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Does Preoperative Decolonization Reduce Surgical Site Infections in Elective Orthopaedic Surgery? A Prospective Randomized Controlled Trial

Felix Rohrer MD, Hubert Nötzli, Lorenz Risch, Thomas Bodmer MD, Philippe Cottagnoud, Tanja Hermann BSc, Andreas Limacher PhD, Niklaus Fankhauser PhD, Karoline Wagner PhD, Jan Brügger MD

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Abstract

Background Surgical site infections (SSIs) after elective orthopaedic surgery are very stressful for patients due to frequent rehospitalizations with reoperations and poorer functional outcomes. Prevention of such events is therefore

crucial. Although an evidence-based consensus is still lacking, preoperative decolonization could decrease SSI. Specifically, more information is needed about the effect of a preoperative decolonization procedure on SSI

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This trial is registered at Clinicaltrials.gov: NCT02560155, kofam.ch SNCTP000001557.

Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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F. Rohrer, P. Cottagnoud, T. Hermann, J. Brügger, Department of Internal Medicine, Sonnenhofspital, Bern, Switzerland

F. Rohrer, H. Nötzli, L. Risch, P. Cottagnoud, University of Bern, Bern, Switzerland

H. Nötzli, Orthopaedic Department, Sonnenhofspital, Bern, Switzerland

L. Risch, T. Bodmer, Labormedizinisches Zentrum Dr Risch, Microbiology, Koeniz, Switzerland

A. Limacher, N. Fankhauser, CTU Bern and Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

K. Wagner, Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland

J. Brügger, University of Zurich, Zurich, Switzerland

J. Brügger (✉), Department of Internal Medicine, Sonnenhofspital, Buchserstrasse 30, 3006 Bern, Switzerland
Email: janbruegger@sonnenhof.ch

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proportions in both *Staphylococcus aureus* carriers and non-*S. aureus* carriers after general orthopaedic surgery.

Questions/purposes Our study addressed the following questions: (1) Does preoperative decolonization reduce the risk of SSI after general elective orthopaedic surgery in patients colonized with *S. aureus*? (2) Does preoperative decolonization reduce the risk of SSI among patients who are not colonized with *S. aureus*?

Methods In this prospective, randomized, single-blinded trial, we recruited patients undergoing general elective orthopaedic surgery in one tertiary care center in Switzerland. Between November 2014 and September 2017, 1318 of 1897 screened patients were enrolled. Patients were allocated into either the *S. aureus* carrier group (35%, 465 of 1318 patients) or the noncarrier group (65%, 853 of 1318 patients) according to screening culture results. In the *S. aureus* group, 232 patients were allocated to the intervention arm and 233 were allocated to the control arm. Intervention was 5 days of daily chlorhexidine showers and mupirocin nasal ointment twice a day. Of the 853 noncarriers, 426 were allocated to the intervention arm and 427 were allocated to the control arm. All patients in both groups were analyzed in an intention-to-treat manner. The primary endpoint was SSI occurrence at 90 days postoperative and the secondary endpoint was SSI occurrence at 30 days postoperative.

The initial sample size calculation was made for the *S. aureus* carrier group. Based on the literature review, a 4% proportion of SSI was expected in the control group. Thus, 726 carriers would have been needed to detect a relative risk reduction of 80% with a power of 80% at a two-sided α -error of 0.048 (adjusted for interim analysis). Assuming carrier prevalence of 27%, 2690 patients would have been needed in total. An interim analysis was performed after including half of the targeted *S. aureus* carriers (363 of 726). Based on the low infection rate in the control group (one of 179), a new sample size of 15,000 patients would have been needed. This was deemed not feasible and the trial was stopped prematurely.

Results Among carriers, there was no difference in the risk of SSI between the intervention and control arms (decolonized SSI risk: 0.4% [one of 232], control SSI risk: 0.4% [one of 233], risk difference: 0.0% [95% CI -1.2% to 1.2%], stratified for randomization stratification factors; $p > 0.999$). For noncarriers, there was no difference in risk between the intervention and control arms (decolonized SSI risk: 0.2% [one of 426], control SSI risk: 0.2% [one of 247], stratified risk difference: -0.0% [95% CI -0.7 to 0.6]; $p = 0.973$).

Conclusions We found no difference in the risk of SSI between the decolonization and control groups, both in *S. aureus* carriers and noncarriers. Because of the low event numbers, no definite conclusion about efficacy of routine preoperative decolonization can be drawn. The results, however, may be helpful in future meta-analyses.

