MAJOR ARTICLE

Staphylococcus aureus Infections After Elective Cardiothoracic Surgery: Observations From an International Randomized Placebo-Controlled Trial of an Investigational *S aureus* Vaccine

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Background. An unmet need to prevent *Staphylococcus aureus* (SA) infections after cardiothoracic surgery persists despite current practices. Cost-effective implementation of preventive strategies requires contemporary knowledge about modifiable risk factors.

Methods. From 2007 to 2011, an international, double-blind, randomized placebo-controlled trial of a novel SA vaccine (V710) was conducted in 7664 adults scheduled for median sternotomy at 164 sites. We analyzed SA infections developing up to 360 days postoperatively in 3832 placebo recipients.

Results. Coronary artery bypass grafting was performed in 80.8% (3096 of 3832) of placebo recipients. The overall incidence of any postoperative SA infection was 3.1% (120 of 3832). Invasive SA infections (including bacteremia and deep sternal-wound infections) developed in 1.0%. Methicillin-resistant SA (MRSA) accounted for 19% (23 of 120) of SA infections, with 57% (13 of 23) of the MRSA infections occurring in diabetic patients. All-cause mortality was 4.1% (153 of 3712) in patients without SA infection, 7.2% (7 of 97) in methicillin-susceptible SA (MSSA) infections, and 17.3% (4 of 23) in MRSA infections ($P < .01$). *Staphylococcus aureus* nasal carriage was detected preoperatively in 18.3% (701 of 3096) patients, including 1.6% colonized with MRSA. Postoperative SA infections occurred in 7.0% (49 of 701) of colonized patients versus 2.3% (71 of 3131) of patients without colonization (relative risk = 3.1 [95% confidence interval, 2.2–4.4]).

Conclusions. In this large international cohort of patients undergoing cardiac surgery and observed prospectively, invasive postoperative SA infections occurred in 1% of adult patients despite modern perioperative management. The attributable mortality rates were 3% for MSSA and 13% for MRSA infections. Preoperative nasal colonization with SA increased the risk of postoperative infection threefold. The utility of strategies to reduce this incidence warrants continued investigation.

Keywords. cardiac surgery; Merck V710 vaccine; postoperative infection; *Staphylococcus aureus*.

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Postoperative *Staphylococcus aureus* (SA) infections continue to cause substantial morbidity and mortality [1–3]. Invasive infections such as mediastinitis negatively impact both short- and long-term survival after heart operations [4]. Active surveillance and selective decolonization, universal decontamination, perioperative interventions (including the choice and duration of antibiotic prophylaxis), and targeted immunization have all been used to reduce the incidence of SA

infections with inconsistent success [5–12]. Infections after cardiothoracic surgery have come under increased scrutiny from payers and are now considered never-events by Medicare. Implementation of pay-for-performance measures governing postoperative infections has further spurred interventions to reduce this serious complication.

Efficient implementation of preventive measure requires contemporary knowledge of postoperative SA infection rates, modifiable risk factors, and impact on surgical outcomes. An international, double-blind, randomized placebo-controlled Phase IIb/III trial of a novel SA vaccine (V710; Merck) was recently completed in 7664 adults scheduled for full median sternotomy [12]. As previously reported, V710 was not efficacious in preventing SA bacteremia and/or deep sternal wound infection based on predefined criteria for efficacy. Although overall survival rates were not significantly different for vaccine and placebo recipients, vaccine recipients who later developed postoperative SA infections had a higher mortality rate than placebo recipients with SA infections. Using the data from the 3832 placebo recipients enrolled in the V710-P003 trial, we analyzed the incidence, timing, risk, and consequences of postoperative SA infections in this large contemporary international cohort.

