When the timing is right: Antibiotic timing and infection after cardiac surgery

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Objectives: Guidelines recommend antibiotic prophylaxis 60 minutes before skin incision; however, it is unclear whether more precise timing would further reduce sternal wound infection. Our objectives were to examine the relationship between antibiotic timing and infection, test potential efficacy of optimal antibiotic timing in preventing infection, and determine whether patient comorbidity is related to timing and infection.

Methods: From 1/1/1995–1/1/2008, 28,250 patients underwent 28,702 cardiac surgical procedures involving a median sternotomy; 85% received only cefuroxime and 15% received only vancomycin prophylaxis. Multivariable analysis identified factors associated with infection within each phase, and risk-adjusted optimal timing was determined using patient data, risk variables, and hypothetical values of antibiotic timing.

Results: Prevalence of sternal wound infection was 2.0% (489 patients) for cefuroxime and 2.3% (101 patients) for vancomycin. Minimum prevalence for infection was 1.8% observed when cefuroxime was administered 15 minutes before incision; risk increased to 2.2% with administration more than 45 minutes before incision and to 2.8% at 60 minutes before incision. Minimum prevalence of infection in patients who received vancomycin was 1.8% observed with initiation 32 minutes before incision; risk increased to 2.2% for administration 45 minutes before incision and 3.2% with administration 60 minutes before incision. Simulation for optimal timing found that it was influenced by phase-specific risk factors.

Conclusions: Refining current antibiotic prophylaxis guidelines may lower sternal wound infections. Antibiotic administration timing resulting in lowest likelihood for infection varied with antibiotic and patient-specific factors. Optimal risk-adjusted timing could potentially reduce infections by 9%-31%. (*J Thorac Cardiovasc Surg* 2012;144:931-7)

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Safety for the 30 million Americans who undergo surgical procedures annually is at the heart of strategies for preventing surgical site infections. There are guidelines for proper choice, timing of administration, and duration of prophylactic antibiotics in cardiac surgery, of which optimal timing of antibiotic administration has been the most problematic to define. Previous studies have identified the importance of

prophylactic administration of antibiotics within 60 minutes before skin incision; however, it is unclear whether more precise timing of administration within that period would be more effective in lowering occurrence of postoperative sternal wound infection. The primary objectives were to examine the relationship between timing of prophylactic antibiotic administration and occurrence of postoperative sternal wound infection and to test the potential efficacy of optimal timing for choice of antibiotic in preventing infection. Our secondary objective was to determine whether patient comorbidity was related to optimal timing of antibiotic administration and subsequent postoperative sternal wound infection.

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PATIENTS AND METHODS

Patients

From January 1, 1995, to January 1, 2008, a total of 28,250 patients underwent 28,702 cardiac surgical procedures involving a median sternotomy at Cleveland Clinic. Patients who had active endocarditis, surgical approach without a median sternotomy, lacked documentation for antibiotic administration, had more than 1 operation on the same date, or who received antibiotics other than cefuroxime and vancomycin were excluded from the analysis (Figure E1). Two study groups consisted of 24,272 (85%) patients who received only cefuroxime and 4430 (15%) who received only vancomycin prophylaxis. Baseline characteristics and perioperative variables by antibiotic status are presented in Table 1.

Abbreviations and Acronyms

BMI	= body mass index
COPD	= chronic obstructive pulmonary disease
ITA	= internal thoracic artery
STS	= The Society of Thoracic Surgeons

Data

Demographics and perioperative variables were extracted from the Cardiovascular Information Registry and timing of antibiotic administration from chart abstraction and the Cardiothoracic Anesthesia Registry electronic anesthesia record (Table 1). The Cleveland Clinic Institutional Review Board approved these registries for use in research, with patient consent waived.