Level of Evidence Level II, therapeutic study

Introduction

Surgical site infections (SSIs) are a major postoperative complication caused mainly by the patient's endogenous organisms such as *Staphylococcus aureus* [21]. Given that approximately 25% of the general population is permanently colonized with *S. aureus* [36], prevention is crucial as treatment options for SSI are very stressful for patients (rehospitalizations, reoperations, reduction in quality of life) [9, 38]. One longitudinal study used whole genome sequencing to evaluate the routes of *S. aureus* transmission in an intensive care unit [29]. They found that colonization occurred with genetically diverse *S. aureus* strains. Transmission from healthcare workers to patients was infrequent and mostly originated from the patient's own flora [8]. Consequently, concentrating on vertical transmission control could be more effective than adding horizontal infection control measures. Decolonization can be effective in *S. aureus* carriers by following protocols stipulating the use of intranasal mupirocin and showering with chlorhexidine [4]. One groundbreaking randomized controlled trial by Bode et al. [1] analyzed the effect of preoperative decolonization of *S. aureus* carriers on the incidence of hospital-associated infections. The procedure reduced infection rates from 7.7% in the control group to 3.4% in the intervention group.

In general orthopaedic surgery, however, the possibility of reducing SSI through decolonization remains controversial. In the trial by Bode et al. [1], most patients underwent cardiothoracic surgery, which presents a higher risk for SSI than orthopaedic surgery. As a result, no conclusion from this trial can be transferred to orthopaedic surgery. To date, only retrospective studies favor preoperative decolonization procedures in orthopaedic surgery [7, 12, 31, 32] and other studies failed to find any substantial effect of a "screen and treat" strategy [13, 20, 22, 28]. A randomized controlled trial did not demonstrate any reduction in SSI, but patients underwent decolonization independent of their carrier status [15]. "Non-carriers only" were never addressed separately in these trials and the possible effects of decolonization in this population is unknown. A further difficulty of implementing decolonization is ensuring adherence to the protocol; which can be as low as one third [3]. Studies investigating decolonization protocols should, therefore, also focus on methods to improve how patients follow instructions. As a whole, systematic reviews recommended further prospective randomized trials on the effect of decolonization before orthopaedic surgery and the subsequent creation of widely applicable evidence-based guidelines [9, 33].

Therefore, we asked: (1) Does preoperative decolonization reduce the risk of SSI after general elective orthopaedic surgery in patients colonized with *S. aureus*? (2) Does preoperative decolonization reduce the risk of SSI among patients who are not colonized with *S. aureus*?

Patients and Methods

Study Design

The present DECO-SSI (DECOLonization and SSI) study is a prospective, randomized, controlled, interventional, single-blinded trial (the outcome assessors were blinded) performed at one tertiary care center in Bern, Switzerland. It was designed with carrier and noncarrier groups, which included two parallel arms each. Patients with a positive nose swab culture for *S. aureus* were allocated to the carrier group and those with a negative nose swab culture were allocated to the noncarrier group. Patients in each group were then randomized to either a control or an intervention arm. Intervention consisted of a decolonization procedure 5 days before surgery.

The primary outcome was the overall 90-day postoperative incidence of SSI. Secondary outcomes were defined as early (30-day postoperative) and late (31-day to 90-day postoperative) SSI, death related to infection, SSI caused by documented bacteria and time from surgery to SSI or death. *S. aureus* strains identified in SSI were compared with colonizing strains from the same patient using next-generation sequencing (see Appendix, Supplemental Digital Content, <http://links.lww.com/CORR/A295>).

The study protocol was approved by the local ethics committee (PB_2016_00256). Written informed consent was obtained from each patient during a screening visit. The trial was monitored by an external expert of the clinical trial unit, University of Bern, Switzerland.

Participants

All patients scheduled for elective orthopaedic surgery were evaluated for eligibility. Inclusion criteria were a minimum age of 16 years, written and signed informed consent, and a period of at least 14 days before surgery. This timeframe was needed to perform nasal swabbing and decolonization. Exclusion criteria were allergy to mupirocin or chlorhexidine, the presence of any foreign nasal body, pregnancy, ongoing intervention for a documented infection or prior enrollment in the study. Withdrawal criteria were the withdrawal of patient consent, death, and loss to follow-up. All available data were evaluated in an intention-to-treat manner.

Randomization and Masking

Patients in the carrier and noncarrier groups were allocated either to an intervention or a control arm on a 1:1 basis in the electronic data entry system (REDCap v 8.5.19, Vanderbilt


University, Nashville, TN, USA). Randomization was stratified by procedure type (upper extremities and pelvic/hip versus spine versus knee and foot) and American Society of Anesthesiologists criteria (I versus II versus III-V). A randomization list was generated by an independent statistician not otherwise involved in the trial. Allocation was concealed using central randomization, which was implemented in REDCap.

