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Safety of Targeted Perioperative Mupirocin Treatment for Preventing Infections After Cardiac Surgery

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Background. Indiscriminate antibiotic use may lead to development of antibiotic resistance. Preoperative mupirocin treatment decreases *Staphylococcus aureus* carriage and may reduce subsequent surgical site infection, but is unlikely to benefit noncarriers. This study was undertaken to evaluate whether avoiding mupirocin in noncarriers places them at increased risk for subsequent postoperative infection.

Methods. We conducted a retrospective cohort study examining incidence of postoperative infection in patients undergoing cardiac surgery at the Cleveland Clinic after introduction of a protocol of polymerase chain reaction screening for nasal *S aureus* carriage, and avoiding mupirocin treatment of noncarriers.

Results. Between August 1, 2002, and May 31, 2004, 6,334 patients were screened for nasal carriage of *S aureus* before undergoing cardiac surgery. There was no significant difference in infection rates between carriers and

noncarriers when examining the incidence of all infections (5.6% and 5.0%; relative risk [RR] 1.11 [95% confidence interval (CI): 0.86 to 1.43]), infections caused specifically by *S aureus* (1.04% and 0.80%; RR 1.30 [95% CI: 0.71 to 2.39]), any surgical site infection (3.1% and 3.2%; RR 0.97 [95% CI: 0.69 to 1.36]), *S aureus* surgical site infection (0.82% and 0.58%; RR 1.41 [95% CI: 0.71 to 2.82]), any bloodstream infection (3.1% and 2.5%; RR 1.21 [95% CI: 0.86 to 1.71]), and *S aureus* bloodstream infection (0.37% and 0.48%; RR 0.77 [95% CI: 0.30 to 2.03]). Mupirocin use declined substantially after introduction of the protocol.

Conclusions. A strategy of targeting perioperative mupirocin treatment to carriers leads to significant reduction in mupirocin use without increasing early postoperative infectious complications in noncarriers.

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About 20% of surgical site infections are caused by *Staphylococcus aureus* [1]. Most *S aureus* infections are due to strains of bacteria that are part of a person's endogenous flora, and not due to exogenously acquired infection [2]. Persons with nasal colonization with *S aureus* (carriers) are at higher risk for subsequent postoperative *S aureus* infections [3]. Nasal and cutaneous carriage of *S aureus* can be eradicated by intranasal application of mupirocin [4–6]. There is reasonable expectation that a reduction of *S aureus* carriage preoperatively might reduce the incidence of surgical site infections due to *S aureus*. A randomized controlled trial examining the efficacy of mupirocin in reducing the incidence of surgical site infections found no reduction in risk overall, but a subset analysis of *S aureus* carriers found a 50% reduction in their risk of subsequent postoperative infection [7]. Thus, the benefit of preoperative mupirocin use appears to be limited to carriers of *S aureus* and not to the general population.

Universal preoperative mupirocin prophylaxis is probably unnecessary. However, a recent survey found that in

centers that practice nasal decolonization for *S aureus*, it was common practice to decolonize without ascertaining carrier status (Infectious Diseases Society of America Emerging Infections Network Preliminary Report for Periodic Query on "decolonization of nasal staphylococcal carriers," Larry Strausbaugh, MD, personal communication). The biggest barrier to a practice of carrier identification and targeted prophylaxis is probably the unavailability in many centers of a rapid test to determine carrier status. Other barriers may reside in economic concerns, or fear of not providing prophylaxis to noncarriers. A test and treat strategy has been shown to be cost effective from an institutional perspective when compared with universal prophylaxis [8]. The same study demonstrated that targeted treatment based on testing by different methods, conventional and molecular, were all more cost effective than universal prophylaxis. Thus, economic concerns should not be the basis for choosing universal prophylaxis over targeted prophylaxis. A remaining concern about targeted prophylaxis may be that withholding mupirocin from noncarriers might somehow lead them to have higher rates of infection than carriers.

