Original Investigation

Association of a Bundled Intervention With Surgical Site Infections Among Patients Undergoing Cardiac, Hip, or Knee Surgery

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IMPORTANCE Previous studies suggested that a bundled intervention was associated with lower rates of *Staphylococcus aureus* surgical site infections (SSIs) among patients having cardiac or orthopedic operations.

OBJECTIVE To evaluate whether the implementation of an evidence-based bundle is associated with a lower risk of *S aureus* SSIs in patients undergoing cardiac operations or hip or knee arthroplasties.

DESIGN, SETTING, AND PARTICIPANTS Twenty hospitals in 9 US states participated in this pragmatic study; rates of SSIs were collected for a median of 39 months (range, 39-43) during the preintervention period (March 1, 2009, to intervention) and a median of 21 months (range, 14-22) during the intervention period (from intervention start through March 31, 2014).

INTERVENTIONS Patients whose preoperative nares screens were positive for methicillin-resistant *S aureus* (MRSA) or methicillin-susceptible *S aureus* (MSSA) were asked to apply mupirocin intranasally twice daily for up to 5 days and to bathe daily with chlorhexidine-gluconate (CHG) for up to 5 days before their operations. MRSA carriers received vancomycin and cefazolin or cefuroxime for perioperative prophylaxis; all others received cefazolin or cefuroxime. Patients who were MRSA-negative and MSSA-negative bathed with CHG the night before and morning of their operations. Patients were treated as MRSA-positive if screening results were unknown.

MAIN OUTCOMES AND MEASURES The primary outcome was complex (deep incisional or organ space) *S aureus* SSIs. Monthly SSI counts were analyzed using Poisson regression analysis.

RESULTS After a 3-month phase-in period, bundle adherence was 83% (39% full adherence; 44% partial adherence). Overall, 101 complex *S aureus* SSIs occurred after 28 218 operations during the preintervention period and 29 occurred after 14 316 operations during the intervention period (mean rate per 10 000 operations, 36 for preintervention period vs 21 for intervention period, difference, −15 [95% CI, −35 to −2]; rate ratio [RR], 0.58 [95% CI, 0.37 to 0.92]). The rates of complex *S aureus* SSIs decreased for hip or knee arthroplasties (difference per 10 000 operations, −17 [95% CI, −39 to 0]; RR, 0.48 [95% CI, 0.29 to 0.80]) and for cardiac operations (difference per 10 000 operations, −6 [95% CI, −48 to 8]; RR, 0.86 [95% CI, 0.47 to 1.57]).

CONCLUSIONS AND RELEVANCE In this multicenter study, a bundle comprising *S aureus* screening, decolonization, and targeted prophylaxis was associated with a modest, statistically significant decrease in complex *S aureus* SSIs.

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Editorial page 2131

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Staphylococcus aureus carriage increases the risk of *S aureus* surgical site infections (SSIs).[1-4] The risk for these infections may be decreased by screening patients for nasal carriage of *S aureus* and decolonizing carriers during the preoperative period.[2,5] In addition, perioperative prophylaxis with agents such as vancomycin may reduce rates of methicillin-resistant *S aureus* (MRSA) SSIs.[6,7] A meta-analysis found that a bundle comprising screening for *S aureus* nasal carriage, decolonizing carriers with intranasal mupirocin and chlorhexidine gluconate (CHG) bathing, and using vancomycin for prophylaxis among MRSA carriers was associated with lower rates of *S aureus* SSIs among patients undergoing select cardiac operations or hip or knee arthroplasties.[8]

SSI *surgical site infection*

MRSA *methicillin-resistant* Staphylococcus aureus

MSSA *methicillin-susceptible* Staphylococcus aureus

CHG *chlorhexidine gluconate*

Despite this evidence, surveys in the United States indicate that adoption of screening and decolonization bundles varies substantially; most clinicians do not screen patients for *S aureus* carriage before operations and those that screen patients often screen for MRSA alone.[9,10] Similarly, clinicians that decolonize patients preoperatively usually decolonize only patients carrying MRSA despite the greater frequency of colonization by methicillin-susceptible *S aureus* (MSSA) and the severity of MSSA infections.[9,10]

The effectiveness of the bundle assessed in the meta-analysis[8] had, to our knowledge, not been evaluated in a multicenter study. Thus, we conducted a 20-hospital quasi-experimental pragmatic study—the Study to Optimally Prevent SSIs in Select Cardiac and Orthopedic Procedures (STOP SSI)—to determine whether an evidence-based bundle (screening for *S aureus*, decolonizing carriers, and prescribing optimal perioperative antibiotics) would be associated with a lower incidence of *S aureus* SSIs compared with standard practice. We hypothesized that bundle implementation would be associated with a lower incidence of complex (ie, deep incisional or organ space[11,12]) *S aureus* SSIs among patients undergoing cardiac operations or hip or knee arthroplasties.

