Original Investigation

Timing of Surgical Antibiotic Prophylaxis and the Risk of Surgical Site Infection

Mary T. Hawn, MD, MPH; Joshua S. Richman, MD, PhD; Catherine C. Vick, MS; Rhiannon J. Deierhoi, MPH; Laura A. Graham, MPH; William G. Henderson, MPH, PhD; Kamal M. F. Itani, MD

IMPORTANCE Timing of prophylactic antibiotic administration for surgical procedures is a nationally mandated and publicly reported quality metric sponsored by the Centers for Medicare and Medicaid Services Surgical Care Improvement Project. Numerous studies have failed to demonstrate that adherence to the Surgical Care Improvement Project prophylactic antibiotic timely administration measure is associated with decreased surgical site infection (SSI).

OBJECTIVE To determine whether prophylactic antibiotic timing is associated with SSI occurrence.

DESIGN Retrospective cohort study using national Veterans Affairs patient-level data on prophylactic antibiotic timing for orthopedic, colorectal, vascular, and gynecologic procedures from 2005 through 2009.
SETTING National Veterans Affairs Surgical Care Improvement Project data from 112 Veterans Affairs hospitals and matched Veterans Affairs Surgical Quality Improvement Program data.
PATIENTS Patients undergoing hip or knee arthroplasty, colorectal surgical procedures, arterial vascular surgical procedures, and hysterectomy.

INTERVENTION Timing of prophylactic antibiotic administration with respect to surgical incision time.

MAIN OUTCOMES AND MEASURES Data for prophylactic antibiotic agent, prophylactic antibiotic timing with respect to surgical incision, and patient and procedure risk variables were assessed for their relationship with the occurrence of a composite superficial or deep incisional SSI within 30 days after the procedure. Nonlinear generalized additive models were used to examine the association between antibiotic timing and SSI.

RESULTS Of the 32 459 operations, prophylactic antibiotics were administered at a median of 28 minutes (interquartile range, 17-39 minutes) prior to surgical incision, and 1497 cases (4.6%) developed an SSI. Compared with procedures with antibiotic administration within 60 minutes prior to incision, higher SSI rates were observed for timing more than 60 minutes prior to incision (unadjusted odds ratio [OR] = 1.34; 95% CI, 1.08-1.66) but not after incision (unadjusted OR = 1.26; 95% CI, 0.92-1.72). In unadjusted generalized additive models, we observed a significant nonlinear relationship between prophylactic antibiotic timing and SSI when considering timing as a continuous variable (P = .01). In generalized additive models adjusted for patient, procedure, and antibiotic variables, no significant association between prophylactic antibiotic timing and SSI was observed. Vancomycin hydrochloride was associated with higher SSI occurrence for orthopedic procedures (adjusted OR = 1.75; 95% CI, 1.16-2.65). Cefazolin sodium and quinolone in combination with an anaerobic agent were associated with fewer SSI events (cefazolin: adjusted OR = 0.49; 95% CI, 0.34-0.71; quinolone: adjusted OR = 0.55; 95% CI, 0.35-0.87) for colorectal procedures.

CONCLUSIONS AND RELEVANCE The SSI risk varies by patient and procedure factors as well as antibiotic properties but is not significantly associated with prophylactic antibiotic timing. While adherence to the timely prophylactic antibiotic measure is not bad care, there is little evidence to suggest that it is better care.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Mary T. Hawn, MD, MPH, Section of Gastrointestinal Surgery, Department of Surgery, University of Alabama at Birmingham, 1922 Seventh Ave S, KB 428, Birmingham, AL 35294 (mhawn@uab.edu).

Preventing surgical site infection (SSI) is a national priority and a major focus of the Centers for Medicare and Medicaid Services Surgical Care Improvement Project (SCIP).[1] The efficacy of prophylactic antibiotics in reducing SSI for major surgical procedures has been proven in clinical trials. However, the SCIP implemented timing standards for appropriate antibiotic prophylaxis in an effort to reduce SSI. The SCIP measure assesses compliance for prophylactic antibiotic administration within 60 minutes prior to surgical incision, not whether an antibiotic is administered.