Patients undergoing cardiac surgery at the Cleveland Clinic Foundation since July 2002 have been screened for *S aureus* nasal carriage preoperatively using a real-time

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polymerase chain reaction (PCR) assay to avoid preoperative mupirocin treatment of noncarriers. The purpose of this study was to determine whether the relative risk of post operative infection was lower in carriers, which would suggest that the practice of withholding mupirocin may have resulted in an increase in surgical site infections among noncarriers.

Patients and Methods

We conducted a retrospective cohort study examining surgical site infections in patients who underwent cardiac surgery at the Cleveland Clinic Foundation since the introduction of the PCR-based nasal *S aureus* amplification test in July 2002. A targeted mupirocin prophylaxis protocol had been introduced at the same time as the *S aureus* amplification test, whereby all patients admitted for cardiac surgery at the Cleveland Clinic were screened for nasal carriage of *S aureus*, and only carriers were targeted for treatment with topical mupirocin. In some instances mupirocin had been started before the PCR result was available, but stopped if the test yielded a negative result. Screening was done by real-time PCR using an assay developed in house, targeting the *sa442* DNA fragment of *S aureus*. The test had been determined to have high negative predictive values at all levels of *S aureus* carriage prevalence likely to be encountered in the population [8].

The study was approved by the Institutional Review Board on June 6, 2005, and a waiver of informed consent was granted. The total number of patients who underwent cardiac surgery was obtained from the Cardiovascular Information Registry database. Persons not screened for *S aureus* carriage were excluded from the analysis. Baseline characteristics of the carriers and noncarriers were compared. Clinical characteristics examined were age, sex, race, preoperative body mass index, history of diabetes mellitus, hypertension, smoking, peripheral vascular disease, carotid disease, chronic obstructive pulmonary disease, past infective endocarditis, and whether patients had had prior cardiac surgery. Comparison of the proportion of patients in each group that were admitted through the "To come in" ambulatory clinic provided a rough impression of the proportion of patients who had been in the hospital for some time before surgery. Although by no means perfect, this could serve as a marker of the load of comorbidity in the patients in the two groups. The laboratory parameters examined were hematocrit, serum creatinine, glycosylated hemoglobin (hemoglobin A1c), and serum bilirubin. Perioperative factors examined were whether the surgery was emergency surgery, receipt and timing of antibiotic prophylaxis, receipt of preoperative steroids, lowest core body temperature, transfusion of blood products, and the type of surgery performed. The number of infections, surgical site infections, blood stream infections, and also specifically *S aureus* infections were obtained from the CardioVascular Information Registry and verified by independent surveillance by one infection control

practitioner (M.W.). Surgical site infection was defined as any infection occurring at the median sternotomy surgical site (infections defined using the Centers for Disease Control and Prevention definitions), determined on clinical grounds and supported by ancillary investigation [9]. By these definitions, simple wound dehiscence would not have been classified as a surgical site infection. Infections included superficial, deep and organ space infections. Infections occurring at the saphenous vein graft harvest sites were not included.

Statistical Methods

We described the baseline characteristics among carriers and noncarriers using mean \pm SE for continuous measures, and percent for categorical measures. We compared the incidence of any infection, any *S aureus* infection, any surgical site infection, any *S aureus* surgical site infection, any bloodstream infection, and *S aureus* bloodstream infection between carriers (who were targeted to receive mupirocin) and noncarriers (who should have been denied mupirocin) using χ^2 tests. The incidence rates were used to calculate relative risk for any infection, any *S aureus* infection, any surgical site infection, any *S aureus* surgical site infection, any bloodstream infection, and *S aureus* bloodstream infection in carriers compared with noncarriers. All analyses and data manipulations were performed using version 9.1 of the SAS System for Unix (SAS Institute, Cary, North Carolina).