Enrollment, Intervention and Follow-up

Patients scheduled for surgery after an orthopaedic consultation were enrolled, and informed consent was obtained by a member of the trial team. To screen for *S. aureus*, a nasal swab was obtained 2 to 4 weeks before surgery; either by a trained clinical research coordinator or by the patients themselves according to verbal and written instructions. The intervention arms of both groups received a decolonization kit per mail one week before surgery. For *S. aureus* carriers, the kit contained mupirocin 2% nasal ointment (BACTROBAN® Nasal ong, 3 g, GSK, Muenchenbuchsee, Switzerland) with instructions to apply the ointment to each nostril twice a day for 5 days before admission and to shower daily using ample amounts of chlorhexidine gluconate soap (Lifo-Scrub sol 4%®, 500 mL, B. Braun, Sempach, Switzerland). For non-carriers, the decolonization procedure was performed using only chlorhexidine gluconate soap (Lifo-Scrub sol 4% 500 mL, B. Braun) (Table 1). For practical reasons, we did not consider the use of a placebo kit in the control group. To improve and measure compliance, mobile phone text message reminders were sent at the start of decolonization and patients had to complete a daily checklist during the decolonization period. Participants in the control arm were instructed to shower before the intervention with conventional soap according to our standard infection prevention protocol. Patients in both arms received cefuroxime antibiotic prophylaxis (1.5 g, IV) 30 minutes to 60 minutes before incision and at 8 hours and 16 hours postoperatively. The operative field was disinfected three times with povidone-iodine alcoholic solution (Betaseptic®, Mundipharma Medical Company, Basel, Switzerland), in line with national hygiene and infection control guidelines [27]. No specific antiseptic wound dressings were applied postoperatively.

At 30 days and 90 days after surgery, a clinical research coordinator interviewed patients by telephone using a standardized form to assess the possibility of SSI (local wound symptoms, fever, and antibiotic treatment prescribed). The questionnaire was designed by the Swiss National Nosocomial Infection Monitoring Institution and is used routinely in this context. When SSI was suspected, the responsible orthopaedic surgeon was contacted and

Table 1. Study intervention according to groups

<p><i>S. aureus</i> carrier group</p> <ul style="list-style-type: none"> • Mupirocin 2% nasal ointment <ul style="list-style-type: none"> • Nasal application twice a day • Chlorhexidine gluconate soap <ul style="list-style-type: none"> • Daily showers 	<p style="writing-mode: vertical-rl; transform: rotate(180deg);">Decolonization for 5 days</p> 	<p>Non-carrier group</p> <ul style="list-style-type: none"> • Chlorhexidine gluconate soap <ul style="list-style-type: none"> • Daily showers
<p>Surgery</p>		

asked to confirm the diagnosis. SSIs were defined by Centers for Disease Control criteria [14]. Surgeons were blinded to the carrier status and the study arm of their patient. Patients were instructed, both verbally and in writing, not to inform their surgeon about the possible decolonization treatment.

Accounting for Patients

Between November 1, 2014 and September 30, 2017, 1897 patients were screened for study eligibility; 1403 met the inclusion criteria and were enrolled (Fig. 1). The main reason patients declined to participate was the additional time and effort required before surgery. Data was not collected for non-participants; thus, no comparison could be made with the active participants. A further 85 patients were excluded before randomization because of missing nose swabbing results. Of 1318 returned nose swabs, 465 tested positive for *S. aureus* (35%) and 853 negative (65%). *S. aureus* carriers were slightly younger than noncarriers (median 59 years versus 61 years; $p = 0.001$) and predominantly male (56% versus 43%, $p < 0.001$) (Table 2). Other baseline characteristics were not markedly different between carriers and noncarriers. The most common operations were on the hip, knee, and spine. Overall, 43% (571 of 1318) of the patients underwent prosthetic surgery. Baseline characteristics of the two arms of the carrier and noncarrier groups were well-balanced. Adherence to the treatment regimen was defined as the use of the intervention drugs for at least 4 days, and was 87% and 86% in the carrier and noncarrier groups, respectively.

Of the 465 carriers, 232 were allocated to the intervention arm and 233 were allocated to the control arm. In the intervention arm, 225 patients received the decolonization kit. No patient was lost to follow-up. Of the 853 noncarriers, 426 were allocated to the intervention arm and 427 were allocated to the control arm. In the intervention arm, 396 patients received the decolonization kit. In total, four patients were lost to follow-up.

Procedures

Nasal swabs were taken using nylon fiber flocked swabs treated with Amies liquid transport medium (SwabAX, Axon Lab AG, Baden, Switzerland) and processed on a BD Kiestra Total Laboratory Automation system (Becton-Dickinson, Sparks, MD, USA). Specimens were vortexed, flocked swabs were removed, and 100 µL of transport medium was transferred into tubes containing 3 mL of selective enrichment broth (Staphylokokken Anreicherungsbouillon, Axon Lab AG, Baden, Switzerland). After incubation at 35° C for 16 to 24 hours, broths were sub-cultured onto chromID *S. aureus* Elite agar media (bioMérieux, Marcy l’Etoile, France). Agar media were incubated at 35° C in an aerobic atmosphere and observed after 16 hours to 24 hours and after 32 hours to 48 hours. Suspicious colonies were identified at the species level using matrix-assisted laser desorption/ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany). Comprehensive antibiograms of *S. aureus* isolates were obtained using VITEK-2 AST-P636 (bioMérieux) and interpreted according to current European Committee on Antimicrobial Susceptibility Testing guidelines [10]. Isolates from patients with *S. aureus* were stored at -80° C (Cryobank, Mast Diagnostica, Germany).