Methods

Study Design

The Hospital Corporation of America (HCA) research group determined that the intervention was a quality improvement initiative and not human participants research.[13] Institutional review boards from the University of Iowa and The Joint Commission exempted the study because analyzing deidentified data (University of Iowa) and evaluating implementation (The Joint Commission) were not human participants research. Twenty HCA-affiliated hospitals participated in a 5-year, quasi-experimental, pragmatic study[14,15] that utilized preintervention observational measurements, a prospective intervention group, and time-series analysis to evaluate an evidence-based bundle to prevent *S aureus* SSIs (trial protocol in Supplement 1). The preintervention period extended from March 1, 2009, to the date on which a hospital began the intervention. Hospitals implemented the bundle on a rolling basis with the earliest implementations occurring June 1, 2012, and the latest October 9, 2012.

Intervention

Hospital staff swabbed patients' nares during scheduled preoperative clinic visits (usually 10-14 days, but no more than 30 days before the operations). Each laboratory used their standard tests (eg, polymerase chain reaction, culture on chromogenic agar, standard bacterial culture) to determine MRSA and MSSA carrier status. The most common tests were chromogenic agar for MRSA and standard culture for MSSA. Patients with positive screening tests for either MRSA or MSSA applied mupirocin intranasally twice daily and bathed with CHG once daily for up to 5 days immediately before their operations. Patients that received fewer than 10 doses of mupirocin before their operations received the remaining doses during the postoperative period. The CHG bathing was not continued after the operation. Patients with negative MRSA and MSSA nasal screens bathed with CHG the night before and the morning of their operations.[8,13]

Perioperative prophylaxis was administered using weight-based dosing and redosing according to the 2013 American Society of Health-System Pharmacists (ASHP) guidelines.[16] The antimicrobial agents used for perioperative prophylaxis varied by the patients' *S aureus* carrier status; noncarriers and MSSA carriers received either cefazolin or cefuroxime for perioperative prophylaxis, whereas MRSA carriers received both cefazolin or cefuroxime and vancomycin. If a patient had a confirmed β-lactam allergy, surgeons were encouraged to provide perioperative prophylaxis with vancomycin rather than cefazolin or cefuroxime and to add either gentamicin or aztreonam for gram-negative coverage. Patients with negative screening tests but with documented histories of MRSA carriage or infection were treated as carriers. Patients who were either not screened because they had emergent operations or whose screening results were not known at the time of their operations received vancomycin and cefazolin or cefuroxime for perioperative prophylaxis. In these situations, nasal swabs were obtained for MSSA and MRSA screening and patients began the decolonization regimen immediately before their operations. Mupirocin was continued until screening test results were known; mupirocin was discontinued if test results were negative.

We categorized each operation as fully adherent, partially adherent, or not adherent based on the elements of the bundle that the patient received (eTable 1 in Supplement 2). Because implementation of the bundle elements varied among individual surgeons, we also documented the extent of surgeon implementation as "full," "partial" (eg, did not give vancomycin prophylaxis to patients undergoing emergent operations), or "not at all."

Recruitment and Eligibility Criteria

Hospital sites were selected as described previously.[13] Hospitals using some, but not all, bundle elements during the preintervention period could participate (eAppendix 1 in Supplement 2). Eligible patients were 18 years or older and un-

derwent scheduled, urgent, or emergent primary hip or knee arthroplasty (ie, replacement or resurfacing) or primary cardiac operation through a median sternotomy incision (eTable 2 in Supplement 2). Arthroplasty revisions, cardiac transplants, transapical valve implantation, and operations performed using percutaneous or thoracotomy approaches were not eligible for this study. We excluded operations among patients with preexisting infections at the surgical site.

Surveillance and Data Collection

Patients were followed up for 90 days after their operations by infection preventionists at participating hospitals. The infection preventionists identified patients who met the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network's (NHSN) SSI definitions.[17-20] An NHSN form was completed for each SSI in both the preintervention and intervention periods. The site infection preventionists were instructed to perform surveillance consistently throughout the study period. We attributed SSIs to the months during which the operations were performed. Each site audited at least 5 cases per month for concurrent review to assess adherence to bundle elements and identify areas for improvement. Additionally, an experienced infection preventionist reviewed medical records from 10% of patients with SSIs and confirmed that all met the CDC NHSN SSI definition. Other variables were obtained from corporate data warehouses, which undergo validation until 99% to 100% accuracy is achieved.

Laboratory Methods

Antimicrobial Susceptibility Testing

Available *S aureus* isolates from SSIs occurring during the intervention period were sent to a reference laboratory and tested for mupirocin and chlorhexidine susceptibility. For CHG susceptibility testing, laboratory staff used chlorhexidine digluconate 20% aqueous solution (Sigma-Aldrich) and the standard Clinical and Laboratory Standards Institute broth dilution method with a complete inhibition end point at 18 to 24 hours of incubation.[21] Staff assessed mupirocin susceptibility with the epsilometer method (Etest, bioMérieux).[22]

qac Polymerase Chain Reaction

Laboratory staff tested isolates for the genes encoding quaternary ammonium compound (*qac*) efflux proteins (*qacA/B* genes), which have been associated with CHG nonsusceptibility. They used single primer pair sequences to detect *qacA/B*.[23]

Outcomes

To minimize ascertainment bias, the primary study outcome was the rate of complex MSSA or MRSA SSIs. Patients with complex SSIs after cardiac operations or joint replacements were likely to be seen by their surgeons for diagnosis and treatment. Thus, infection preventionists would identify these patients during routine surveillance, whereas patients with superficial infections could be missed. We conducted subgroup analyses to assess rates of complex *S aureus* SSIs stratified by the following variables chosen a priori: MRSA or MSSA and operation group (ie, cardiac operations or joint arthroplasties). Also, based on our experiences with the study implementation, we performed stratified analyses on the following variables chosen ad hoc: operation scheduling, adherence with the bundle elements, and the extent of surgeon implementation.