METHODS

Design of Parent Study

V710-P003 (ClinicalTrials.gov NCT00518687) was a randomized, multicenter, placebo-controlled double-blind, group-sequential clinical trial conducted worldwide from 2007 to 2011 to evaluate the efficacy, immunogenicity, and safety of a single dose of the Merck SA vaccine (V710) in adult patients scheduled for cardiothoracic surgery via full median sternotomy [12]. Conduit harvesting and operative techniques, type and duration of perioperative antibiotic prophylaxis, and other interventions were not standardized across the 164 sites. The primary endpoints were postoperative bacteremia and/or deep sternal wound infection (including mediastinitis) caused by SA, but all SA infections were to be reported and adjudicated using standardized definitions for SA infections adapted from the Centers for Disease Control and Prevention Guidelines for Nosocomial Infections [13]. Mediastinitis was categorized as a subset of deep sternal wound infection with documented mediastinal involvement by culture or inspection. Patients exhibiting evidence of a postoperative infection (including fever, leukocytosis, severe sternal pain or instability, wound drainage, or other concerning symptoms or signs) were to be comprehensively evaluated. The assessment was explicitly detailed for suspected infections during the primary 90-day postoperative time frame in the protocol.

Preoperative colonization with SA was determined by culture of a single nasal swab taken at study entry 14–60 days before the scheduled operation and processed according to local custom. Decontamination was not mandated by protocol, and techniques were not standardized across sites. Systematic information in this regard was neither prospectively collected nor retrospectively retrievable in a consistent fashion. Knowledge of colonization status at the time of operation may have influenced perioperative management at some sites.

Exploratory Analyses

The main objective of the current post hoc hypothesis-generating analyses was to describe the incidence and implications of postoperative SA infections complicating cardiothoracic surgery in contemporary practice worldwide. We were particularly interested in preoperative SA colonization and other possible risk factors for postoperative infection. Because receipt of V710 may have perturbed or confounded some outcome measures (such as the mortality rate after postoperative SA infection [11]), we limited the current analysis to placebo recipients.

An inclusive secondary modified intention-to-treat population of placebo recipients from the V710-P003 trial (composed of all 3832 placebo recipients who underwent any cardiothoracic procedure without incurring a serious preoperative SA infection) was selected for analysis. Every SA infection (whether or not adjudicated) up to 360 days postoperatively (despite the protocol-stipulated 90-day postoperative period for the primary efficacy analysis) was included [12]. Results from a single site that did not adhere to good clinical practices were excluded here because the data were deemed unreliable.

A subject was considered to have methicillin-resistant SA (MRSA) infection if any of the pertinent cultures were positive for MRSA. Nominal *P* values were computed post hoc for selected comparisons by the Pearson χ^2 or Wilcoxon rank-sum tests without correction for multiplicity. Asymptotic confidence limits for the relative risk were based on the standard normal distribution.

RESULTS

From December 17, 2007 to April 8, 2011, a total of 8010 patients from 164 sites in 26 countries were enrolled, 7963 participants received vaccine or placebo, and 7647 subjects (including 3832 placebo recipients) ultimately underwent cardiothoracic surgery between 14 and 60 days postvaccination. All 21 randomized participants (12 to the V710 arm and 9 to the placebo arm) from one site with questionable clinical practices discovered during multiple audits were excluded from the current analyses; there were no infections in the placebo group at this hospital. The large majority (>99%) of procedures involved a median sternotomy. Overall, 80.8% (3096 of 3832) of placebo recipients underwent coronary artery or cardiac valve operations, including coronary artery bypass grafting in 41.7% (1598 of 3832) (Table 1).

A postoperative SA infection of any kind or severity was reported in 120 (3.1%) of the 3832 placebo recipients.

Table 1. Baseline Characteristics for the Placebo Group in the MITT Population[a]