Of note, our standard protocol for prophylaxis in cardiac surgical patients included administration of cefuroxime for non-penicillin-allergic patients (1.5 g every 12 hours $\times$ 3 doses); penicillin-allergic patients received vancomycin prophylaxis (1 g every 12 hours $\times$ 3 doses); subsequent to this study, in 2009, aztreonam 1 g $\times$ 1 dose was added to the vancomycin regimen. Since 2003, we have used preoperative screening for *Staphylococcus aureus* carriage with use of mupirocin for decolonization, if positive.¹ In addition, strict attention was directed toward control of perioperative blood sugar per standardized perioperative protocol.²

End Point

End points of the investigation were occurrence of deep and superficial sternal wound infection. Case ascertainment done for sternal wound infection was defined by The Society of Thoracic Surgeons (STS).

Data Analysis

Simple descriptive statistics were used to summarize the data: mean $\pm$ standard deviation and 15th/50th/85th percentiles for continuous variables and frequencies and percentages for categorical variables. Comparisons were made using the Wilcoxon rank-sum tests and χ^2 tests, respectively.

Because cefuroxime and vancomycin have different dosing administration times, all analyses for each were performed separately.

All analyses were performed using SAS statistical software (SAS v9.5, SAS, Inc, Cary, NC) and R statistical software.³

Missing Data

In this prospective observational data, many baseline variables have missing data, with the degree ranging from 0% to 17%. Hence, to avoid eliminating the missing cases in the multivariable analyses, we have used completed data sets obtained by multiple imputation. It was performed using the Markov Chain Monte Carlo⁴ technique to impute missing values using 5-fold multiple imputation with PROC MI (SAS v9.1). In the logistic modeling, for each imputed data set, we estimated regression coefficients and their variance-covariance matrix. Following Rubin,⁴ we combined estimates from the 5 models using PROC MIANALYZE.

Temporal pattern of prevalence of infection. Using a non-linear binary logistic regression, we first analyzed the temporal pattern of the prevalence over the timing of antibiotic (interval from time of incision to time of antibiotic administration). PROC NLMIXED (SAS, Inc) was used to identify the additive phases (of timing of antibiotic) in the odds domain. Asymmetric 68% confidence intervals for prevalence of infection (equivalent to ± 1 standard error) were obtained by the bootstrap percentile method.⁵

Multivariable analyses. Multivariable analysis of preoperative variables (Table 1) was performed to identify factors associated with infection within each phase (see Appendix E1 for details). Variable selection

was performed using bootstrap bagging (bootstrap aggregation).^{6,7} At each step of the aggregation, the original data set was sampled with replacement, and using stepwise selection with entry criterion of $P = .1$ and retention criterion of $P = .05$, variables associated with infection were identified and stored. These steps were repeated 500 times. All variables with bootstrap reliability of 50% or more were retained in the guided analysis.

Optimal timing. Optimal timing was defined as the time of antibiotic administration when the likelihood of sternal wound infection was lowest.

For each patient, risk-adjusted optimal timing was determined by solving the multivariable equations using that patient's actual data, the risk variables, and hypothetical values of antibiotic timing. We then obtained optimal timing by identifying the hypothetical time when the predicted risk of infection was lowest.

RESULTS**Antibiotic Timing**

Overall, nearly 90% of patients received antibiotics within the protocol time frame. However, in the cefuroxime group, where the protocol is administration within 60 minutes before incision, 4.6% received it too early and 3.8% too late. In the vancomycin group, where the protocol is administration within 120 minutes before incision, 0.61% received it too early and 10% too late (Figure 1).

Sternal Wound Infection

Overall prevalence of sternal wound infection was 2.1% (590 patients); superficial wound infection prevalence was 1.3% (379), and deep wound infection 0.74% (211). In-hospital mortality was higher among patients with a sternal wound infection than those without, 8.6% versus 1.8%; $P < .0001$. Morbidity was substantially greater in patients with than without sternal wound infections: stroke, 4.1% versus 1.5%, $P < .0001$; renal failure, 8.5% versus 1.4%, $P < .0001$; respiratory insufficiency, 30% versus 6.1%, $P < .001$; and septicemia/sepsis, 26% versus 2.1%, $P < .0001$, respectively. Similarly, median length of hospital stay was 17 days (15th and 85th percentiles = 8 and 36 days) for patients with sternal wound infections versus 6 days (15th and 85th percentiles = 5 and 11 days) for those without; $P < .0001$. Among patients who received cefuroxime alone, prevalence of sternal wound infection was 2.0% (489 patients); prevalence with vancomycin alone was 2.3% (101 patients), $P = .3$.