Other outcomes of interest chosen a priori were the rates of all SSIs (superficial and complex SSI, caused by any pathogen); all gram-negative SSIs; all complex SSIs; the patient's postoperative length of stay during the index admission (available for operations performed after June 2011); and readmissions to the index hospital or another facility for treatment of SSIs within the first 90 days after the operation. Study-related adverse events were documented by each study site using standardized forms (Supplement 3).

Sample Size

On the basis of the surgical volumes and SSI rates at the 20 hospitals during 2010 (67 *S aureus* SSIs/10 000 cardiac operations, 92/10 000 hip arthroplasties, 43/10 000 knee arthroplasties), we needed at least 8905 operations in the intervention group to reach 70% power to detect a 30% relative reduction (rate ratio [RR], 0.70) in the *S aureus* SSI rate. Thus, the sample size at the 20 participating hospitals was sufficient.

Statistical Analysis

We used SAS software (SAS Institute), version 9.2, to perform intention-to-treat analyses comparing patients during the intervention period with patients during the preintervention period. The significance level was .05 using a 2-sided test.

Patient-Level Analysis

We used logistic regression to evaluate the intervention's association with SSIs and with readmissions related to SSIs while adjusting for patient-level confounders (age, diabetes, Charlson comorbidity index,[24] history of MRSA). We used traditional regression to analyze log-transformed postoperative length of stay while adjusting for patient-level confounders. We fit all models with generalized estimating equations to accommodate hospital-level clustering effects and we used an exchangeable working correlation structure.

Hospital-Level Time-Series Analysis of SSI Rates

We analyzed monthly SSI counts (ie, time-series data) using Poisson regression models with a log link and with log-transformed monthly operation counts as an offset variable. If a hospital implemented the intervention in the middle of a month, we attributed the SSI rate for that month to the intervention period. To account for temporal autocorrelation within hospitals and for hospital-level clustering effects, we fit the models with generalized estimating equations, specifying a first-order autoregressive working correlation structure. We built separate models for each SSI outcome and for each operation group, using rate ratios to express the association between the intervention and the SSI outcome.

We obtained estimates of mean SSI rates for the preintervention and the intervention periods, and estimates of their corresponding differences, from Poisson regression models. To obtain CIs for the mean SSI rate differences for all operations, hip or knee arthroplasties, and cardiac operations, we

analyzed monthly SSI rates using Gaussian linear regression models with an identity link. This model was fit using generalized estimating equations as previously described. Because the SSI rates were right-skewed, Gaussian regression was a suboptimal modeling framework in this setting, yet it provided a convenient method for obtaining interval estimates for mean rate differences.

Results

Twenty urban hospitals in 9 US states met the eligibility criteria and were willing to participate in the study. Bed size ranged from 52 to 514 beds; 5 hospitals were minor teaching hospitals and 15 were nonteaching (eAppendix 2 in Supplement 2). Eight hospitals implemented the bundle for joint arthroplasties, 4 for cardiac operations, and 8 for both categories. Eleven hospitals (55%) implemented the bundle by July 1, 2012. One hospital stopped the intervention on March 31, 2013; 19 continued through March 31, 2014. The median preintervention period was 39 months (range, 39-43) and the median intervention period was 21 months (range, 14-22).

During the study period, participating sites performed 43 087 operations of interest (28 593 preintervention; 14 494 intervention). We removed 552 operations from this cohort: 292 were performed among pediatric patients, 219 were performed among patients with infections, and 41 were revision arthroplasties. The final study population was 42 534 operations among 38 049 unique patients (preintervention period, 28 218 operations; intervention period, 14 316 operations). Among patients undergoing cardiac operations, those during the intervention period were more likely to have diabetes mellitus than those during the preintervention period. Among patients having hip or knee arthroplasties, those during the intervention period were younger, had lower Charlson comorbidity index scores, and were less likely to have a history of MRSA carriage than those during the preintervention period (**Table 1**). During the intervention period, 2135 patients (14.9%) had documented β-lactam allergies.