	No SA Infection N = 3712	Any SA Infection N = 120	MSSA Infection N = 97	MRSA Infection N = 23
Gender, *n* (%)				
Male	2487 (67.0)	79 (65.8)	63 (64.9)	16 (69.6)
Female	1225 (33.0)	41 (34.2)	34 (35.1)	7 (30.4)
Self-identified Race, *n* (%)				
White	2834 (76.3)	110 (91.7)	93 (95.9)	17 (73.9)
Black	71 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	514 (13.8)	5 (4.2)	3 (3.1)	2 (8.7)
Multiracial	282 (7.6)	4 (3.3)	1 (1.0)	3 (13.0)
Other or Unknown	11 (0.3)	1 (0.8)	0 (0.0)	1 (4.3)
Self-reported Ethnicity, *n* (%)				
Hispanic or Latino	824 (22.2)	14 (11.7)	9 (9.3)	5 (21.7)
Region, *n* (%)				
Asia/Pacific	501 (13.5)	5 (4.2)	3 (3.1)	2 (8.7)
Europe/Russia	1844 (49.7)	82 (68.3)	75 (77.3)	7 (30.4)
Latin America	657 (17.7)	11 (9.2)	6 (6.2)	5 (21.7)
United States	710 (19.1)	22 (18.3)	13 (13.4)	9 (39.1)
Age				
Median (range), years	66 (19–93)	66 (36–85)	66 (40–85)	70 (36–83)
≥70 years, *n* (%)	1393 (37.5)	47 (39.2)	35 (36.1)	12 (52.2)
Underlying metabolic conditions, *n* (%)				
Diabetes mellitus	878 (23.7)	48 (40.0)[b]	35 (36.1)	13 (56.5)
BMI ≥ 30 kg/m^2	939 (25.3)	51 (42.3)[b]	45 (46.4)	6 (26.1)
Diabetes and BMI ≥ 30	355 (9.6)	31 (25.8)	26 (26.8)	5 (21.7)
Society of Thoracic Surgeons infection-risk score[c]				
Median (range)	6 (0–26)	8.5 (0–26)	8 (0–26)	9 (0–19)
Nasal colonization, *n* (%)				
Colonized by SA	652 (17.6)	49 (40.8)[b]	42 (43.3)	7 (30.4)
with MSSA	595 (16.0)	46 (39.3)[b]	42 (43.3)	4 (17.4)
with MRSA	57 (1.5)	3 (2.5)	0 (0.0)	3 (13.0)
Type of cardiothoracic surgery,[d] *n* (%)				
CABG only	1181 (31.8)	60 (50.0)	48 (49.5)	12 (52.2)
Aortic valve	973 (26.2)	18 (15.0)	14 (14.4)	4 (17.4)
Mitral valve	479 (12.9)	5 (4.2)	3 (3.1)	2 (8.7)
Tricuspid valve	23 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
CABG and valve	339 (9.1)	18 (15.0)	17 (17.5)	1 (4.3)
Other	717 (19.3)	19 (15.8)	15 (15.5)	4 (17.4)
Full median sternotomy				
Number (%) of patients	3688 (99.4)	119 (99.2)	96 (99.0)	23 (100)
Timing of infection				
Median [IQR] POD[e]		28.5 [16.5–45]	28 [19–42]	40 [13–63]
Number (%) of patients				
<14 days		19 (15.8)	13 (13.4)	6 (26.1)
14–40 days		63 (52.5)	57 (58.8)	6 (26.1)
41–60 days		18 (15.0)	14 (14.4)	4 (17.4)
61–90 days		11 (9.2)	6 (6.2)	5 (21.7)
>90 days		9 (7.5)	7 (7.2)	2 (8.7)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; IQR, interquartile range; MITT, modified intention to treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S aureus*; POD, postoperative day; SA, *Staphylococcus aureus*.

[a] The secondary modified intention-to-treat population of placebo recipients from the V710-P003 trial (used for the current analysis) was composed of all 3832 placebo recipients who underwent any cardiothoracic procedure without incurring a serious preoperative *S aureus* infection. The 21 patients randomized at the site with questionable clinical practices (12 to the V710 arm and 9 to the placebo arm) have been excluded from this table and all analyses.

[b] Nominal $P < .001$ for SA-infected vs noninfected patients; P values for all other pairwise comparisons between SA-infected and noninfected subgroups were >.05.

[c] Adapted from Fowler et al [4].

[d] The type of cardiothoracic procedure was collected using the case-report form which contained the prespecified choices listed in the above table. The "Other" category was a free-text field that could have included procedures either specified or not listed on the form in various combinations as entered by the site investigator.

[e] The median follow-up time for placebo recipients without infection was 359 days (IQR = 254–366 days).