Results

Study Flow

Between August 1, 2002, and May 31, 2004, 7,768 patients underwent cardiac surgery at the Cleveland Clinic. Of those, 1,434 patients (18%) were excluded because they were not screened for *S aureus* carriage. In all, 6,334 patients were screened for *S aureus* carriage, of whom 1,342 (21.2%) were found to be carriers. All patients who were screened for *S aureus* carriage were evaluated for outcomes. The study flow is outlined in Figure 1.

Descriptive Epidemiology

The baseline characteristics of the carriers and noncarriers are compared in Table 1, which also details the number (and proportion) of patients for whom data about each variable were available from the registry. The carrier group had a higher proportion of males. Carriers and noncarriers were otherwise similar. The study patients were predominantly male Caucasians and 60% of patients were admitted through the "To come in" clinic. A quarter of the patients were diabetics, and more than half were smokers. About 13% of patients had had prior cardiac surgery. Over 99% of patients received perioperative antibiotic prophylaxis and the mean antibiotic-to-incision interval time was 27 minutes. Ninety percent of patients received antibiotic prophylaxis within 60 minutes before the surgical incision.

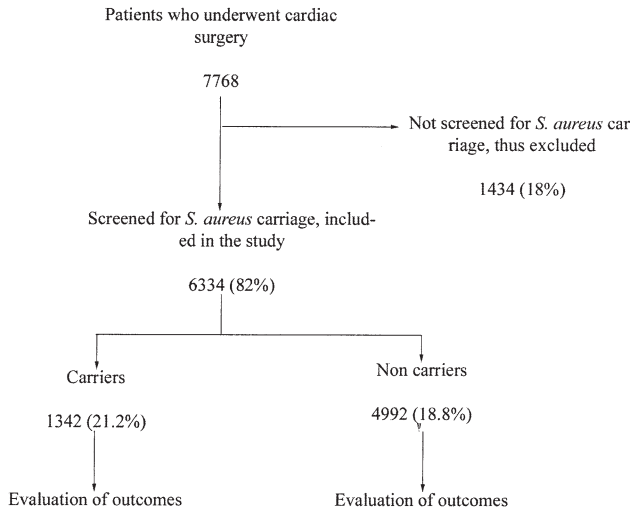


Fig 1. Study flow. (*S. aureus* = *Staphylococcus aureus*.)

Analytical Epidemiology

There was no significant difference in infection rates between carriers and noncarriers when examining all infections, and infections caused specifically by *S aureus*. There was no significant difference in the incidence of surgical site infection caused by any pathogen, and surgical site infection caused by *S aureus*. There was no significant difference in the incidence of any bloodstream infection, and in the incidence of *S aureus* bloodstream infection (Table 2).

Mupirocin Usage

After the implementation of a protocol for PCR testing for *S aureus* carriage and targeted prophylaxis for patients undergoing cardiac surgery, mupirocin use in the Cardiothoracic Surgery department at the Cleveland Clinic declined by 70% from a peak of 918 units per month just before introduction of the test in July 2002, to a mean of 278 units per month in 2003 and 2004 (Fig 2).

Conclusion

A strategy of *S aureus* carrier identification for targeted perioperative mupirocin treatment led to significant reduction in unnecessary mupirocin use without an increase in early infectious complications among noncarriers.

Comment

Our study shows that reducing mupirocin use by an approach of targeted treatment of carriers before cardiac surgery does not result in an increase in early postoperative infections in noncarriers. Although a higher proportion of carriers in this study were males, this is a reflection of male sex being a risk factor for nasal colonization with *S aureus* as consistently shown in earlier studies [10-12]. This study does not make any assumptions or claims about the efficacy of mupirocin or of when, how, or how much of it should be used. It simply examines the

safety of reducing mupirocin use by adopting a strategy of targeted mupirocin prophylaxis.

