher exact test.

The modified intent to treat (MITT) analysis included those who were enrolled and met eligibility requirements for the study, and the per protocol (PP) analysis included all eligible enrolled subjects who completed the assigned study regimen. Completion of the study regimen was defined as 2 applications of 6 chlorhexidine wipes to specific areas of skin from chin to toe, receiving appropriate perioperative antimicrobial prophylaxis, and receiving either 7-10 applications of mupirocin to the nares over the 5 days before surgery or

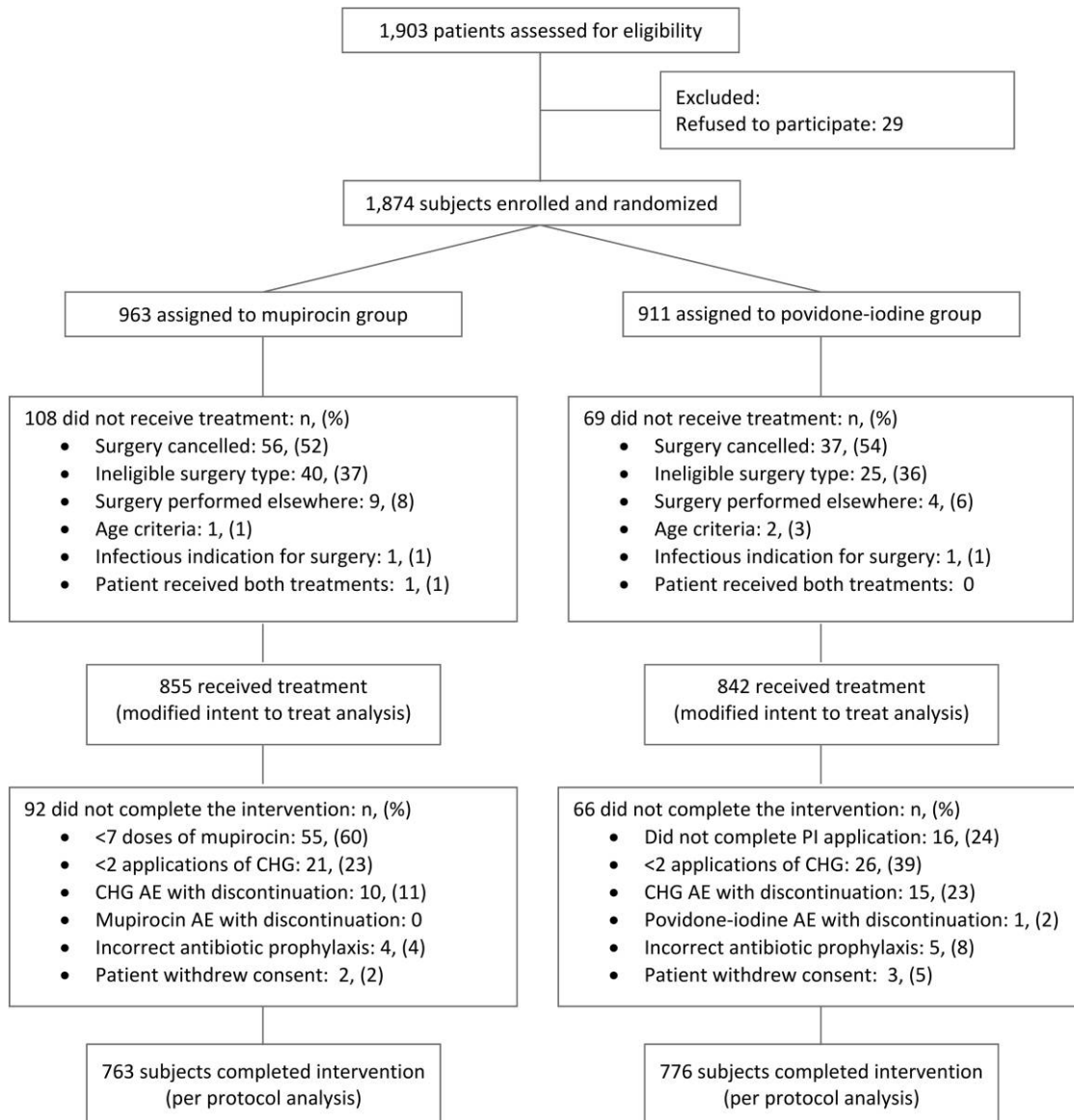


FIGURE 1. Flow diagram of study participants. AE, adverse event; CHG, chlorhexidine gluconate; PI, povidone-iodine.

2 applications of povidone-iodine to each nostril within 2 hours of surgical incision.