Table 2. Outcomes for Placebo Recipients With and Without Postoperative SA Infections in the MITT Population During the Entire Study[a,b]

	No SA Infection N = 3712	Any SA Infection N = 120	MSSA Infection N = 97	MRSA Infection N = 23
Type of SA Infection, *n*				
Any		120	97	23
Invasive		39	26	13
Bacteremia		25	19	6
Deep sternal wound		11	7	4
All-cause Mortality, *n* (%)				
Died	153 (4.1)	11 (9.2)	7 (7.2)	4 (17.4)
Had SA bacteremia		5 (4.2)	4 (4.1)	1 (4.3)

Abbreviations: MITT, modified intention to treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S aureus*; SA, *Staphylococcus aureus*.

[a] All adjudicated and nonadjudicated endpoints were tabulated up to 360 days postoperatively. Patients could be included in >1 subcategory of infection. A patient was considered to have MRSA infection if at least 1 culture grew MRSA.

[b] The secondary modified intention-to-treat population used for the present analysis included all 3832 placebo recipients who underwent any type of cardiothoracic operation after vaccination. The 21 patients randomized at the 1 site with questionable clinical practices (12 to the V710 arm and 9 to the placebo arm) have been excluded from these analyses. There were no SA infections of any type in placebo recipients from the excluded site, although 1 V710 recipient reached the primary endpoint of SA bacteremia.

Table 3. Types of Postoperative SA Infections in Placebo Recipients Diagnosed Anytime During the Study[a]

	Placebo Group	
Category	*N*	%
Subjects randomized to placebo arm	4005	
Subjects given placebo	3982	
Placebo recipients in the MITT population	3832	
Patients with SA infections of any type or severity	120	3.1
Patients with any invasive SA infections	39	1.0
Patients with SA bacteremia and/or DSWI (primary endpoints)	33	0.9
Patients with any SA SSI	97	2.5
Specific infections (in alphabetical order)	n	%
Aortic root abscess	1	<0.1
Bacteremia	25	0.7
Deep incisional SSI at leg or arm donor/harvest site	7	0.2
DSWI with mediastinitis	10	0.3
DSWI without mediastinitis	1	<0.1
Endocarditis	4	0.1
Noninvasive skin/soft tissue infection	5	0.1
Osteomyelitis	1	<0.1
Pancreatic abscess	1	<0.1
Pneumonia	9	0.2
Septic arthritis (knee prosthesis)	1	<0.1
Superficial incisional SSI at chest incision site	26	0.7
Superficial incisional SSI at leg or arm donor/harvest site	40	1.0
Superficial incisional SSI at catheter or tube insertion site	8	0.2
Tracheobronchitis	2	<0.1
Urinary tract infection	1	<0.1

Abbreviations: DSWI, deep sternal wound infection; MITT, modified intention to treat; N, number of patients with the specified infection (% with specified infection); n, number of infections; SA, *Staphylococcus aureus*; SSI surgical site infection.

[a] Patients may have had multiple infections and be included in multiple categories.

Methicillin-resistant SA was recovered from 23 cases (19%). Invasive SA infections including bacteremia and deep sternal-wound infection (with or without mediastinitis) occurred in 39 patients (1%), accounting for 33% of the 120 total observed infections (Table 2). Overall, superficial wound infections were the most common type of SA infections reported in our patients (Table 3). Nine infections (7.5%) were diagnosed >90 days postoperatively (Table 4).

Staphylococcus aureus infections occurred relatively more often after coronary artery bypass grafting with or without valve surgery than after other cardiothoracic procedures (relative risk = 1.59, 95% confidence interval [CI], 1.38, 1.82). Compared with patients without SA infection, patients with SA infections more often had a body mass index (BMI) $\geq$ 30 kg/m^2 (42% [51 of 120] vs 25% [939 of 3712]; relative risk = 1.68 [95% CI, 1.35, 2.08], $P < .001$) and diabetes (40% [48 of 120] vs 24% [878 of 3712]; relative risk = 1.69 [95% CI, 1.35, 2.12], $P < .001$). Both diabetes and a BMI $\geq$ 30 kg/m^2 were present in 25.8% of infected patients compared with 9.6% of uninfected patients. Of the 97 methicillin-susceptible SA (MSSA) infections, 35 (36.1%) occurred in diabetic patients; in contrast, 13 (56.5%) of the 23 MRSA infections occurred in diabetic patients. Numerical differences in SA infection rates and patterns were observed across continents. Infection rates were different even at a country level, but small numbers of patients and variations in operating procedures at the site level precluded detailed analysis. Methicillin-resistant SA infections were more often invasive and diagnosed later than MSSA infections (median postoperative day 40 vs 28, $P > .05$). All-cause mortality rate was 4.1% (153 of 3712) in patients without SA infection, compared with 7.2% (7 of 97) in MSSA infections and 17.4% (4 of 23) in MRSA infections ($P < .01$).