SSI Rates

During the preintervention period, there were 101 complex *S aureus* SSIs (MRSA, 45; MSSA, 44; unknown methicillin susceptibility, 12) compared with 29 during the intervention period (MRSA, 14; MSSA, 13; unknown methicillin susceptibility, 2) . In the patient-level analysis, a logistic regression model controlling for age, diabetes, Charlson comorbidity index, and MRSA history found that implementation of the bundle was associated with a significant reduction in complex *S aureus* SSIs (odds ratio [OR], 0.60 [95% CI, 0.37-0.98]). The number of months without any complex *S aureus* SSIs increased from 2 of 39 months (5.1%) to 8 of 22 months (36.4%; $P = .006$ by Fisher exact test). In the hospital-level time-series analysis, a Poisson regression model found that the monthly rates of complex *S aureus* SSIs decreased significantly from 36 to 21 per 10 000 operations (mean difference, −15 [95% CI, −35 to −2]; rate ratio [RR], 0.58 [95% CI, 0.37 to 0.92]) during the intervention (**Figure 1** and **Table 2**). The rates of MRSA (RR, 0.60 [95% CI, 0.32 to 1.14]) and the rates of MSSA (RR, 0.64 [95% CI, 0.38 to 1.07]) complex SSIs did not change significantly when analyzed separately.

In the subgroup analyses, the rates of complex *S aureus* SSIs decreased significantly after scheduled operations (RR, 0.55 [95% CI, 0.35 to 0.86]) but did not decrease after urgent or emergent operations (Table 2). The rates of complex *S aureus* SSIs decreased significantly after hip or knee arthroplasties (difference per 10 000 operations, −17 [95% CI, −39 to 0]; RR, 0.48 [95% CI, 0.29 to 0.80]), whereas the rates of complex *S aureus* SSIs after cardiac operations did not (difference per 10 000 operations, −6 [95% CI, −48 to 8]; RR, 0.86 [95% CI, 0.47 to 1.57]). Similarly, the rates of all *S aureus* SSIs (mean rate per 10 000 operations, 47 for the preintervention period vs 30 for the intervention period; RR, 0.64 [95% CI, 0.38 to 1.09]), all gram-negative SSIs (mean rate per 10 000 operations, 28 for the preintervention period vs 23 for the intervention period; RR, 0.86 [95% CI, 0.42 to 1.75]), and of complex SSIs caused by any pathogen (mean rate per 10 000 operations, 68 for the preintervention period vs 45 for the intervention period; RR, 0.67 [95% CI, 0.44 to 1.00]) did not decrease significantly.

Adherence to the Bundle

After a 3-month phase-in period, bundle adherence remained constant at 83% (full adherence, 39%; partial adherence, 44%; **Figure 2**). **Figure 3** illustrates adherence by operation scheduling and by screening results; eFigure 1 in Supplement 2 illustrates adherence to each bundle element. The complex *S aureus* SSI rates decreased significantly among patients in the fully adherent group compared with the preintervention period (RR, 0.26 [95% CI, 0.10-0.69]), but rates did not decrease significantly in the partially adherent or nonadherent group (RR, 0.80 [95% CI, 0.49-1.31]).

During the intervention period, surgeons that implemented at least some bundle elements (fully and partially implemented) performed 10 850 scheduled operations (92.3%) and 909 emergent operations (7.7%). Among these surgeons, bundle adherence was 87.6% for scheduled operations (full adherence, 47.8%; partial adherence, 39.8%) compared with 61.8% for urgent or emergent operations (full adherence, 1.7%; partial adherence, 60.1%). The rates of complex *S aureus* SSIs decreased significantly (RR, 0.54 [95% CI, 0.34-0.88]) after operations performed by these surgeons, but not after operations done by surgeons that did not implement any bundle elements (RR, 0.80 [95% CI, 0.33-1.98]).

Patients reported they did not use mupirocin or CHG as directed before 328 operations. The most common reasons for nonadherence were problems with the prescription or supply (27.1%), patients forgot or did not understand instructions (18.0%), elements were not applicable (14.9%), allergy (2.1%), and patient preference (1.5%).

Other Outcomes

The median postoperative length of stay for both the preintervention and intervention periods was 3 days. A smaller proportion of patients was readmitted for SSIs within 90 days of their operations during the intervention period (0.12%) than during the preintervention period (0.21%; OR, 0.57 [95% CI,

Table 1. Characteristics of Patients Undergoing Selected Operations During the Preintervention and Intervention Periods[a]