Timing and Infection

Cefuroxime. Unadjusted minimum prevalence for infection was 1.8% and observed when cefuroxime was administered 15 minutes before surgical incision (Figure 2). Predicted percentages of sternal wound infection varied considerably for antibiotic timing both within protocol guidelines and for protocol deviations (Table 2). Risk for sternal wound infection increased when cefuroxime was administered more than 15 minutes before surgical incision, yet within protocol recommendations. Prevalence of infection was 2.2% at 45 minutes and 2.8% at 60 minutes before skin incision. Protocol

TABLE 1. Patient and perioperative characteristics by antibiotic status

Variable	Vancomycin (total n = 4,430)		Cefuroxime (total n = 24,272)	
	n*	No. (%) or mean $\pm$ SD	n*	No. (%) or mean $\pm$ SD
Demography				
Age (y)	4430	66 $\pm$ 12	24,272	65 $\pm$ 12
Male	4430	2602 (59)	24,272	17,364 (72)
BMI (kg $\cdot$ m ⁻²)	4426	28 $\pm$ 5.7	24,249	28 $\pm$ 5.4
Cardiac comorbidity				
NYHA functional class III/IV	4429	1613 (36)	24,268	7929 (33)
Emergency operation	4430	82 (1.9)	24,272	326 (1.3)
Previous myocardial infarction	4430	2011 (45)	24,271	11,145 (46)
Complete heart block/pacer (ECG)	4430	186 (4.2)	24,272	816 (3.4)
Reoperation	4430	1163 (26)	24,272	5540 (23)
Coronary artery disease†				
LAD	3508	2416 (69)	19,359	14,005 (72)
LCx	3504	2112 (60)	19,336	12,216 (63)
RCA	3496	2194 (63)	19,321	12,685 (66)
LMT	3497	690 (20)	19,328	3598 (19)
Noncardiac comorbidity				
Peripheral arterial disease	4430	2017 (46)	24,272	9716 (40)
COPD	3927	1061 (27)	20,256	4527 (22)
Smoking	4381	2631 (60)	23,996	14,285 (60)
Hypertension	4332	3195 (74)	23,654	16,592 (70)
Treated diabetes	4366	1204 (28)	23,770	5921 (25)
Dialysis	3642	51 (1.4)	20,055	197 (0.98)
Stroke	4430	416 (9.4)	24,272	1918 (7.9)
Bilirubin (mg $\cdot$ dL ⁻¹)	3683	0.71 $\pm$ 0.56	20,373	0.72 $\pm$ 0.63
Blood urea nitrogen (mg $\cdot$ dL ⁻¹)	4361	21 $\pm$ 11	23,861	20 $\pm$ 10
Hematocrit (%)	3844	38 $\pm$ 5.4	21,046	39 $\pm$ 5.4
Procedure				
Aortic valve	4430	1299 (29)	24,272	5978 (25)
Mitral valve	4430	1309 (30)	24,272	6602 (27)
Tricuspid valve	4430	273 (6.2)	24,272	1124 (4.6)
No. of ITA grafts	4430		24,271	
0		2143 (48)		10,498 (43)
1		2026 (46)		11,672 (48)
2		261 (5.9)		2101 (8.7)
CABG	4430	3120 (70)	24,272	17,642 (73)
Surgical approach: less invasive incision	4430	488 (11)	24,272	2781 (11)
Support				
Cardiopulmonary bypass time (min)	4430	96 $\pm$ 47	24,271	95 $\pm$ 45
Experience				
Date of operation (y)‡	4430	6.2 $\pm$ 3.4	24,272	5.9 $\pm$ 3.7