Staphylococcus aureus nasal carriage was detected preoperatively by culture in 18.3% (701 of 3832) of placebo recipients, including 1.6% (60 of 3832) colonized with MRSA. *Staphylococcus aureus* infections developed postoperatively in 49 of 701 (7.0%) of colonized patients at baseline vs 71 of 3131 (2.3%) of patients without detected colonization (relative risk = 3.1 [95% CI, 2.2, 4.4], $P < .001$) (Table 5). Baseline nasal colonization

Table 4. Types of Postoperative *Staphylococcus aureus* Infections in Placebo Recipients Diagnosed After Postoperative Day 90

Postoperative Day	*Staphylococcus aureus* Infection Code
91	DEEP INCISIONAL SURGICAL SITE INFECTION - right leg venectomy site
96	NONINVASIVE INFECTION
100	SUPERFICIAL INCISIONAL SURGICAL SITE INFECTION – harvest site
104	BACTEREMIA
153	SUPERFICIAL INCISIONAL SURGICAL SITE INFECTION – chest site
162	SUPERFICIAL INCISIONAL SURGICAL SITE INFECTION - harvest site
178	BACTEREMIA
246	NONINVASIVE INFECTION
319	INVASIVE INFECTION PNEUMONIA

rates were 41% (49 of 120) in patients who developed postoperative SA infections compared with 18% (652 of 3712) in patients without postoperative SA infection ($P < .001$). The likelihood of a postoperative SA infection was numerically higher with preoperative MSSA colonization (7.2%) than with preoperative MRSA colonization (5.0%), but this difference was not statistically significant ($P > .50$). All 3 patients with preoperative MRSA colonization who subsequently developed postoperative SA infections were infected by MRSA, but these cases represent the only 3 (13%) of the 23 postoperative MRSA infections associated with preoperative MRSA colonization. On the other hand, MRSA infections developed in 4 (9%) of 46 patients colonized with MSSA.

DISCUSSION

Staphylococcus aureus remains an important cause of postoperative complications despite advances in surgical practices worldwide. The most serious invasive SA infections including bacteremia and deep sternal wound infections currently complicate cardiothoracic procedures involving median sternotomy in ~1% of adult patients worldwide [1–4]. In our analysis of placebo recipients from a randomized, event-driven, double-blinded clinical trial, SA infections occurred relatively more often after coronary artery bypass grafting than after other cardiothoracic procedures. The majority of SA infections were superficial wound infections involving the sternal incision or vein harvest site. Methicillin-resistant SA caused 19% of the 120 postoperative SA infections. The all-cause mortality rate was 4.1% in patients without SA infection, compared with 7.2% for MSSA infections and 17.4% for MRSA infections. Although potentially confounded by covariates, attributable mortality rates for MSSA infections can be crudely estimated at 3% and 13% for MRSA infections, attesting to the continued high case-fatality rate of this postoperative complication.

Table 5. Predictive Value of Preoperative SA Nasal Carriage for Postoperative SA Infection

Results of Preoperative SA Nasal Culture	Number With Postoperative SA Infection	Number Without Postoperative SA Infection	Probability of Postoperative SA Infection
Negative	71	3060	2.3%
Positive	49	652	7.0%
MSSA	46	595	7.2%
MRSA	3	57	5.0%
Totals	120	3721	3.1%

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S aureus*; SA, *Staphylococcus aureus*.