The selection of the 60-minute window for prophylactic antibiotic administration was primarily based on 2 types of evidence: pharmacokinetics of the antibiotic agents and 1 large single-institution cohort study analyzing the association between timing of antibiotic administration and subsequent SSI.[1,2] However, in the cohort study of 2847 patients, only 44 (1.5%) developed an SSI. Furthermore, the only significant associations between SSI and prophylactic antibiotic timing were for the categories of antibiotic administration more than 120 minutes prior to incision or more than 180 minutes after incision. Subsequent studies examining the relationship between timing of prophylactic antibiotic administration and SSI have failed to demonstrate the superiority of the 60-minute preincision window.[3-9] Moreover, all studies to date have assessed prophylactic antibiotic administration in arbitrary timing categories rather than as a continuous variable.

Prophylactic antibiotic timing is a nationally mandated quality metric used for public reporting and performance pay initiatives based on limited evidence to support the effectiveness in reducing SSI. We undertook this study to assess the relationship of timing as a continuous variable and postoperative SSI in a large, national, contemporary surgical cohort to determine whether timing is significantly associated with SSI occurrence.

Methods

Overview

We conducted a retrospective cohort study of surgical procedures meeting criteria for the SCIP measure from 2005 through 2009 to examine the relationship between prophylactic antibiotic timing and SSI in the Veterans Affairs (VA) system. National VA SCIP data from 112 VA hospitals with information on antibiotic name and time of administration were matched to VA Surgical Quality Improvement Program (VASQIP) data containing information on time of surgical incision and the occurrence of SSI. The association of the time in minutes between prophylactic antibiotic administration and surgical incision with subsequent SSI was assessed. The study protocol was reviewed and approved by the local VA institutional review board with waiver of informed consent.

Data Sources

Information on antibiotic agent and timing was obtained from the VA Office of Information and Analytics External Peer Review Program. The VA contracts with the West Virginia Medical Institute to collect VA hospital SCIP measures according to guidelines set forth by The Joint Commission and the Centers for Medicare and Medicaid Services.[10]

Patient, procedure, and outcome variables were obtained from matched records in the VASQIP data. The VASQIP assesses risk-adjusted 30-day postoperative morbidity and mortality data within the VA health care system.[3,4] The methods of the noncardiac VASQIP have been previously published.[11] The VASQIP collects demographic characteristics, preoperative risk data, operative data, and 30-day postoperative mortality and morbidity outcomes on a sample of patients undergoing major surgery in the VA health care system. Clinical nurse reviewers trained in clinical medicine and quality assurance complete in-depth training on the data collection procedures and detailed definition of each variable.[12]

Patient Sample

The SCIP population for the prophylactic antibiotic measures includes patients undergoing 5 types of major surgical procedures: (1) cardiac surgery, (2) hip or knee arthroplasty, (3) colorectal surgery, (4) arterial vascular surgery, and (5) hysterectomy.[10] Cardiac cases were excluded because the VASQIP only assesses mediastinitis as an SSI outcome for cardiac procedures.

Study Variables

The independent variable of interest was timing of antibiotic administration in minutes relative to surgical incision time. If more than 1 antibiotic was administered, the prophylactic antibiotic administered closest to but before incision was used. The dependent variable of interest was the occurrence of a superficial or deep incisional SSI within 30 days postoperatively as reported by the VASQIP, following the Centers for Disease Control and Prevention definition.[13] Superficial and deep incisional SSIs were combined to create a composite SSI outcome variable, and sensitivity analyses were performed with organ-space SSI included in the outcome.