	All	Preintervention	Intervention	*P* Value
Cardiac Operations				
No. of operations	10 833	7576	3257	
Women	3409 (31.5)	2408 (31.8)	1000 (30.7)	.27
Age, median (range), y	67 (18-95)	67 (18-94)	67 (18-95)	.78
Diabetes	4402 (40.6)	3023 (39.9)	1379 (42.3)	.02
Renal disease	31 (0.3)	25 (0.3)	6 (0.2)	.19
Cancer	184 (1.7)	127 (1.7)	57 (1.8)	.79
Charlson comorbidity score ≥2	5100 (47.1)	3600 (47.5)	1500 (46.1)	.16
MRSA history	449 (4.2)	329 (4.3)	120 (3.7)	.11
Smoking history[b]	2998 (60.0) (n = 5001)	1517 (60.9) (n = 2490)	1481 (60.0) (n = 2511)	.16
Albumin, mean (SD), g/dL[b]				
Preoperative[c]	3.53 (0.53) (n = 5475)	3.53 (0.53) (n = 2993)	3.53 (0.52) (n = 2482)	.88
Postoperative[c]	3.08 (0.59) (n = 3085)	3.17 (0.61) (n = 1881)	2.94 (0.52) (n = 1204)	<.001
Creatinine, mean (SD), mg/dL[b]				
Preoperative[d]	1.17 (0.97) (n = 6689)	1.20 (0.96) (n = 3746)	1.14 (1.00) (n = 2943)	<.001
Postoperative[d]	1.16 (0.88) (n = 8142)	1.20 (0.91) (n = 4930)	1.11 (0.86) (n = 3212)	<.001
Glucose, mean (SD), mg/dL[b]				
Preoperative[e]	126.9 (48.1) (n = 6805)	126.9 (49.0) (n = 3812)	126.9 (47.0) (n = 2993)	.96
Postoperative[e]	143.4 (46.9) (n = 8165)	142.5 (48.9) (n = 4955)	144.7 (43.6) (n = 3210)	<.001
Hip or Knee Arthroplasties				
No. of operations	31 701	20 642	11 059	
Women	19 395 (61.2) (n = 31 692)	12 661 (61.4) (n = 20 633)	6734 (60.9)	.41
Age, median (range), y	68 (18-107)	68 (21-107)	68 (18-101)	<.001
Diabetes	6304 (19.4)	4158 (20.1)	2146 (19.4)	.12
Renal disease	26 (0.08)	17 (0.08)	9 (0.08)	.98
Cancer	393 (1.2)	250 (1.2)	143 (1.3)	.53
Charlson comorbidity score ≥2	3590 (11.3)	2446 (11.9)	1144 (10.3)	<.001
MRSA history	1122 (3.5)	788 (3.8)	334 (3.0)	<.001
Smoking history[b]	7749 (46.6) (n = 16 631)	3656 (47.4) (n = 7717)	4093 (45.9) (n = 8914)	.06
Albumin, mean (SD), g/dL[b]				
Preoperative[c]	3.72 (0.46) (n = 6918)	3.73 (0.46) (n = 3682)	3.71 (0.46) (n = 3236)	.03
Postoperative[c]	2.89 (0.46) (n = 3157)	2.91 (0.49) (n = 1832)	2.84 (0.41) (n = 1325)	<.001
Creatinine, mean (SD), mg/dL[b]				
Preoperative[d]	1.00 (0.58) (n = 14 474)	1.03 (0.57) (n = 7435)	0.97 (0.58) (n = 7039)	<.001
Postoperative[d]	1.00 (0.66) (n = 21 303)	1.03 (0.75) (n = 11 644)	0.98 (0.54) (n = 9659)	<.001
Glucose, mean (SD), mg/dL[b]				
Preoperative[e]	110.5 (34.0) (n = 15 567)	112.0 (34.1) (n = 8022)	108.9 (33.9) (n = 7545)	<.001
Postoperative[e]	137.6 (38.6) (n = 21 391)	138.3 (37.8) (n = 11 798)	136.8 (39.6) (n = 9593)	.04

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*.

SI conversion factors: To convert creatinine to μmol/L multiply by 88.4; glucose to mmol/L, multiply by 0.0555.

[a] To compare patient characteristics in the 2 study groups, we used the χ^2 test for categorical variables and the Wilcoxon rank-sum test for quantitative variables.

[b] Many missing values.

[c] Most albumin samples were obtained within 2 days before the operations (median [range], 2 days [0-49]) and within 1 day after the operations (median [range], 0.7 days [0-2]).

[d] Most creatinine samples were obtained within 2 days before the operations (median [range], 1.2 days [0-44]) and within 1 day after the operations (median [range], 0.6 days [0-2]).

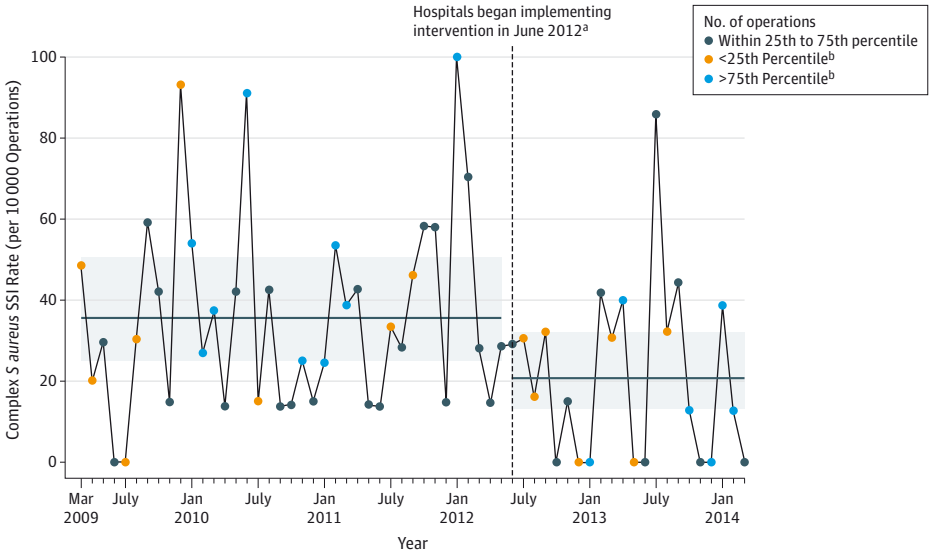
[e] Most glucose samples were obtained within 1 day before the operations (median [range], 0.7 days [2-44]) and within 1 day after the operations (median [range], 0.5 days [0-2]).