The postoperative SA infection risk was threefold higher in patients with preoperative nasal colonization as determined by cultures of nasal swabs obtained 14–60 days before surgery. A total of 49 postoperative SA infections occurred in 701 patients with positive nasal cultures out of the 3832 patients who were cultured, yielding a positive predictive value of 7.0% (the risk of developing a postoperative SA infection in colonized patients). The negative predictive value was a 97.7%, translating into a 2.3% chance of developing a postoperative SA infection in uncolonized patients. The substantial majority of postoperative SA infections (71 of 120, 59%) occurred in patients where our nasal culturing technique did not detect SA at baseline. The number needed to culture preoperatively to identify 1 patient at high risk for a potentially preventable postoperative SA infection was 78 (3832 cultures/49 infections possibly prevented).

A recent interventional study using polymerase chain reaction (PCR) of nasal swabs for screening found an almost identical infection rate (7.8%) in untreated patients as observed in our population [14]. The effect of preoperative application with mupirocin nasal ointment and chlorhexidine bathing in colonized patients reduced the SA infection rate from 7.7% to 3.4%, being most pronounced with respect to deep surgical-site infections. The crude mortality rate was not significantly reduced by the decolonization procedures, but the study was not powered to assess overall survival. Unlike that trial, we unfortunately could not determine whether the 7% infection rate in our study represents the incidence for patients in whom decolonization was or was not attempted. On the other hand, because it is unlikely that decolonization procedures would increase the risk of infection, we can plausibly conclude that the infection rate in nasally colonized patients is no less than 7%.

These exploratory analyses have several obvious and important limitations. Our study was a post hoc hypothesis-generating analysis of a relatively small number of events undertaken after the study data were unblinded without a matched control

group. Perioperative and surgical approaches were performed according to the local standard of care and therefore were not uniform across sites. The international nature of the clinical trial undoubtedly adds a substantial degree of inhomogeneity in surgical practices. Infections other than those caused by SA were not systematically recorded, and thus their impact on morbidity and mortality are unknown. Only surveillance cultures of the nares were performed to assess colonization; PCR techniques were not routinely utilized and extranasal sites were not sampled. Screening a single anatomical site exclusively by culture techniques may have failed to detect a sizeable number of SA carriers [15]. Missing SA carriage in the throat, axilla, or groin could result in an underestimation of the effect of colonization on postoperative outcomes along with an overestimation of the number of patients needed to be screened to potentially reduce the risk of infectious complications. The infecting and colonizing SA strains were not typed in the majority of cases so identity could not be established. Management of nasal carriage was not prescribed by protocol, and the approach to positive nasal cultures was neither standardized nor systemically recorded. If decolonization was attempted and accomplished sporadically in our study population, eradication of SA in some carriers could have surreptitiously reduced the postsurgical infection rates in our colonized patients; consequently, our observed infection rate of 7% may actually represent an artificially low incidence for untreated colonized patients. Knowledge of the antimicrobial susceptibilities of the colonizing strain could have influenced the choice and duration of antibiotic prophylaxis at the time of the procedure.

Although SA infections developed after median sternotomy in only 7% of cardiothoracic-surgical patients colonized in the nares at baseline, the risk of postoperative SA infection was >3 times higher than for patients without culture-documented nasal carriage [14, 16]. Pre- and peri-operative strategies aimed at reducing postoperative SA infections in high-risk surgical patients, such as selective vs universal decolonization, prophylactic antibiotic selection based on susceptibility results for the colonizing strain, or enhancement of immune surveillance, deserve further cost-effectiveness analyses [6–11, 14, 16–22].

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Potential conflicts of interest. The parent study was sponsored and funded by Merck as part of the clinical program for V710, but the company has since discontinued its *S aureus* vaccine development program. The trial was designed, managed, and analyzed by employees of the sponsor in conjunction with external academic investigators under the oversight of an independent Data Review Advisory Board. A penultimate draft of this paper was reviewed by the sponsor. All coauthors approved a substantively final version of the manuscript. The opinions expressed in this report represent the consensus of the coauthors and do not necessarily reflect the formal position of Merck or the other institutions listed as author affiliations.