There are good reasons to avoid unnecessary mupirocin use. Although initial studies suggested that long-term use of mupirocin in patients on peritoneal dialysis did not lead to emergence of mupirocin resistance, longer term follow-up of the same patients revealed development of resistance [13, 14]. At the end of 7 years, 25% of the strains of *S aureus* isolated from these patients were mupirocin-resistant, the majority (75%) demonstrating high-level resistance [15]. These rates are much higher than in the general population, for whom rates of 2% to 6% have been reported [16, 17]. A mupirocin-resistance rate of 25% in *S aureus* was also found in another study a median of 15 months after initiating treatment with mupirocin in peritoneal dialysis patients [18]. Eradication of colonization has been shown to be far less in patients colonized with mupirocin-resistant strains of methicillin-resistant *S aureus* than those colonized with mupirocin-susceptible strains [19]. Patients colonized with mupirocin-resistant strains had a higher incidence of infectious complications when mupirocin was used to prevent peritoneal dialysis catheter-associated infections [18]. Extensive use of mupirocin for nasal decolonization has also been reported to correlate with increasing rates of mupirocin resistance among methicillin-resistant *S aureus* isolates from 2.7% to 65% over a 3-year period [20]. Although use of intranasal mupirocin is generally safe, a case of toxic epidermal necrolysis has been reported with its use [21]. Admittedly, such adverse outcomes are rare, but the possibility of their occurrence warrants prudence in using medications unnecessarily. Thus, there are compelling reasons to avoid unnecessary use of mupirocin.

Our study has several limitations that must be taken into consideration when interpreting the results. Although we could accurately enumerate infections identified before the patients were discharged from hospital, we cannot be assured of complete surveillance for wound infections that occurred after hospital discharge. Information on infection after discharge depended on identification of infection on follow-up, readmission, or on being called by an infection control practitioner from an outside hospital attempting to classify an infection as a postoperative infection. Secondly, the duration of hospitalization was variable, and thus the duration of close follow-up (ie, before hospital discharge) was variable. Mupirocin use before hospitalization was not accounted for. Additionally, we could not verify who received mupirocin and who did not, and precisely how much mupirocin each person received and the timing of the mupirocin in relation to surgery. As the intention of the testing was to target mupirocin to carriers, and 80% of persons tested were not carriers, and mupirocin use declined by 70%, it is assumed that most of the carriers were treated with mupirocin and most of the noncarriers were not treated further once the PCR results were available; but we acknowledge that that assumption is open to question. Nevertheless, it does not negate the validity of the conclusion that a targeted treatment strategy does not place noncarriers at increased risk for infection.