Cases with a single prophylactic antibiotic were classified by name. Cases with a combination of 2 antibiotics were classified as follows: (1) cefazolin sodium plus metronidazole; (2) clindamycin plus gram-negative coverage (aminoglycoside [n = 67] or aztreonam [n = 3]); (3) vancomycin hydrochloride plus other SCIP-approved antibiotic (cefazolin [n = 1227], cefoxitin sodium [n = 59], quinolone [n = 36], or ampicillin sodium/sulbactam sodium [n = 4]); and (4) quinolone plus anaerobic coverage (metronidazole [n = 284] or clindamycin [n = 50]). Cases receiving any non-SCIP-approved antibiotics or combinations were excluded from primary analyses; however, sensitivity analyses were performed including these cases.

Patient-level covariates known to predict the occurrence of SSI, including demographic characteristics, lifestyle variables (eg, tobacco and alcohol use), and cardiovascular, pulmonary, renal, hepatobiliary, nutritional, and immune comorbidities were obtained from the VASQIP.[14] Surgery characteristics considered in our analyses included surgical specialty (orthopedic, colorectal, vascular, and gynecologic), emergent operation, American Society of Anesthesiologists status, wound classification (clean, clean/contaminated, contaminated, or infected), and duration of the operation (incision to surgery end time). To account for the complexity of the operation, the resource-based

relative value units for the *Current Procedural Terminology* code of the performed operation were used.

Statistical Analysis

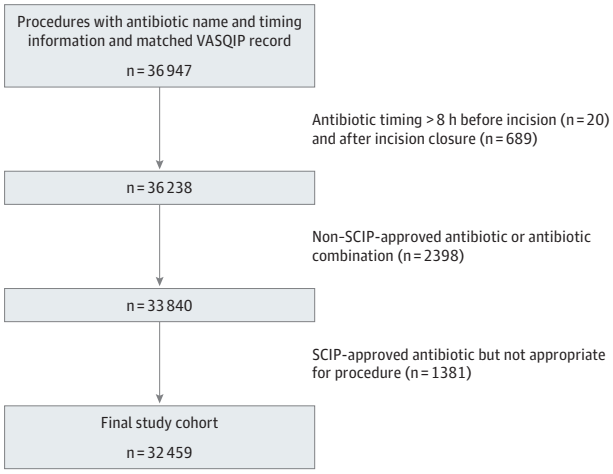
Unadjusted testing for association between patient characteristics, prophylactic antibiotic timing intervals, and SSI was done using χ^2 and Wilcoxon rank sum tests. The relationship between timing and SSI rates was modeled considering time as a nonlinear effect using generalized additive models (GAMs). Age, operative duration, and relative value units were also included as continuous nonlinear terms in GAMs. Separate GAM fits modeled the effect of timing and continuous covariates using both penalized thin plate regression splines and locally weighted scatterplot smoothing; results were similar and the spline models are presented. When the estimated *df* of the adaptive spline was less than 1.1 during model building, the final model considered the effect to be linear. The estimated *df* for timing modeled as a regression spline ranged from less than 1.1 to 7.5. In overall models, timing was ultimately treated as linear in the adjusted model (spline *df* < 1.1), while the *df* for the overall unadjusted model was 6.4. Approximate *P* values for spline terms are derived from analysis of variance χ^2 statistics using the estimated *df*. To minimize the influence of outliers on the partial effect plots, the 51 observations (0.2%) with antibiotic administration more than 180 minutes prior to incision time were excluded from final modeling. All models were fit with the entire cohort adjusting for surgical specialty and repeated stratified by specialty. Full models included adjustment for patient and operative characteristics known to be predictive of SSI.[14] Congestive heart failure and renal insufficiency variables were excluded from the models as there were too few outcomes to provide reliable estimates. To examine the relative contribution of each variable to the adjusted models, we calculated the analysis of variance χ^2 statistic for each variable minus its *df* (estimated for spline terms) following the method recommended by Harrell[15] so that larger values indicated greater contribution to the model. The statistical threshold for significance was set at *P* = .05 for a 2-tailed test.