Sample Size

The sample size calculation was based on the *S. aureus* carrier group. Previous studies reported an approximate 80% relative risk reduction of SSI in decolonized *S. aureus* carriers and an SSI proportion of 4% in general elective orthopaedic surgery in *S. aureus* carriers [5, 12, 28, 31, 32]. As internal SSI proportions at our hospital were unknown, estimations were based on a review of previous studies. Assuming a 4% proportion of SSI in the control group, 726 carriers would have been needed to detect a relative risk reduction of 80% with a power of 80% at a two-sided

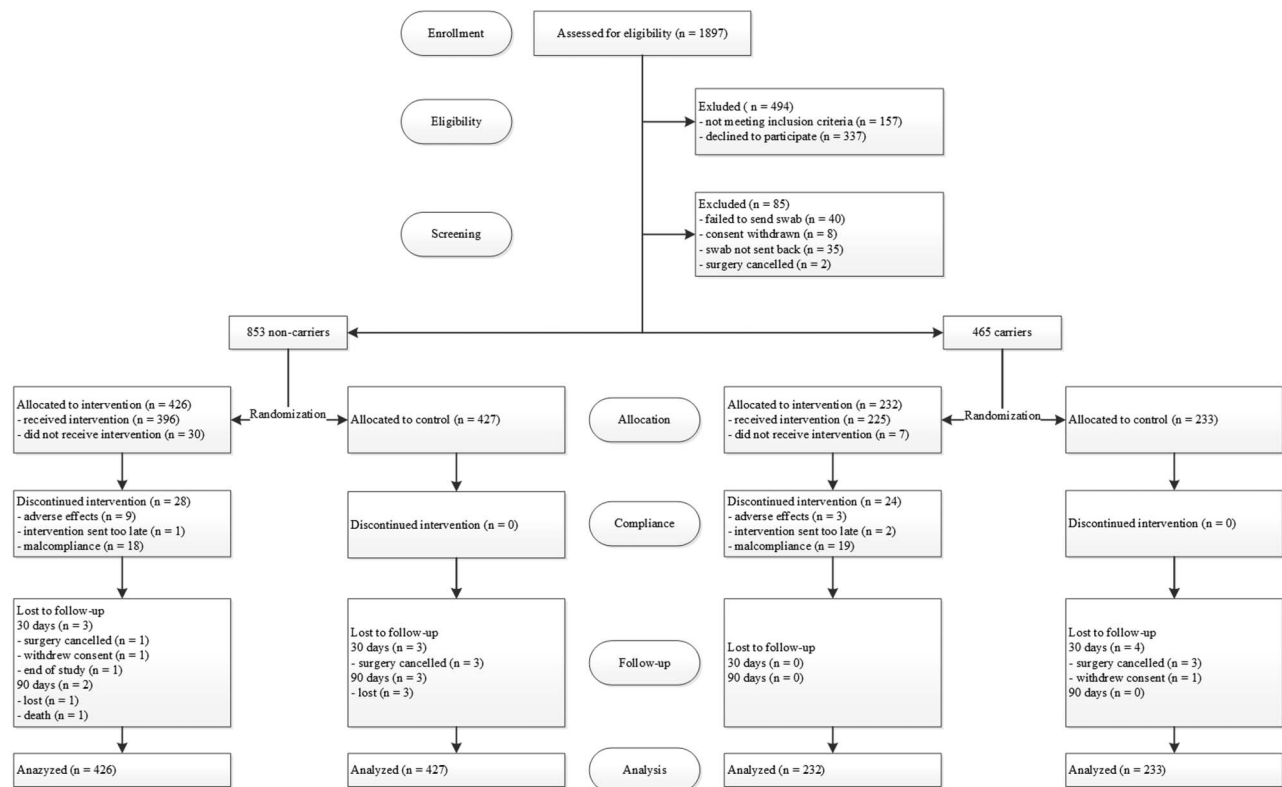


Fig. 1 This flow chart shows the patients included in the study.

α -error of 0.048 (adjusted for interim analysis). Based on 27% carrier prevalence in the general population, 2690 patients would have been needed overall [5, 6, 11-13, 15, 28]. We also performed a power analysis for the noncarrier group. An assumed prevalence of noncarriers of 73%, results in 1964 patients for this study group. Assuming a 2% risk of SSI in noncarriers, we would have detected a relative risk reduction of 71% with a power of 80% at a two-sided α -level of 0.05 [6, 11, 12, 15, 28].