SD, Standard deviation; BMI, body mass index; NYHA, New York Heart Association; ECG, electrocardiogram; LAD, left anterior descending; LCx, left circumflex; RCA, right coronary artery; LMT, left main trunk; COPD, chronic obstructive pulmonary disease; ITA, internal thoracic artery; CABG, coronary artery bypass graft. *Patients with data available. †Fifty percent stenosis or more. ‡Interval from January 1, 1995, to date of operation.

deviations resulted in the highest prevalence for infection, with 3.7% when cefuroxime was administered too early, that is, 75 minutes before incision; for administration after incision the prevalence of infection was 2.4%.

A number of perioperative factors were associated with increased likelihood for postoperative sternal wound infection (Table E1). The following factors were associated overall for the cefuroxime group: diabetes ($P < .0001$), stroke ($P = .0003$), prior myocardial infarction ($P = .0002$), peripheral arterial disease ($P = .0002$), longer preoperative

length of stay ($P = .04$), operative factors such as mitral valve procedure ($P < .0001$), lower preoperative hematocrit ($P = .001$), complete heart block ($P = .02$), and more internal thoracic artery (ITA) grafts ($P < .0001$). The pre-minimum phase risk factors for cefuroxime included history of chronic obstructive pulmonary disease (COPD) ($P < .0001$) and higher blood urea nitrogen ($P = .0002$). The post-minimum phase risk factors for cefuroxime included larger body mass index (BMI) ($P = .0002$) and higher New York Heart Association class ($P = .005$).

FIGURE 1. Distribution of antibiotic timing stratified by antibiotic status (cefuroxime, gray line; vancomycin, black line). Vertical dashed lines represent current protocol guidelines for administration.

Vancomycin. Antibiotic timing and likelihood for infection differed between vancomycin and cefuroxime. Unadjusted minimum prevalence of infection in patients who received vancomycin was 1.8% observed with antibiotic administration initiated 32 minutes before surgical incision (Figure 3). Predicted percentages for development of sternal wound infection varied considerably within protocol boundaries and for protocol deviations. Prevalence of infection was 2.2% for administration 45 minutes before incision: 3.2% with administration 60 minutes before incision and 4.6% with administration 75 minutes before incision. Vancomycin administration after incision resulted in a prevalence of infection of 3.3% (Table 2 and Figure 3).

FIGURE 2. Percentage of postoperative sternal wound infections by time for cefuroxime antibiotic prophylaxis. Solid line represents estimated percentages of infection enclosed within dashed 68% bootstrapped percentile confidence intervals. Symbols represent data grouped within time frame to provide a crude verification of model fit. Vertical dashed lines represent current protocol time frame for administration.

TABLE 2. Predicted percentages of infection at different antibiotic timing administration for cefuroxime and vancomycin

Antibiotic timing (min)	Cefuroxime predicted % (68% CLs)	Vancomycin predicted % (68% CLs)
-75	3.7 (3.2-4.4)	4.6 (2.5-6.8)
-60	2.8 (2.4-3.1)	3.2 (2.1-4.5)
-45	2.2 (2.0-2.3)	2.2 (1.6-2.8)
-30	1.9 (1.8-2.0)	1.8 (1.5-2.2)
-15	1.8 (1.7-2.0)	2.1 (1.8-2.3)
0 (incision)	2.0 (1.8-2.2)	2.6 (2.1-3.0)
15	2.4 (1.9-2.9)	3.3 (2.4-4.0)

CLs, Confidence limits.

Risk factors associated with a higher likelihood of wound infection in the *vancomycin* group (Table E2) were diabetes ($P = .007$), history of chronic obstructive pulmonary disease ($P = .01$), dialysis ($P = .03$), coronary artery disease such as left anterior descending ($P = .01$) or left main trunk disease ($P = .02$), emergency operation ($P = .02$), and no history of hypertension ($P = .02$). The pre-minimum phase risk factor for vancomycin was bilateral ITA grafts ($P = .0001$). The post-minimum phase risk factors for vancomycin were higher blood urea nitrogen ($P = .07$) and larger BMI ($P = .04$).