Table 1. Baseline Characteristics

Characteristics	Patients for Whom Data Available		Values ^a	
	No. (% of Total)	Carriers/Noncarriers	Carriers	Noncarriers
Clinical factors				
Age (years)	6,334 (100)	1,342/4,992	60.7 ± 0.40	62.1 ± 0.20
Male sex	6,334 (100)	1,342/4,992	73.4%	64.9%
Caucasian race	6,334 (100)	1,342/4,992	91.1%	88.9%
Preoperative BMI (kg/m ²)	5,744 (90.69)	1,218/4,526	28.8 ± 0.16	28.2 ± 0.08
Diabetes mellitus	5,748 (90.75)	1,221/4,527	26.62%	23.68%
Hypertension	5,732 (90.50)	1,217/4,515	65.8%	68.6%
Smokers	5,751 (90.80)	1,222/4,529	52.5%	56.6%
History of MI	5,681 (89.69)	1,202/4,479	35.1%	35.1%
History of infective endocarditis	5,676 (89.61)	1,203/4,473	3.8%	4.1%
History of PVD	6,264 (98.89)	1,327/4,937	40.5%	42.9%
History of carotid disease	5,702 (90.02)	1,208/4,494	38.4%	40.3%
History of COPD	5,653 (89.25)	1,200/4,453	17.8%	20.9%
"To come in" clinic patient	5,606 (88.51)	1,191/4,415	60.1%	61.5%
Previous cardiac or thoracic surgery	6,334 (100)	1,342/4,992	12.8%	13.2%
Laboratory measurements				
Hematocrit [%]	5,596 (88.35)	1,190/4,406	38.4 ± 0.16	38.0 ± 0.08
Serum creatinine [mg/dL]	5,648 (89.17)	1,195/4,453	1.1 ± 0.02	1.1 ± 0.01
HbA1c [g/dL] ^b	1,422 (22.45)	324/1,098	7.1 ± 0.09	7.0 ± 0.06
Total bilirubin [mg/dL]	5,465 (86.28)	1,153/4,312	0.8 ± 0.02	0.7 ± 0.01
Perioperative factors				
Emergency surgery	6,305 (99.54)	1,334/4,971	0.60%	0.80%
Antibiotic prophylaxis	5,656 (89.30)	1,199/4,457		
Any antibiotic		1,196/4,437	99.75%	99.55%
Cefuroxime		920/3,323	76.73%	74.56%
Vancomycin		192/809	16.01%	18.15%
Other		84/305	7.01%	6.84%
Antibiotic prophylaxis within 60 minutes before incision	5,603 (88.46)	1,190/4,413	90.00%	89.53%
Antibiotic to incision time (min)	5,603 (88.46)	1,190/4,413	26.7 ± 1.14	27.0 ± 0.63
Preoperative steroids	5,830 (92.04)	1,243/4,587	3.9%	4.7%
Lowest core body temperature [°C]	5,688 (89.74)	1,209/4,479	34.5 ± 0.10	34.5 ± 0.05
Transfusion of blood products	5,684 (89.74)	1,205/4,479	31.6%	33.7%
RBC transfusions per patient (units) ^c	5,684 (89.74)	1,205/4,479	1.0 ± 0.08	1.0 ± 0.04
Surgery type				
CABG	6,333 (99.98)	1,341/4,992		
CABG		444/1,539	33.11%	30.83%
Valve		279/1,097	20.81%	21.98%
CABG + valve		167/695	12.45%	13.92%
CABG + other		47/200	3.50%	4.01%
Valve + other		200/697	14.91%	13.96%
CABG + valve + other		89/380	6.64%	7.61%
Other		115/384	8.58%	7.69%
CABG during index surgery	6,333 (99.98)	1,341/4,992	55.7%	56.4%
Valve during index surgery	6,333 (99.98)	1,341/4,992	54.8%	57.5%

^a Values expressed as mean ± SE for continuous variables (units in parentheses in the first column), and percentage for categorical variables. ^b Glycosylated hemoglobin (HbA1c) levels were available for 954 of the 1,397 patients (68.3%) identified as diabetic patients in the registry, the remaining 468 values being from other patients. ^c Median (25th, 75th percentile) was 0 (0, 1).

BMI = body mass index; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PVD = peripheral vascular disease; RBC = red blood cells.

Table 2. Comparison of Infection in Carriers and Noncarriers

Infection	Carriers (n = 1,342) No. (%)	Noncarriers (n = 4,992) No. (%)	Relative Risk (95% CI)	p Value
All infections	75 (5.6)	251 (5.0)	1.11 (0.86,1.43)	0.41
<i>Staphylococcus aureus</i> infections	14 (1.04)	40 (0.80)	1.30 (0.71,2.39)	0.39
Surgical site infections (SSIs)	42 (3.1)	161 (3.2)	0.97 (0.69,1.36)	0.86
<i>S. aureus</i> SSIs	11 (0.82)	29 (0.58)	1.41 (0.71,2.82)	0.33
Blood stream infections (BSIs)	41 (3.1)	126 (2.5)	1.21 (0.86,1.71)	0.28
<i>S. aureus</i> BSIs	5 (0.37)	24 (0.48)	0.77 (0.30,2.03)	0.60

CI = confidence interval.