Outcomes: Interim Analysis

An interim analysis was pre-specified in the study protocol and statistical analysis plan to assess efficacy, futility, and recalculate the sample size. Sample size recalculations were based on the carrier group only; as the most pronounced effect was expected in this group. This was conducted after evaluating 363 of the targeted 726 carriers. The sample size re-estimation was based on the originally predicted risk reduction of 80%, the actually observed proportion of SSI in the *S. aureus* carrier control group, and the prevalence of *S. aureus* carriers at the time of the interim analysis. To assess futility, we calculated the conditional power to obtain a statistically significant risk difference in the carrier group at the end of the trial based

on the original sample size assumptions. We pre-specified that if the conditional power was less than 10%, the trial would be stopped for futility. To assess efficacy, we adopted the O'Brien-Fleming group sequential design: testing the primary hypothesis of the carrier group at a significance level of 0.0052 for the interim analysis and 0.048 for the final analysis. An independent statistician performed the work, which was evaluated by a data safety monitoring board. In the end, the data safety monitoring board halted the trial because of futility and non-feasibility. The conditional power for the original sample size was only 4.2%. The sample size recalculation stipulated that 14,752 patients instead of the original 2690 would be needed, and this was deemed unfeasible. Patient recruitment continued during the interim analysis. The final analysis was then conducted with all patients included. No SSIs were observed in the carrier group between the interim analysis and termination of the trial.

Statistical Analysis

We applied a hierarchical test procedure to account for double hypothesis testing in the carrier and noncarrier groups. Expecting a more pronounced effect in the carrier group, we first tested the superiority of the decolonization

Table 2. Participant baseline characteristics and comparison between carriers and noncarriers

Characteristics	Total (n = 1318)	Carriers (n = 465)	Noncarriers (n = 853)	p value
Patients				
Age median, years (range)	61 (50-69)	59 (49-68)	61 (51-69)	0.001
Sex % female (n)	53 (692)	45 (207)	57 (485)	< 0.001
Smokers % (n)	17 (229)	15 (68)	19 (161)	0.059
BMI (kg/m ²) median (range)	26 (24-30)	26 (24-30)	26 (23-30)	0.349
Alcohol %, > two units/day (n)	3 (36)	3 (13)	3 (23)	0.043
COPD % (n)	2 (22)	1 (6)	2 (16)	0.660
Asthma % (n)	4 (49)	3 (12)	4 (37)	0.891
Other severe lung disease % (n)	6 (74)	5 (22)	6 (52)	0.810
Congestive or ischemic heart disease % (n)	7 (87)	7 (31)	7 (56)	> 0.999
Liver disease % (n)	1 (10)	1 (5)	1 (5)	0.504
Renal insufficiency % (n)	1 (12)	0 (1)	1 (11)	0.061
Diabetes % (n)	6 (81)	7 (31)	6 (50)	0.623
Cerebrovascular disease % (n)	4 (47)	2 (11)	4 (36)	0.092
ASA score % (> 2 [n])	19 (247)	18 (81)	20 (166)	0.769
Type of main procedure				0.659
Spine % (n)	18 (241)	19 (89)	18 (152)	
Pelvis/hip or upper extremity % (n)	41 (532)	41 (191)	40 (341)	
Knee or foot % (n)	41 (545)	40 (185)	42 (360)	
Sub-type spine				0.690
Spine: decompression % (n)	18 (43)	16 (14)	19 (29)	
Spine: stabilization % (n)	40 (96)	37 (33)	41 (63)	
Spine: decompression and stabilization % (n)	38 (91)	43 (38)	35 (53)	
Sub-type hip				0.142
Hip: primary % (n)	75 (398)	75 (144)	75 (254)	
Hip: revision % (n)	6 (29)	5 (9)	6 (20)	
Shoulder: primary % (n)	12 (66)	11 (20)	14 (46)	
Shoulder: revision % (n)	2 (11)	4 (8)	1 (3)	
Sub-type knee/foot				0.856
Knee: primary % (n)	58 (317)	55 (101)	60 (216)	
Knee: revision % (n)	11 (57)	11 (21)	10 (36)	
Foot: primary % (n)	21 (115)	24 (44)	20 (71)	
Foot: revision % (n)	3 (14)	2 (4)	3 (10)	

Table not exhaustive. The two populations were compared using the chi-square or Mann-Whitney U-test, as appropriate. Definition "unit" of alcohol = 2 cL of liquor, 1 dL of wine, 3 dL of regular lager beer (approximations). Percentage calculations of the procedures' sub-type were performed using the total number of the respective main procedure; revision = revision surgery of a previous prosthetic implant.

procedure to control infection in the carrier group at the two-sided α -level of 0.048. Secondary hypothesis testing in the noncarrier group would have been performed only if the primary null hypothesis in the carrier group was rejected. The primary analysis was performed according to an intention-to-treat principle. A per-protocol analysis was performed for sensitivity, excluding patients who did not fulfill the minimal adherence criteria or had missing

outcome data. We compared the characteristics of the two study populations using the chi-square or Mann-Whitney U test, as appropriate. For the primary binary outcome, we calculated the proportion and Mantel-Haenszel risk difference with a corresponding 95% confidence interval stratified for randomization stratification factors (surgical procedure type and American Society of Anesthesiologists category) according to Klingenberg et al.'s method [19].