0.33-0.97]). After adjusting for age, diabetes, Charlson comorbidity index, and MRSA history, the intervention was not associated with a significant decrease in postoperative length of stay (multiplicative mean decrease, 0.95 [95% CI, 0.87-1.03]) or readmissions (OR, 0.58 [95% CI, 0.22-1.52]).

Adverse Events

Four patients reported mild skin irritation associated with preoperative CHG bathing; symptoms quickly abated when the product was discontinued. No patients reported adverse reactions to mupirocin.

Figure 1. Pooled Rate of Complex *Staphylococcus aureus* Surgical Site Infections (SSIs) by Admission Month



The spike in the rate of complex *S aureus* SSI rate in July 2013 occurred among patients whose surgeons did not implement the bundle. The complex *S aureus* SSI rate was 50 per 10 000 operations in the subgroup of operations done by surgeons implementing the bundle and was 240 per 10 000 operations in the subgroup of operations done by surgeons not implementing the bundle.

[a] The number of months without any complex *S aureus* SSIs increased from 2 of 39 (5.1%) to 8 of 22 (36.4%; *P* = .006 by the Fisher exact test). Poisson regression analysis found a significant decrease in complex *S aureus* SSIs from 36/10 000 operations (95% CI, 25-51) during preintervention period to 21 per 10 000 operations (95% CI, 13-32) during intervention period (rate ratio, 0.58 [95% CI, 0.37-0.92]); the shaded areas indicate the 95% CIs of the Poisson regression analysis. Hospitals implemented the bundle on a rolling basis (earliest, June 1, 2012; latest, October 9, 2012). Eleven hospitals (55%) implemented the bundle by July 1, 2012.

[b] See eTable 3 in Supplement 2 for the monthly number of complex *S aureus* SSIs, number of operations, and rate of complex *S aureus* SSIs for each hospital.

Table 2. Poisson Regression Analysis of Monthly Rates of Complex *Staphylococcus aureus* Surgical Site Infections per 10 000 Operations

	Preintervention Period		Intervention Period		Rate Ratio for Bundled Intervention (95% CI)	*P* Value
	No. of Operations	Mean Rate (95% CI)	No. of Operations	Mean Rate (95% CI)		
All operations	28 218	36 (25-51)	14 316	21 (13-32)	0.58 (0.37-0.92)[a]	.02
Urgent/emergent			1189	37 (15-88)	1.03 (0.41-2.57)[a]	.95
Scheduled			13 127	20 (13-30)	0.55 (0.35-0.86)[a]	.009
Cardiac operations	7576	46 (26-82)	3257	40 (23-70)	0.86 (0.47-1.57)[b]	.63
Urgent/emergent			571	67 (32-137)	1.44 (0.53-3.91)[b]	.48
Scheduled			2686	33 (18-62)	0.72 (0.45-1.15)[b]	.17
Hip or knee arthroplasties	20 642	32 (21-48)	11 059	15 (10-24)	0.48 (0.29-0.80)[c]	.005
Urgent/emergent			618	14 (3-75)	0.44 (0.07-2.72)[c]	.38
Scheduled			10 441	16 (10-26)	0.51 (0.30-0.85)[c]	.009

Abbreviations: SSI, surgical site infection.

[a] Compared with the monthly rates of complex *S aureus* SSIs after all operations performed during the preintervention period.

[b] Compared with the monthly rates of complex *S aureus* SSIs after all cardiac operations performed during the preintervention period.

[c] Compared with the monthly rates of complex *S aureus* SSIs after all hip or knee arthroplasties performed during preintervention period.

Antimicrobial Susceptibility

Thirty-six *S aureus* isolates from wound cultures were tested for mupirocin and CHG susceptibility, of which 1 isolate had high-level resistance to mupirocin. CHG minimum inhibitory concentrations clustered at 1 to 2 µg/mL; 1 isolate had a CHG minimum inhibitory concentration of 4 µg/mL. No isolates carried *qac*.