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References

1. Kanafani ZA, Arduino JM, Muhlbaier LH, et al. Incidence of and preoperative risk factors for *Staphylococcus aureus* bacteremia and chest wound infection after cardiac surgery. Infect Control Hosp Epidemiol **2009**; 30:242–8.
2. Chen LF, Arduino JM, Sheng S, et al. Epidemiology and outcome of major post-operative infections following cardiac surgery: risk factors and impact of pathogen type. Am J Infect Control **2012**; 40:963–8.
3. Fowler VG Jr, O'Brien SM, Muhlbaier LH, et al. Clinical predictors of major infections after cardiac surgery. Circulation **2005**; 112(Suppl 9):358–5.
4. Milano CA, Kesler K, Archibald N, et al. Mediastinitis after coronary artery bypass graft surgery. Risk factors and long-term survival. Circulation **1995**; 92:2245–51.
5. Chen AF, Wessel CB, Rao N. *Staphylococcus aureus* screening and decolonization in orthopaedic surgery and reduction of surgical site infections. Clin Orthop Relat Res **2013**; 471:2383–99.
6. Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med **2013**; 368: 533–42.
7. Deeny SR, Cooper BS, Cookson B, et al. Targeted versus universal screening and decolonization to reduce healthcare-associated methicillin-resistant *Staphylococcus aureus* infection. J Hosp Infect **2013**; 85:33–44.
8. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med **2013**; 368: 2255–65.
9. Edmond MB, Wenzel RP. Screening inpatients for MRSA–case closed. N Engl J Med **2013**; 368:2314–5.
10. Schweizer M, Perencevich E, McDanel J, et al. Effectiveness of a bundled intervention of decolonization and prophylaxis to decrease Gram positive surgical site infections after cardiac or orthopedic surgery: systematic review and meta-analysis. BMJ **2013**; 346:f2743.
11. Worby CJ, Jeyaratnam D, Robotham JV, et al. Estimating the effectiveness of isolation and decolonization measures in reducing transmission of methicillin-resistant *Staphylococcus aureus* in hospital general wards. Am J Epidemiol **2013**; 177:1306–13.
12. Fowler VG, Allen KB, Moreira ED, et al. Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery: a randomized trial. JAMA **2013**; 309:1368–78.
13. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections. In: Olmsted RN, ed. APIC Infection Control and Applied Epidemiology: Principles and Practice. St. Louis: Mosby, **1996**: pp A1–20.
14. Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. N Engl J Med **2010**; 362:9–17.

15. Yang ES, Tan J, Eells S, et al. Body site colonization in patients with community-associated methicillin-resistant *Staphylococcus aureus* and other types of *S. aureus* skin infections. Clin Microbiol Infect **2010**; 16:425–31.
16. Kalra L, Camacho F, Whitener CJ, et al. Risk of methicillin-resistant *Staphylococcus aureus* surgical site infection in patients with nasal MRSA colonization. Am J Infect Control **2013**; 41:1253–57.
17. Archer NK, Harro JM, Shirtliff ME. Clearance of *Staphylococcus aureus* nasal carriage is T cell dependent and mediated through interleukin-17A expression and neutrophil influx. Infect Immun **2013**; 81:2070–5.
18. Anderson DJ, Arduino JM, Reed SD, et al. Variation in the type and frequency of postoperative invasive *Staphylococcus aureus* infections according to type of surgical procedure. Infect Control Hosp Epidemiol **2010**; 31:701–9.
19. Datta R, Shah A, Huang SS, et al. High nasal burden of methicillin-resistant *Staphylococcus aureus* increases risk of invasive disease. J Clin Microbiol **2014**; 52:312–4.
20. Ziakas PD, Anagnostou T, Mylonakis E. The prevalence and significance of methicillin-resistant *Staphylococcus aureus* colonization at admission in the general ICU setting: a meta-analysis of published studies. Crit Care Med **2014**; 42:433–44.
21. Boyer AF, Kollef MH. Prevention and treatment of methicillin-resistant *Staphylococcus aureus* colonization in the ICU: a process of care that should be considered mandatory. Crit Care Med **2014**; 42:477–80.
22. Apisarnthanarak A, Mundy LM. Infection prevention control bundle of multidrug-resistant *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus*: Which one is more important? Infect Control Hosp Epidemiol **2014**; 35:207–8.