Table 3. Proportions of patients with SSI and types of SSI

Group	Total number	SSI	Risk difference (95% CI)	Surgery type for SSI	Organism
Carrier control	233	0.4% (1)	0.0% (-1.2% to 1.2%) p > 0.999	Spine	<i>S. epidermidis</i>
Carrier decolonization	232	0.4% (1)		Foot	<i>S. aureus</i>
Noncarrier control	427	0.2% (1)	-0.0% (-0.7% to 0.6%) p = 0.973	Knee	No germ found
Noncarrier decolonization	426	0.2% (1)		Spine	No germ found

SSI = surgical site infection.

We compared groups using the stratified Cochran-Mantel-Haenszel test. “R” software (R core team, version 3.5.1, Vienna, Austria,) for the statistical analysis.

Results

Among carriers, there was no difference in the risk of SSI between the intervention and control arms (risk difference: 0.0% [95% CI -1.2 to 1.2], stratified for randomization stratification factors; $p \geq 0.999$) (Table 3). The overall SSI risk was 0.4% (one of 232 patients) in decolonized carriers and 0.4% (one of 233 patients) in control *S. aureus* carriers. Both SSIs were early-onset, and no deaths occurred. A subgroup analysis was not conducted because of low SSI numbers. In the per-protocol analysis, 32 patients in the intervention arm and five in the control arm were excluded, mainly because the intervention was discontinued. There was no difference in risk between the arms (stratified risk difference: -0.1% [95% CI -1.4 to 1.2]; $p = 0.941$).

S. aureus carrier proportions were 35% (465 of 1318) and 0.08% of patients (one of 1318) was a carrier of methicillin-resistant *S. aureus* (MRSA). All *S. aureus* isolates responded to mupirocin.

For noncarriers, there was no risk difference between the intervention and control arms (stratified risk difference: -0.0% [95% CI -0.7 to 0.6]; $p = 0.973$) (Table 3). Overall,

the SSI incidence was 0.2% (one of 426 patients) in decolonized carriers and 0.2% (one of 427 patients) in control noncarriers. Both SSIs were early-onset. One death unrelated to SSI occurred in the intervention arm. A subgroup analysis was not conducted because of low SSI numbers. In the per-protocol analysis, 64 patients in the intervention arm and seven in the control arm were excluded, mainly because the intervention was discontinued. There was no risk difference between the arms (stratified risk difference: -0.1% [95% CI -0.8 to 0.6]; $p = 0.896$).

Overall, one of four SSIs occurred due to documented *S. aureus*. The patient had been identified as a nasal carrier before undergoing elective orthopaedic surgery and had completed our decolonization protocol. Vertical transmission was suspected and confirmed by whole genome sequence strain typing (Fig. 2). One SSI was caused by *Staphylococcus epidermidis* and in two SSIs, no pathogen was identified.

Discussion

SSI is a major complication and patients are severely affected by the subsequent long and stressful treatments. One independent risk factor for SSI is colonization with *S. aureus* [21]. Preoperative decolonization has therefore been proposed as a preventive measure to reduce SSI. It has been

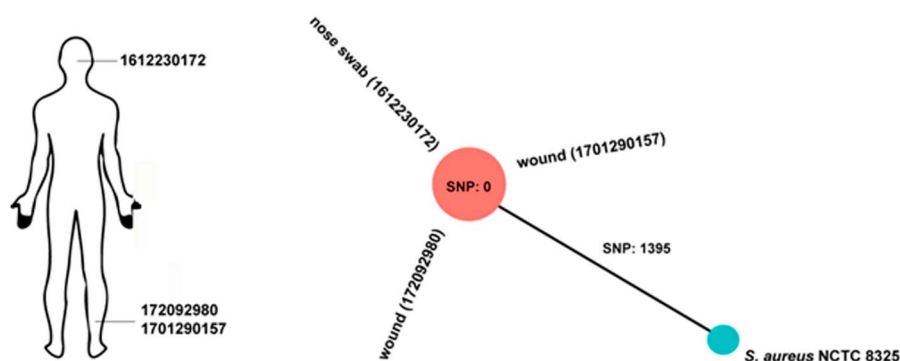


Fig. 2 A minimum spanning tree was calculated for the allelic profiles of the 1865 cgMLST targets of *Staphylococcus aureus*, including an *S. aureus* reference strain and three *S. aureus* strains isolated from different sites in the same patient.