Simulation and Optimal Timing

Cefuroxime. Risk-adjusted optimal timing was defined as the time of antibiotic administration resulting in the lowest likelihood for postoperative sternal wound infection. Cefuroxime timing varied between 75 minutes before incision to the time of incision. Mean optimal risk-adjusted time for cefuroxime administration was 27 minutes (± 14 minutes) before surgical incision. However, optimal timing was influenced by phase-specific risk factors. In patients with COPD, mean optimal timing was 18 minutes before incision versus those without COPD, for whom it was 30 minutes. Patients with greater BMI ($>30 \text{ kg} \cdot \text{m}^{-2}$) had an optimal time of cefuroxime administration of 39 minutes versus

FIGURE 3. Percentage of postoperative sternal wound infections by time for vancomycin antibiotic prophylaxis. Format is as in Figure 2.

TABLE 3. Risk-adjusted optimal cefuroxime timing and predicted reduction in sternal wound infection

Group	No.	Optimal timing (min, mean ± SD)	Predicted reduction (%)*
Overall	24,034	−27 ± 14	46 (9.5)
Risk-adjusted individual patient timing†	—	—	85 (18)
COPD			55 (11)
No	17,835	−30 ± 12	
Yes	6199	−18 ± 13	
BMI			60 (12)
≤30 kg · m ^{−2}	16,701	−21 ± 10	
>30 kg · m ^{−2}	7333	−39 ± 11	
COPD and BMI			67 (14)
No COPD			
BMI ≤30 kg · m ^{−2}	12,500	−24 ± 8.9	
BMI >30 kg · m ^{−2}	5335	−43 ± 10	
COPD			
BMI ≤30 kg · m ^{−2}	4201	−12 ± 9.2	
BMI >30 kg · m ^{−2}	1998	−31 ± 11	

SD, Standard deviation; COPD, chronic obstructive pulmonary disease; BMI, body mass index. *Predicted reduction in sternal wound infection when using optimal timing. †Based on individual risk-adjusted optimal timing (Figure E2).

those with a BMI of 30 kg · m^{−2} or less, for whom optimal time of administration was 21 minutes before incision. Optimal time of cefuroxime administration also differed with combinations of risk factors (Table 3 and Figure E2).

Using the mean risk-adjusted optimal timing of 27 minutes for administration of cefuroxime could result in a 9.5% reduction in postoperative sternal wound infection, and with consideration of individual optimal antibiotic timing related to patient-specific risk factors, reductions of up to 18% could be realized (see Table 3).

Vancomycin. Mean risk-adjusted optimal timing for vancomycin administration was 32 minutes before incision. Risk for sternal wound infection was similarly related to patient-specific factors. Simulation suggested a closer time for antibiotic administration to incision in patients with bilateral ITA grafting and greater time from vancomycin administration to incision (39 minutes) for patients with higher BMI (>30 kg · m^{−2}) (Table 4 and Figure E3).

Overall percent reduction in the prevalence of postoperative sternal wound infection could be achieved with consideration of optimal antibiotic timing and patient-specific risk factors. For example, use of mean optimal vancomycin timing could result in an overall 18% reduction in postoperative sternal wound infection, and with consideration of patient-specific risk factors, a 31% reduction in sternal wound infection could be achieved (see Table 4).