Discussion

This multicenter study showed that implementation of an SSI prevention bundle was associated with reduced *S aureus* SSI rates. We did not find evidence suggesting that SSIs caused by other pathogens replaced those caused by

Figure 2. Bundled Intervention Adherence by Month During the Intervention Period (N=14 316 Operations)

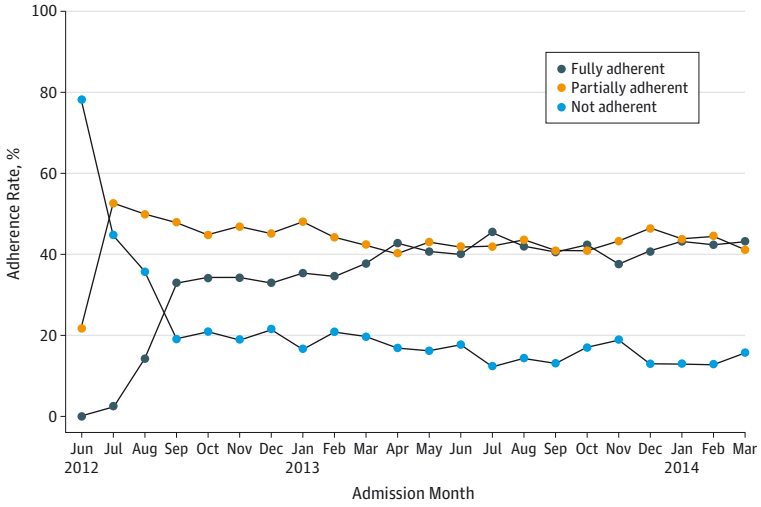
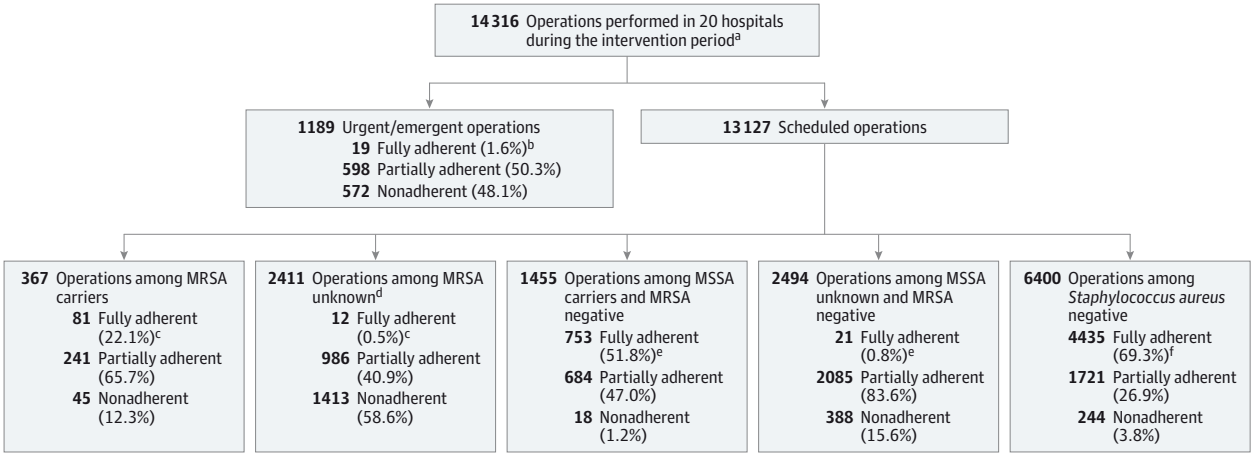


Figure 3. Bundled Intervention Adherence by Operation Scheduling and *Staphylococcus aureus* Carriage Status



CHG indicates chlorhexidine gluconate; MSSA, methicillin-susceptible *S aureus*; MRSA, methicillin-resistant *S aureus*.

[a] Includes patients whose surgeons did not implement the bundle.

[b] Fully adherent defined as patient received both mupirocin (≥ 1 day) and prophylaxis with vancomycin and cefazolin or cefuroxime.

[c] Fully adherent defined as patient received CHG bathing, mupirocin for 3 days or more, and prophylaxis with vancomycin and cefazolin or cefuroxime.

[d] Among MRSA unknown, 1924 operations (79.8%) were MSSA unknown, 376 operations (15.6%) were MSSA noncarriers, and 111 operations (4.6%) were MSSA carriers.

[e] Fully adherent defined as patient received CHG bathing, mupirocin for 3 days or more, and cefazolin or cefuroxime prophylaxis.

[f] Fully adherent defined as patient received both CHG bathing and cefazolin or cefuroxime prophylaxis.

S aureus and we identified very few adverse events. These results are notable because this was a pragmatic study that included operations often excluded in randomized clinical trials (eg, emergent operations). To our knowledge, STOP SSI is the largest study to test an SSI prevention bundle under pragmatic clinical conditions. Even though the baseline rate of complex *S aureus* SSI was low (0.36 per 10 000 operations), the full adherence rate was only 39%, and hospitals had implemented some bundle elements before the study began, rates of complex *S aureus* SSIs decreased significantly. Given that approximately 400 000 cardiac operations and 1 million total joint arthroplasties are performed in the United States each year,[25] numerous *S aureus* SSIs, which can have catastrophic consequences, may be preventable. Moreover, 1 SSI adds from $13 000 to $100 000 to the cost of health care.[26-28] Thus, implementation of this bundle might reduce patient morbidity and the costs of care substantially.