We performed sensitivity analyses to evaluate whether results were changed by including the following: (1) cases with prophylactic antibiotic deemed inappropriate by SCIP guidelines; (2) VA facilities as random effects; and (3) inclusion of the timely discontinuation of prophylactic antibiotic within 24 hours of surgery end time (SCIP-INF-3 measure). Of the 32 459 surgical procedures, 26 327 (81.1%) had information on the SCIP-INF-3 measure, of which 22 753 (86.4%) were adherent. All analyses and figure preparations were completed using SAS/STAT statistical software version 9.2 (SAS Institute, Inc) and R statistical software version 2.15.1 (R Foundation).[16] The GAMs used the R packages GAM and MGCV for locally weighted scatterplot smoothing and spline models, respectively (R software version 1.06.2; R Foundation).[17]

Results

A total of 36 947 noncardiac SCIP cases with information on antibiotic name, infusion route, time of administration, and matched VASQIP records were identified (**Figure 1**). The following cases were excluded: (1) prophylactic antibiotic administered more than 8 hours prior to incision (n = 20); (2) prophylactic antibiotic administered after surgery end time (n = 689); (3) non-SCIP-approved prophylactic antibiotic (n = 2398); and (4) SCIP-approved prophylactic antibiotic inappropriate for procedure (n = 1381). The final 2 exclusions were applied to limit the analyses to antibiotics with appropriate coverage for the surgical procedure.

Figure 1. Inclusion and Exclusion Criteria for the Study Cohort



SCIP indicates Surgical Care Improvement Project; VASQIP, Veteran Affairs Surgical Quality Improvement Program.

Of the 32 459 cases performed at 112 VA hospitals included in the study, 1497 (4.6%) developed an SSI within 30 days of surgery. The demographic characteristics, comorbidities, and procedure characteristics of the study population stratified by prophylactic antibiotic timing intervals are shown in **Table 1**. Patients with comorbid conditions (*P* < .05) and those with an emergent, colorectal, or vascular procedure, a contaminated/dirty wound classification, and longer operations were more likely to have antibiotic administered more than 60 minutes prior to or after incision (*P* < .001). Higher SSI rates were observed with administration more than 60 minutes prior to incision (odds ratio [OR] = 1.34; 95% CI, 1.08-1.66) but not after incision (OR = 1.26; 95% CI, 0.92-1.72) compared with administration within 60 minutes prior to incision. There was a significant relationship between prophylactic antibiotic timing and SSI in an unadjusted GAM (*P* = .003) (**Figure 2**A). Significantly higher unadjusted odds of SSI were observed both within and outside the 60-minute preincision window as represented where the 95% CI does not cross 1.0.

The relationships between antibiotic class, timing, and SSI stratified by surgical procedure type are shown in **Table 2**. The median time between prophylactic antibiotic administration and surgery was 28 minutes (interquartile range, 17-39 minutes). In unadjusted analysis of antibiotic choice and SSI risk, several SCIP-approved antibiotics had observed differences in SSI. For orthopedic procedures, vancomycin alone was associated with a higher SSI occurrence (OR = 1.75; 95% CI, 1.24-2.46; cefazolin as reference group). For colorectal procedures, compared with cefoxitin, cefazolin plus metronidazole

Table 1. Characteristics of the Study Cohort Stratified by Antibiotic Timing Window Relative to Surgical Incision Time