With due acknowledgement of these limitations, the study demonstrates that a strategy of targeting perioperative mupirocin to carriers only does not put noncarriers at increased risk for postoperative infection at least in the immediate postoperative period. The efficacy of mupirocin for the prevention of postoperative infection is a separate issue, and this study was not designed to answer that question. If carriers are assumed to be at greater risk for postoperative infection, this study would suggest that treating carriers with mupirocin may have reduced their risk to that of noncarriers. The current best study regarding efficacy of preoperative mupirocin use indicates that the benefit in terms of reduction of postoperative infection was limited to carriers [7].

The Society for Healthcare Epidemiology of America/Centers for Disease Control and Prevention guideline for

prevention of surgical site infections does not make any recommendation regarding use of mupirocin [9]. Many institutions and clinicians choose to use mupirocin for this purpose. It must be acknowledged that it is not difficult to identify carriers. The availability of rapid tests for carrier identification, preferably point-of-care tests, would probably decrease unnecessary treatment of noncarriers with mupirocin. Without making any assumptions about the efficacy of mupirocin in preventing postoperative infections, we argue that if mupirocin is to be used, it should be used in a targeted manner treating only carriers.

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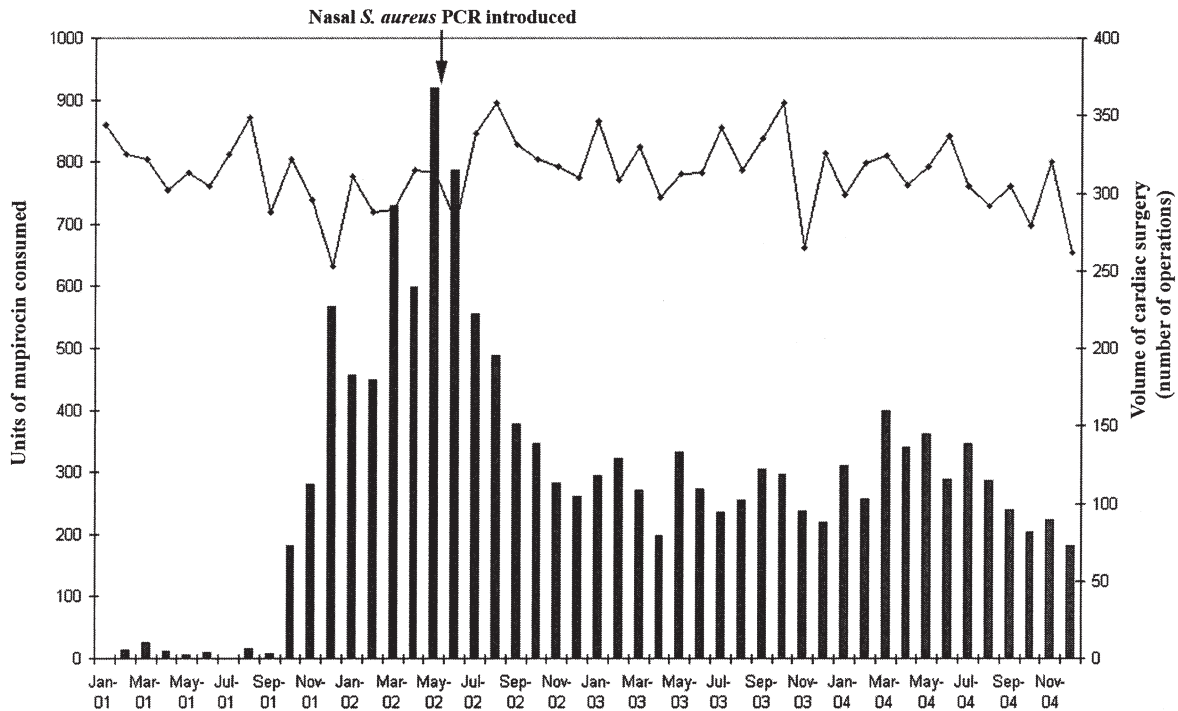


Fig 2. Use of mupirocin (bars) at the Cleveland Clinic (cardiac surgery volume is indicated by line). (PCR = polymerase chain reaction; S. aureus = Staphylococcus aureus.)

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