Study Oversight

The study was approved by the institutional review board at our institution, and informed consent was obtained from all study participants. The authors designed the study and were solely responsible for the collection, analysis, interpretation, and presentation of the data.

RESULTS

Subjects

During the 12-month enrollment period, 1,874 of the 1,903 patients assessed were enrolled and randomized; 177 of the

enrolled patients did not receive the study intervention, the surgery for most of these individuals was cancelled or the actual surgical procedure performed was not eligible for inclusion in the study. The demographic and clinical characteristics and surgery types of the remaining 1,697 subjects in the MITT analysis are provided in Table 1. The 1,539 subjects who completed the intervention are included in the PP analysis (Figure 1).

End Points

In the MITT analysis, a deep SSI developed after 14 surgical procedures in the mupirocin group and 6 surgical procedures in the povidone-iodine group ($P = .1$). The 17 pathogens isolated from the 14 deep SSI in the mupirocin group in-

TABLE 2. Number of Subjects with Deep Surgical Site Infection (SSI) and SSI Rates

Analysis	No. of subjects	Overall			<i>Staphylococcus aureus</i> infection		
		No. of cases	Rate, cases per 100 subjects	<i>P</i> ^a	No. of cases	Rate, cases per 100 subjects	<i>P</i> ^a
Intent to treat							
Mupirocin	855	14	1.6	.1	5	0.6	.2
Povidone-iodine	842	6	0.7		1	0.1	
Per protocol							
Mupirocin	763	13	1.7	.06	5	0.7	.03
Povidone-iodine	776	5	0.6		0	0	

^a By χ^2 test.

cluded methicillin-susceptible *S. aureus* ($n = 4$), MRSA ($n = 1$), coagulase-negative staphylococci ($n = 4$), *Enterococcus faecalis* ($n = 1$), *Propionibacterium acnes* ($n = 1$), *Escherichia coli* ($n = 1$), *Proteus mirabilis* ($n = 2$), and *Bacteroides fragilis* ($n = 2$). The bacteria isolated from the 6 deep SSI in the povidone-iodine group included MRSA ($n = 1$), coagulase-negative staphylococci ($n = 1$), *Streptococcus agalactiae* ($n = 1$), *E. faecalis* ($n = 1$), *E. coli* ($n = 1$), and *P. aeruginosa* ($n = 1$). As the use of nasal mupirocin and povidone-iodine is intended to suppress *S. aureus* colonization and reduce risk of subsequent *S. aureus* infection, deep *S. aureus* SSI in both groups was analyzed. In the MITT analysis, 5 deep *S. aureus* SSI developed in the mupirocin group, and 1 developed in the povidone-iodine group ($P = .2$); in the PP analysis, 5 deep *S. aureus* SSI developed in the mupirocin group, and none developed in the povidone-iodine group ($P = .03$; Table 2).

Adverse Events

In the MITT analysis, an adverse event resulted in study discontinuation for 10 (1.2%) of the subjects in the mupirocin group and 16 (1.9%) of the subjects in the povidone-iodine group ($P = .24$); most discontinuations were attributable to skin reactions to topical chlorhexidine (Figure 1). One subject in the povidone-iodine group discontinued the study after a vasovagal reaction during the application of the study medication. Subjects in the mupirocin group were more likely than those in the povidone-iodine group to report headache (15 [1.8%] vs 2 [0.2%]), rhinorrhea (47 [5.5%] vs 1 [0.1%]), congestion (15 [1.8%] vs 3 [0.4%]), sore throat (10 [1.2%] vs 0), or any treatment-related symptom (76 [8.9%] vs 15 [1.8%]; all $P < .05$).

S. aureus Antibiotic Susceptibility Testing and Strain Typing

The median interval from preoperative *S. aureus* nasal culture to date of surgery was 14 days (range, 7–31 days). Available *S. aureus* isolates from preoperative nasal cultures, postoperative nasal cultures, and surgical site infections were tested for methicillin and mupirocin susceptibility. The proportion of subjects colonized with MRSA and methicillin-susceptible

S. aureus before surgery was equivalent in both treatment groups (Table 1). Mupirocin resistance was detected in 4 (1.8%) of 219 preoperative *S. aureus* isolates; the mupirocin minimum inhibitory concentration of all resistant isolates was 1,024 or greater. No deep *S. aureus* SSI occurred in subjects with a preoperative nasal culture yielding mupirocin-resistant *S. aureus*. In subjects with a preoperative nasal culture yielding *S. aureus*, the proportion of postoperative nasal cultures with no growth was 78 (92%) of 85 subjects in the mupirocin group and 45 (54%) of 84 subjects in the povidone-iodine group ($P = .03$). Isolates from subjects with both a preoperative and postoperative nasal culture yielding MRSA ($n = 4$) or methicillin-susceptible *S. aureus* ($n = 29$) were characterized by *spa* typing. Two different *spa* types were identified in the 4 MRSA isolates, and 23 different *spa* types were identified in the 29 methicillin-susceptible *S. aureus* isolates. The methicillin-susceptible *S. aureus* strain isolated from preoperative cultures was different by *spa* typing from the postoperative strain in 2 (7%) of 29 subjects.