Characteristic	No.	No. (%)						*P* Value
		Preincision Time, min			Postincision Time, min			
		>120	120-60	59-0	0-59	60-120	>120	
Patients	32 459	141 (0.4)	1721 (5.3)	29 830 (91.9)	671 (2.1)	56 (0.2)	18 (0.1)	
Demographic								
Age, y								
<65	18 653	73 (0.4)	942 (5.1)	17 199 (92.2)	392 (2.1)	25 (0.1)	22 (0.1)	.04
≥65	13 806	68 (0.5)	779 (5.6)	12 631 (91.5)	279 (2.0)	31 (0.2)	18 (0.1)	
Sex								
Male	29 874	131 (0.4)	1615 (5.4)	27 424 (91.8)	609 (2.0)	55 (0.2)	40 (0.1)	.005
Female	2548	10 (0.4)	103 (4.0)	2372 (93.1)	62 (2.4)	1 (0.04)	0	
Race								
White	20 112	85 (0.4)	1039 (5.2)	18 577 (92.4)	359 (1.8)	30 (0.2)	22 (0.1)	.04
Black	4330	16 (0.4)	213 (4.9)	4017 (92.8)	71 (1.6)	5 (0.1)	8 (0.2)	
Other	3755	21 (0.6)	229 (6.1)	3414 (90.9)	81 (2.2)	9 (0.2)	1 (0.03)	
Comorbidities								
Diabetes								
Oral agents	4666	25 (0.5)	243 (5.2)	4297 (92.1)	87 (1.9)	7 (0.2)	7 (0.2)	.37
Insulin	2284	16 (0.7)	123 (5.4)	2083 (91.2)	54 (2.4)	3 (0.2)	5 (0.2)	
No	25 509	100 (0.4)	1355 (5.3)	23 450 (91.2)	530 (2.1)	46 (0.2)	28 (0.1)	
COPD								
Yes	4082	21 (0.5)	252 (6.2)	3702 (90.7)	92 (2.3)	8 (0.2)	7 (0.2)	.08
No	28 377	120 (0.4)	1469 (5.2)	26 128 (92.1)	579 (2.0)	48 (0.2)	33 (0.1)	
CHF								
Yes	201	4 (2.0)	10 (5.0)	177 (88.1)	9 (4.5)	1 (0.5)	0	.002
No	32 258	137 (0.4)	1711 (5.3)	29 653 (91.9)	662 (2.1)	55 (0.2)	40 (0.1)	
Steroid use								
Yes	590	4 (0.7)	39 (6.6)	535 (90.7)	12 (2.0)	0	0	.46
No	31 869	137 (0.4)	1682 (5.3)	29 295 (91.9)	659 (2.1)	56 (0.2)	40 (0.1)	
Dyspnea								
Yes	3496	25 (0.7)	202 (5.8)	3184 (91.1)	73 (2.1)	5 (0.1)	7 (0.2)	.05
No	28 893	116 (0.4)	1516 (5.3)	26 579 (92.0)	598 (2.1)	51 (0.2)	33 (0.1)	
Smoker								
Yes	10 129	52 (0.5)	596 (5.9)	9212 (91.0)	232 (2.3)	19 (0.2)	18 (0.2)	.33
No	22 312	88 (0.4)	1125 (5.0)	20 601 (92.3)	439 (2.0)	37 (0.2)	22 (0.1)	
Alcohol use								
Yes	2652	15 (0.6)	146 (5.5)	2430 (91.6)	52 (2.0)	6 (0.2)	3 (0.1)	.84
No	29 776	126 (0.4)	1573 (5.3)	27 373 (91.9)	617 (2.1)	50 (0.2)	37 (0.1)	
Renal insufficiency								
Yes	218	3 (1.4)	22 (10.1)	187 (85.8)	5 (2.3)	1 (0.5)	0	.006
No	32 241	138 (0.4)	1699 (5.3)	29 643 (91.9)	666 (2.1)	55 (0.2)	40 (0.1)	
ASA class								
1 or 2	8262	19 (0.2)	355 (4.3)	7720 (93.4)	146 (1.8)	12 (0.2)	10 (0.1)	<.001
3	21 792	94 (0.4)	1202 (5.5)	19 973 (91.7)	460 (2.1)	39 (0.2)	24 (0.1)	
4 or 5	2405	28 (1.2)	164 (6.8)	2137 (88.9)	65 (2.7)	5 (0.2)	6 (0.3)	
Surgery								
Status								
Elective	31 751	132 (0.4)	1688 (5.3)	29 204 (92.0)	640 (2.0)	49 (0.2)	38 (0.1)	<.001
Emergent	708	9 (1.3)	33 (4.7)	626 (88.4)	31 (4.4)	7 (1.0)	2 (0.3)	
Type								
Orthopedic	20 528	47 (0.2)	978 (4.8)	19 148 (93.3)	310 (1.5)	35 (0.2)	10 (0.1)	<.001
Colorectal	5469	48 (0.9)	317 (5.8)	4895 (89.5)	186 (3.4)	9 (0.2)	14 (0.3)	
Vascular	5138	41 (0.8)	401 (7.8)	4525 (88.1)	143 (2.8)	12 (0.2)	16 (0.3)	
Gynecologic	1324	5 (0.4)	25 (1.9)	1262 (95.3)	32 (2.4)	0	0	