COMMENT

Principal Findings

Prevalence of postoperative sternal wound infection varied considerably when prophylactic administration was within standard protocol guidelines. Lowest observed

TABLE 4. Risk-adjusted optimal vancomycin timing and predicted reduction in sternal wound infection

Group	No.	Optimal timing (min, mean ± SD)	Predicted reduction (%)*
Overall	4356	−32 ± 10	18 (18)
Risk-adjusted individual patient timing†	—	—	30 (31)
Bilateral ITA			27 (28)
No	4100	−34 ± 7.1	
Yes	256	−1.9 ± 2.4	
BMI			18 (18)
≤30 kg · m ^{−2}	2918	−29 ± 8.2	
>30 kg · m ^{−2}	1438	−39 ± 11	

SD, Standard deviation; ITA, internal thoracic artery; BMI, body mass index. *Predicted reduction in sternal wound infection when using optimal timing. †Based on individual risk-adjusted optimal timing (Figure E3).

prevalence for infection was administration to skin incision time of 19 minutes for cefuroxime and 32 minutes for vancomycin. Protocol deviations in antibiotic administration increased occurrence of sternal wound infections. By following mean optimal risk-adjusted timing of antibiotic administration, potential for reducing the likelihood of sternal wound infection was 9.5% with cefuroxime and 18% with vancomycin. Furthermore, when patient-specific risk factors were considered in antibiotic prophylaxis timing, opportunity for reducing postoperative sternal wound infection reached 18% for cefuroxime and 31% for vancomycin.

Recommendations for antimicrobial prophylaxis include antibiotic administration within 60 minutes of surgical incision for cephalosporins and within 120 minutes for vancomycin. Intent of guidelines in terms of proper timing of therapy is to allow time for adequate blood and tissue concentrations to exceed minimum inhibitory concentration of the pathogens, thereby preventing an infection at the surgical site.^{8,9} Published guidelines address both timing and duration of antimicrobial therapy in the surgical setting.¹⁰

An investigation of surgical site infections and antibiotics with shorter administration times reported a trend toward lower risk when cephalosporins were given within 30 minutes of (before) incision time. Infection risk increased as the time interval between preoperative antibiotic and incision increased or if antibiotic was administered after skin incision. Infection risk after administration of antibiotic within 30 minutes before incision was 1.6% compared with 2.4% with administration between 31 to 60 minutes before incision.¹¹ Their data suggested that optimal timing is perhaps closer to incision, similar to our findings.

In contrast, others have reported that cefuroxime administration immediately before surgical incision may be less effective than antimicrobial therapy given between 30 and 60 minutes of incision.¹² Differences among reported studies may be related to patient-specific factors, such as obesity, and factors related to the surgical procedure, such as use of ITA grafting.

Garey and colleagues¹³ examined timing of vancomycin prophylaxis and risk of surgical site infections in cardiac surgical patients. Vancomycin administration initiated within 16 to 60 minutes before surgical incision reduced the risk of surgical site infections. In a separate investigation, they demonstrated that optimizing vancomycin administration before surgical incision could lead to economic benefits by decreasing surgical site infections and subsequent length of hospital stay.¹⁴

Risk Factors

Reported prevalence of deep and superficial sternal wound infections after cardiac surgery range from 0.25% to 4% and 2% to 6%, respectively.¹⁵⁻²² In coronary artery bypass grafting, Crabtree and colleagues reported a 2.2% prevalence of superficial and 1.8% prevalence of deep sternal wound infections. Risk factors for superficial infections were higher BMI, female gender, active smoking, use of bilateral ITA grafts, and transfusion. Risk factors for deep sternal wound infections included increasing BMI, diabetes, and platelet transfusion.²⁰ Our investigation and others have similarly reported that patient demographics, comorbidity, and operative factors are related to an increased risk for developing sternal wound infections.^{18,19,23}

Clinical Implications

Morbid complications related to sternal wound infections are significant, with mortality estimates of 5% to 23%.^{15,20,24,25} From STS data, Fowler and colleagues¹⁶ reported an overall 3.5% occurrence of major infection, among which 25% were due to mediastinitis (0.6% overall). Patients with major postoperative infections had higher mortality and longer postoperative length of stay than patients without major infections. Braxton and colleagues similarly reported increased mortality in patients who developed mediastinitis following isolated coronary artery bypass grafting¹⁷ and, in a separate investigation, reported lower 1- and 4-year survival.²⁶