Our results suggest that adherence to the full bundle is important. Given that adherence rates for patients who had urgent or emergent operations performed by surgeons who implemented the bundle were substantially lower than for patients who underwent scheduled operations, we hypothesize that institutional barriers may prevent full bundle adherence for patients undergoing urgent or emergent operations.

This bundle is concordant with current SSI prevention guidelines. For example, the bundle stipulates that vancomycin be given as perioperative prophylaxis only for patients who are MRSA-positive or for patients whose *S aureus* carriage status is unknown at the time of the operation, which meets Surgical Care Improvement Project criteria.[29] Similarly, guidelines from ASHP, the Society of Thoracic Surgeons, the Infectious Diseases Society of America, the Surgical Infection Society, and the Society for Healthcare Epidemiology of America state that mupirocin may have utility among *S aureus* carriers, and that patients carrying MRSA should receive vancomycin and cefazolin or cefuroxime because vancomycin is not active against gram-negative organisms[16,30] and it prevents MSSA SSIs less effectively than cefazolin or cefuroxime.[8] Cefazolin or cefuroxime also provide some gram-negative coverage, which is important because these organisms cause an estimated 34% of SSIs after cardiac operations and 18% after total joint arthroplasty.[11]

Consistent with results of prior studies, only 1 *S aureus* isolate in this study had high-level resistance to mupirocin.[31,32] As surgical patients are at risk for SSI during a relatively narrow period[18] and 70% of *S aureus* nasal carriers treated preoperatively with mupirocin and CHG are still decolonized after a mean of 156 days,[33] a single short course of mupirocin should be adequate to protect patients and minimize the risk of selecting resistant isolates.[5] Although screening and decolonization are more difficult than treating all patients with intranasal mupirocin, we screened patients for MRSA and MSSA nasal carriage and treated carriers to lower the risk of resistance further.

This was a pragmatic study because each hospital implemented the bundle to accommodate their resources and practice patterns.[14,15] Nevertheless, resources from the health system—a shared electronic medical record, a quality and infection prevention infrastructure, and corporate support for system-wide implementation of best practices—facilitated bundle implementation and data collection at individual hospitals. Recently, investigators demonstrated that bundled interventions for preventing catheter-related bloodstream infections[34] or surgical complications[35] can be maintained long-term. Similarly, the current bundle should be relatively simple to maintain because it does not require expensive technology or additional staff.

This study had limitations. First, surveillance for SSI varied somewhat among the hospitals. For example, some infection preventionists did active surveillance after discharge and some learned that specific patients had SSIs from other clinicians in the area. A survey conducted after the intervention found that sites had not changed surveillance practices during the study, which was more important to this study design than having all hospitals use identical surveillance methods, particularly because the primary outcome (complicated *S aureus* SSIs) should be identified by any surveillance system. Second, the study results may not be generalizable to large academic health centers or to hospitals without strong infrastructures for quality improvement. However, the results may be more generalizable than the results of most randomized trials because this pragmatic study more closely mimicked the clinical situation.[14,15] Third, neither patients nor facilities were randomized and thus the results may be biased by regression to the mean, seasonal effects, or secular trends.[36] However, these biases are unlikely because we compared monthly endemic SSI rates during a 39- to 43-month preintervention period and a 14- to 22-month intervention period, and modeling analyses did not identify evidence of long-term trends or seasonal effects over these periods. The results of the subset analyses also mitigate this concern because complex *S aureus* SSIs decreased significantly only among the subset of patients who had scheduled operations and the subset of fully adherent patients but not among the subset of patients who had urgent or emergent operations and the subset of partially adherent or nonadherent patients. If our results were due to temporal biases, the decrease would be seen among all subsets. Rolling implementation may have helped reduce the likelihood of bias due to seasonal maturation. Additionally, these hospitals did not change other aspects of SSI prevention or surveillance during the entire study. Last, we found some statistically significant differences in patient characteristics between the preintervention group and the intervention group. The presence of these measured confounders, and unmeasured confounders, could have led to biased results.

Conclusions

In this multicenter study, a bundle comprising *S aureus* screening, decolonization, and targeted prophylaxis was associated with a modest, statistically significant decrease in complex *S aureus* SSIs.

ARTICLE INFORMATION

Author Contributions: Dr Schweizer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Schweizer, Septimus, Braun, Hickok, Perencevich, Richards, Cavanaugh, Herwaldt.
Acquisition, analysis, or interpretation of data: Schweizer, Chiang, Septimus, Moody, Braun, Hafner, Ward, Hickok, Perencevich, Diekema, Richards, Cavanaugh, Perlin, Herwaldt.
Drafting of the manuscript: Schweizer, Chiang, Septimus, Moody, Ward, Cavanaugh, Herwaldt.
Critical revision of the manuscript for important intellectual content: Schweizer, Chiang, Septimus, Braun, Hafner, Hickok, Perencevich, Diekema, Richards, Cavanaugh, Perlin, Herwaldt.
Statistical analysis: Chiang, Septimus, Ward, Cavanaugh.
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Study supervision: Schweizer, Septimus, Braun, Hafner, Hickok, Perencevich, Cavanaugh, Perlin, Herwaldt.

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