DISCUSSION

Healthcare systems and providers are challenged to improve patient safety and control cost by identifying important, modifiable SSI risk factors amenable to intervention. The use of nasal mupirocin to suppress *S. aureus* colonization and prevent subsequent invasive infection has proven effective in controlled studies, yet compliance in actual use may be problematic because of adverse effects and out-of-pocket patient expenses. Our study suggests that preoperative nasal povidone-iodine with topical chlorhexidine is a promising regimen to prevent deep *S. aureus* SSI after arthroplasty and spine fusion surgery. Although target enrollment was not met, a statistically significant reduction in *S. aureus* deep SSI in post hoc analysis was observed. Subjects in the povidone-iodine group experienced lower rates of treatment related symptoms. Application of nasal povidone-iodine by the patient care team just before surgery may ensure greater compliance.

In our study, all deep *S. aureus* SSI occurred in subjects with a postoperative nasal culture of no growth. We feel that this likely represents either incomplete suppression of *S. aureus* colonization at sites other than the nares or possibly an

intraoperative or postoperative exposure from exogenous source. Mupirocin was more effective than povidone-iodine at clearing nasal *S. aureus* colonization. This result is not unexpected, given the different mechanisms of the study treatments; the antibiotic mupirocin is intended to eradicate colonization in the nares, whereas the antiseptic povidone-iodine only suppresses *S. aureus* for the duration of surgery. In 2 cases, the preoperative and postoperative *S. aureus spa* type differed, potentially due to colonization with heterogeneous *S. aureus* strains or recolonization during the intraoperative or postoperative period. The rate of mupirocin resistance was low in our study and was not associated with *S. aureus* SSI.

The use of mupirocin to decolonize the nares of patients before orthopedic surgery has been demonstrated as a cost effective intervention.^{18–21} Brand nasal mupirocin is currently the only formulation available for application to the nasal mucosa and costs approximately \$55 to \$130 per course (depending on the location of purchase), whereas nasal povidone-iodine costs approximately \$16 per application; given the equal efficacy of both treatments in our study, povidone-iodine provides more value, defined as quality of outcomes divided by cost.²² Implementing cost-effective interventions to reduce SSI is even more critical as the payors move to reimburse healthcare providers on the basis of episode of care, which requires hospitals and physicians to control costs and assume financial risk for outcomes.²³

Our study has several limitations. First, we failed to achieve our target enrollment because of an overestimation of the number of potential subjects during the study period. Regardless of under-enrollment, the study effect was large enough to detect a statistical difference in the number of deep *S. aureus* SSI infections in the post hoc PP analysis. Second, the small sample size precluded a multivariate analysis. Although this is true, the randomization provided well-balanced treatment groups with respect to clinical, demographic, and surgical variables. Third, nasal culture alone was used as a screen for *S. aureus* colonization, which has a sensitivity of only 48%–66%, and we did not quantify the amount of *S. aureus* in the nares.^{24,25} Although nasal culture alone may miss colonized subjects, we feel study outcome was unaffected, because all subjects received treatment. We agree that certain colonized patients shed more *S. aureus* from the nares than did other colonized patients, and this potential effect on *S. aureus* SSI warrants additional study. Fourth, subjects were not followed up after discharge to identify subjects presenting to other institutions for SSI treatment. We acknowledge this as a potential limitation of our study. Fifth, in subjects with a both a preoperative and postoperative nasal culture yielding *S. aureus*, *spa* typing was used to determine relatedness of isolates, which may potentially underestimate the rate of acquisition of a new, exogenous strain. Although we agree that this is a potential limitation, we feel it is unlikely, given the wide diversity of *spa* types in methicillin-susceptible *S. aureus*, which accounted for the majority of colonizing strains.

Finally, the study was performed at a single institution, and the results may not be applicable to other locations with different patient characteristics, or differing frequencies of *S. aureus* strain types or mupirocin resistance. In conclusion, the use of nasal povidone-iodine may be considered as an alternative to mupirocin and a component of a multifaceted approach to reduce SSI.

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Address correspondence to Michael Phillips, MD, New York University Langone Medical Center, Greenberg Hall, 545 First Avenue, New York, NY 10016 (michael.phillips@nyumc.org).

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