shown to be effective in cardiac and vascular surgery but its benefits remain controversial in connection with orthopaedic surgery [1, 37]. There is insufficient data at this time to implement a routine preoperative decolonization procedure as it requires more effort from the patient and there are concerns regarding the development of microbial resistance [2]. Specifically, more information is needed about the effect of preoperative decolonization on SSI proportions after elective orthopaedic surgery in *S. aureus* carriers and non-*S. aureus* carriers. In this prospective, randomized trial, a preoperative decolonization procedure did not decrease SSI risk in patients undergoing elective orthopaedic surgery, but these results should be interpreted with caution because event numbers were small. The procedure was not effective in either the *S. aureus* carrier group or the noncarrier group. We encountered an unexpectedly low level of SSI at our center compared with that reported in previous studies [5, 12, 28, 31, 32], even though the *S. aureus* carrier proportion was above average and represented a population of patients at high risk of SSI.

Limitations

The key limitation in this study is the theoretical statistical uncertainty. The study was prematurely halted after interim analysis because of the low risk of SSI. Interim analysis calculations were based on the carrier group only, as a more pronounced effect was expected in this high-risk group for SSI. Sample size recalculation based on the *S. aureus* colonization proportions and SSI proportions in the carrier control group found that around 15,000 patients would be necessary to establish definitive proof. Such a mega trial is not justified in our view as, even if a benefit was shown, clinical relevance would be questionable.

The low risk of SSI in our trial was surprising because earlier studies had reported baseline SSI of 2% to 4% [5, 12, 28, 31, 32]. As there was no internal monitoring of SSI at our institution before this trial, SSI risks were based on reported statistics. Possible methodological factors contributing to the low infection proportions at our institution were the follow-up time of 90 days, possible selection bias, and population baseline characteristics and the single-blinded design. We chose the 90-day follow-up according

to CDC criteria for SSI. Periprosthetic joint infections (PJIs), however, can occur even up to 2 years after implantation. In our cohort, 43% of interventions involved prosthetic surgery. According to previous reports involving knee and hip arthroplasty, up to 80% of SSIs are diagnosed within 90 days [23]. The analysis showed further that seven of 11 SSI occurring after 90 days were due to *S. aureus*, but the diagnosis in five of these patients was potentially delayed by the antibiotic treatment administered for poor wound healing. To account for this issue and to substitute for an external outcome assessor—which could have evaluated all study participants for SSI—we performed an ad-hoc analysis adding “possible SSI” to the confirmed cases of SSI (Table 4). We defined possible SSIs as antibiotic treatment prescribed postoperatively by the orthopaedic surgeon despite criteria for SSI having not been met. We identified seven such patients in our study population. Reasons for prescribing antibiotic therapy were delayed wound healing (four patients) or suspected SSI (three patients). Antibiotic therapy was stopped after the wound healed or after negative intraoperative bacterial culture results. The statistical ad-hoc analysis did not show any difference between the intervention and control arms in carriers (stratified risk difference: -0.4% [95% CI -1.0 to 1.9]; $p = 0.570$) or in noncarriers (stratified risk difference: -0.5% [95% CI -0.8 to 1.8]; $p = 0.731$).

Another concern were the baseline characteristics of our study population. As patients appear rather healthy (Table 2), the question arises whether this could be the result of a selection bias. No data was collected on patients who were not screened or on patients who were screened but did not consent or were not eligible. Comparison with other studies is difficult due to the lack of data, but in relation to Sousa et al. [34] and Ramos et al. [30], who reported higher SSI proportions of 2% to 4% for TKA and THA, our population is slightly younger (mean age 57 versus 65 reported in Sousa et al. [34] and 61 in Ramos et al. [30]), lower diabetes proportions (6.7% versus 21.9% in Sousa et al. [34]), lower mean BMI (26 versus 29 in Ramos et al. [30]) and lower ASA ≥ 3 proportions (28.5 versus 17.5% in Sousa et al. [34]). Furthermore, our trial included arthroscopies, diverse foot surgeries, and removal of osteosynthesis material that could have contributed to the low proportion of SSI. According to our study protocol

Table 4. Patients with certain and possible SSI

Group	Total number	Certain SSI	Possible SSI	Total	Risk difference (95% CI)
Carrier control	233	0.4% (1)	0.4% (1)	0.9% (2)	0.4% (-1.0% to 1.9%); $p = 0.570$
Carrier decolonization	232	0.4% (1)	0.0% (0)	0.4% (1)	
Noncarrier Control	427	0.2% (1)	0.9% (4)	1.2% (5)	0.5% (-0.8% to 1.8%); $p = 0.731$
Noncarrier decolonization	426	0.2% (1)	0.5% (2)	0.7% (3)	

SSI = surgical site infection.