Other investigators have suggested an opportunity to reduce occurrence of sternal wound infections by targeting patient-specific factors, such as weight reduction and smoking cessation.¹⁵ Our results offer additional opportunity for reducing infection by refining current guideline recommendations. The best we can do with perfect simulation is to determine whether antibiotic administration should be closer or further from skin incision to get the best results. We demonstrated a “U-shaped” relationship whereby risk for infection increased outside the recommended boundaries. The concept of optimal time exists only when the ideal is within some boundary limits, that is, either too early or too late. Why risk for infection increases when antibiotics are administered more than 60 minutes before incision is unclear, because antibiotic tissue levels should be sufficient until the

next dosing interval (hours later). Our findings demonstrate that there may be an optimal time, yet also that patient-specific risk factors should be considered in this population.

Reality of findings about when to administer antibiotics suggests clinicians think about optimal antibiotic timing in the context of patient-specific risk factors. For example, in patients with higher BMI ($>30 \text{ kg} \cdot \text{m}^{-2}$), simulation suggests a beneficial effect of shifting antibiotic administration to allow for more time between administration and incision, possibly allowing for adequate tissue antimicrobial activity. Limited pharmacokinetic studies have been performed in obese patients, for whom many factors may affect antimicrobial concentrations. Standard doses of cephalosporins may result in low serum and tissue levels in these patients; increasing cefazolin from 1 to 2 g has been reported to reduce their surgical site infections (16% to 5.6%).²⁷ Edmiston and colleagues²⁸ examined patients undergoing open or laparoscopic gastric bypass who received cefazolin 2 g intravenously 30 to 60 minutes before incision and reported decreasing concentrations of cefazolin in the serum, skin, adipose tissue, and omental tissue with increasing BMI.

When considering patient-specific risk factors such as BMI, modifications in cefuroxime administration could reduce infection by 12%. Similarly, with use of ITA grafting, special consideration in vancomycin antibiotic timing could result in reductions in the likelihood of infection by 28%.

Limitations

Our primary outcome was development of deep and superficial wound infections identified during the primary hospitalization. Sternal wound infections becoming manifest after discharge were not included because longitudinal follow-up data for these were unavailable. Lack of this information underestimates occurrence of sternal wound infections. The Cardiothoracic Surgical Trials Network recently completed one of the first in-depth investigations on infectious complications after cardiac surgery. Patients were followed up to 60 days from index surgical procedure for development of infections. A number of postoperative infections occurred after discharge and varied depending on the individual infectious complications. Among patients in whom mediastinitis developed after surgery, approximately 50% were identified after discharge.²⁹ Our sample is based on the data that we and the STS currently have available for reporting infectious complications. We believe that the infections are initiated in the perioperative period yet manifest either early or late. We do not have data to suggest that infections manifesting later after discharge are different from those manifesting in-hospital after the index surgery. We used STS rather than Center for Disease Control definitions for sternal wound infections. In addition, this investigation was a prospective cohort investigation, and unmeasured confounding variables could have affected study results.

CONCLUSIONS

Sternal wound infections are a dreaded complication of cardiac surgery and portend serious morbidity. Patient safety depends on seizing the limited opportunity for control of preoperative risk. Our data demonstrate the importance of refining process-of-care factors such as antibiotic timing. Optimal timing with consideration of patient-specific risk factors reduced the likelihood of developing postoperative sternal wound infections.

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APPENDIX E1.**Nonlinear Multivariable Logistic Regression**

We have used a 2-step modeling strategy to quantify the relationship between timing of antibiotic administration and infection and baseline patient-procedure characteristics and infection. In the first step, because the descriptive investigations revealed a skewed U-shaped relationship between timing of antibiotic administration and infection, we used additive nonlinear equations and logistic regression to identify the decreasing and increasing phases (of timing of antibiotics). We call these pre-minimum and post-minimum phases.