Fig. 3 This figure shows the percentage of methicillin-sensitive *Staphylococcus aureus* carriers in other studies [1, 12, 13, 15, 24, 28, 31, 34, 35] (name of first author and the country of study, are shown).

all patients with at least 2 weeks' time to surgery were eligible for participation and were approached systematically; meaning our study population represents an average preoperative orthopaedic outpatient population. The protocol was designed to answer the question of routine decolonization in elective surgery, not in a specifically selected high-risk population. Other possible factors contributing to the low SSI proportions in our clinic are our highly standardized procedures with strong aseptic conditions and timely antibiotic prophylaxis, which received a rating of 100% in Swiss infection control report that is, unfortunately, not publicly available. Other "soft" factors thought to contribute to low SSI proportions include well-trained surgeons with high workloads and short intervention times [25, 26].

Another limitation is the lack of a placebo in the control group. Opting for a single-blind design was advantageous because no placebo product was available and a double-blinded approach would have increased costs greatly. We do not believe it would have measurably improved our study's robustness; any crossover from the control to the intervention arm seems improbable because patients were not informed about colonization status and the control group did not receive instructions for a full decolonization course. Furthermore, surgeons were blinded to the colonization status and treatment arm, making an influence on SSI rates unlikely.

We only screened for *S. aureus* in the nose; not the throat, axilla, groin or perianal region. With this procedure,

we may have missed approximately 10% of positive swab results, but the nose remains the most significant reservoir for *S. aureus* [24, 39].

SSI Reduction in Patients Colonized with *S. aureus*

We found no benefit of our decolonization protocol in *S. aureus* carriers in terms of reducing the SSI risk in those individuals. Another prospective randomized trial with much higher proportions of 3% to 4% SSI also failed to find any effect with the same decolonization regimen in TKA and THA, but the sample size was too small to reach explanatory power [34]. Studies reporting benefits of decolonization should be interpreted with caution because of their "before and after implementation" or observational study design [12, 31, 35]. SSI risk depends on many factors and prevention bundles often consist of a multimodal approach, which may possibly affect results. For example, the additional use of vancomycin in MRSA carriers could bias effects attributed to decolonization [35]. Our study specifically adds information on decolonization only, as no other measures were added during the study period and we included a broad orthopaedic population. In addition, the very low proportion of MRSA carriers in our study population removes a further bias. Nevertheless, in a population with a high proportion of MRSA carriers, selected decolonization for these patients could be beneficial, as this population is at even greater risk for SSI compared with methicillin-sensitive *Staphylococcus aureus* (MSSA) carriers [18]. This topic requires further studies.

The *S. aureus* carrier proportion was higher in this study than described elsewhere. Only one other screening study by Mertz et al. [24] in Switzerland found more (Fig. 3). Two methodological features of our study may partly explain this phenomenon. First, both we and Mertz et al. [24] used a selective enrichment broth instead of the conventional agar culture media in other studies [1, 12, 13, 15, 28, 31, 35]. This technique may have identified more *S. aureus* in the two studies. Indeed, one Scandinavian screening study tested the difference and found 5% more *S. aureus* carriers with enrichment broth than with agar culture media [17]. However, we still observed higher proportions than described elsewhere, even after subtracting 5% from our carrier proportion. Secondly, our novel and simplified home-based screening approach differs from ambulant or hospital-based methods used in other studies. Our participants received detailed verbal and written instruction on how to swab their noses themselves. A recent study screening of 102 participants found no substantial difference in detection proportions between swabbing performed by a nurse and swabbing by the patients [39]. A home-based approach is also easier for patients, ensures higher recruitment numbers, and has the shortest possible interval

between nose swabbing and the operation date. This in turn minimizes the bias of intermittent carriers.

SSI Reduction in Patients not Colonized with *S. aureus*

We also found no benefit of decolonization in noncarrier patients with respect to reducing SSI risk. Ours is the first trial we know of to study the efficacy of decolonization in noncarriers. This is relevant as universal decolonization protocols without prior screening of *S. aureus* carriers are promoted as more cost-effective than the screen-and treat strategy [16]. Our results suggest that decolonization in this group may be of no benefit. Even worse, such a practice may promote the development of bacterial resistance [2] and expose patients to possible adverse events. In fact, we recorded nine adverse reactions possibly connected to chlorhexidine in the noncarrier group.

In a large retrospective cohort, 2519 decolonized *S. aureus* carriers were identified among 13,828 patients undergoing spine surgery or arthroplasty [30]. Despite decolonization, carriers remained at a substantially higher risk of SSI than noncarriers. Our study adds novel information because results show that decolonized noncarriers did not experience less SSI than noncarriers, in the control arm or in both carriers' arms. This indicates no added benefit of decolonization in practice in this respect as well.

We found no difference in the SSI risk between the decolonization and the control groups; both in *S. aureus* carriers and noncarriers. Due to the low event numbers, no definite conclusion about the efficacy of preoperative decolonization can be drawn, but these results could be helpful for future meta-analyses. A mega trial to establish definitive proof on routine preoperative decolonization in a population with a low prevalence of SSI is probably not justified. Future studies may focus on high-risk patients for SSI or on bundle approaches, as these show the best results.

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