It is believed that there may be some baseline variables that influence (or in other words, interact with the timing

of antibiotics) the infection only in the pre-minimum phase, some only in the post-minimum phase, and some independently of the phases (of the timing of antibiotics). Hence, in the second step, we performed multivariable logistic regression simultaneously to identify the 3 sets of patient-procedure characteristics. The motivation for this analytical strategy was similar to that used by Blackstone, Naftel, and Turner^{E1} to model the time-related phases of hazard of time-to-event data.

E-Reference

E1. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc.* 1986;81:615-24.

FIGURE E1. CONSORT diagram of patient population.

FIGURE E2. Distribution of patient-specific optimal timing in cefuroxime group. A, Overall; B, body mass index; C, diabetes; and D, bilateral ITA grafts. *ITA*, Internal thoracic artery.

PM

FIGURE E3. Distribution of patient-specific optimal timing in vancomycin group. A, Overall; B, body mass index; C, diabetes; D, bilateral ITA grafts. *ITA*, Internal thoracic artery.

TABLE E1. Risk factors associated with higher likelihood of wound infection: cefuroxime group

Factor	Estimate ± SE	P	Reliability (%)*
Overall			
Diabetes	0.52 ± 0.100	<.0001	94
History of PAD	0.32 ± 0.099	.001	46
Previous stroke	0.46 ± 0.13	.0006	87
Lower hematocrit†	12 ± 3.5	.001	82
Longer preoperative LOS‡	0.11 ± 0.049	.02	66
Complete heart block/pacer	0.45 ± 0.203	.02	51
Previous MI	0.33 ± 0.101	.0009	86
Higher number of ITA grafts	0.46 ± 0.085	<.0001	100
Mitral valve procedure	0.55 ± 0.11	<.0001	100
Pre-minimum phase			
History of COPD	0.78 ± 0.18	<.0001	73
Higher BUN§	0.069 ± 0.021	.001	86
Post-minimum phase			
Larger BMI	0.79 ± 0.11	<.0001	76
Higher NYHA functional class¶	-0.26 ± 0.099	.009	90

SE, Standard error; PAD, pulmonary arterial disease; LOS, low output syndrome; MI, myocardial infarction; ITA, internal thoracic artery; COPD, chronic obstructive pulmonary disease; BUN, blood urea nitrogen; BMI, body mass index; NYHA, New York Heart Association. *Percent of times factor appeared in 500 bootstrapped models (based on 3 separate logistic models for each phase). †(1/hematocrit), inverse transformation. ‡Log(preoperative LOS+1), logarithmic transformation. §(BUN/20)², squared transformation. ||(BMI/40), scaled transformation. ¶(1/NYHA functional class), inverse transformation.

TABLE E2. Risk factors associated with higher likelihood of wound infection: vancomycin group

Factor	Estimate ± SE	P	Reliability (%)*
Overall			
Diabetes	0.61 ± 0.23	.007	84
History of COPD	0.57 ± 0.23	.01	67
Dialysis	1.2 ± 0.55	.03	84
Coronary artery disease†			
LAD	1.3 ± 0.53	.01	94
LMT	0.55 ± 0.23	.02	94
Emergency operation	1.3 ± 0.47	.02	66
No history of hypertension	-0.60 ± 0.26	.02	61
Pre-minimum phase			
Bilateral ITA grafts	2.7 ± 0.71	.0001	81
Post-minimum phase			
Higher BUN‡	0.025 ± 0.014	.07	83
Larger BMI§	0.75 ± 0.36	.04	94

SE, Standard error; COPD, chronic obstructive pulmonary disease; LAD, left anterior descending; LMT, left main trunk; ITA, internal thoracic artery; BUN, blood urea nitrogen; BMI, body mass index. *Percent of times factor appeared in 500 bootstrapped models (based on 3 separate logistic models for each phase). †Stenosis > 0%. ‡(BUN/20)², squared transformation. §(BMI/40), scaled transformation.