(continued)

Table 1. Characteristics of the Study Cohort Stratified by Antibiotic Timing Window Relative to Surgical Incision Time (continued)

Characteristic	No.	No. (%)						*P* Value
		Preincision Time, min			Postincision Time, min			
		>120	120-60	59-0	0-59	60-120	>120	
Wound class								
Clean	25 182	85 (0.3)	1324 (5.3)	23 266 (92.4)	440 (1.8)	44 (0.2)	23 (0.1)	<.001
Clean/contaminated	7173	54 (0.8)	386 (5.4)	6480 (90.3)	224 (3.1)	12 (0.2)	17 (0.2)	
Dirty	104	2 (1.9)	11 (10.6)	84 (80.8)	7 (6.7)	0	0	
Operative time, h								
<3	24 721	83 (0.3)	1097 (4.4)	23 084 (93.4)	413 (1.7)	36 (0.2)	8 (0.03)	<.001
≥3	7738	58 (0.8)	624 (8.1)	6746 (87.2)	258 (3.3)	20 (0.3)	32 (0.4)	
Work RVUs								
<22.5	17 397	80 (0.5)	975 (5.6)	15 911 (91.5)	384 (2.2)	30 (0.2)	17 (0.1)	.02
≥22.5	15 062	61 (0.4)	746 (5.0)	13 919 (92.4)	287 (1.9)	26 (0.2)	23 (0.2)	
SSI								
Yes	1497	13 (0.9)	98 (6.6)	1343 (89.7)	34 (2.3)	7 (0.5)	2 (0.1)	.001
No	30 962	128 (0.4)	1623 (5.2)	28 487 (92.0)	637 (2.1)	49 (0.2)	38 (0.1)	

Abbreviations: ASA, American Society of Anesthesiologists; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; RVUs, relative value units; SSI, surgical site infection.

(OR = 0.48; 95% CI, 0.33-0.70) and quinolone plus anaerobic agent (OR = 0.57; 95% CI 0.38-0.85) were associated with lower SSI occurrence.

The relative contributions of GAM covariates to SSI risk as calculated by subtracting the *df* from the χ^2 value are shown in **Table 3**. In the overall model adjusted for surgical specialty, prophylactic antibiotic timing ranked 15th of the 16 variables. Among the 3 specialty-stratified models, antibiotic timing ranked 5th (orthopedic), 14th (vascular), and 11th (colorectal) and was not statistically significant in any model. The most informative variables by model type were surgical specialty (overall model), current smoker (orthopedic model), diabetes (vascular model), and operative duration (colorectal model).

The choice of prophylactic antibiotic for orthopedic and colorectal procedures was associated with SSI. Vancomycin was associated with higher SSI occurrence for orthopedic procedures (adjusted OR = 1.75; 95% CI, 1.16-2.65), whereas cefazolin or quinolone in combination with an anaerobic agent were associated with fewer SSI events (cefazolin: adjusted OR = 0.49; 95% CI, 0.34-0.71; quinolone: adjusted OR = 0.55; 95% CI, 0.35-0.87) for colorectal procedures. We substituted half-life in minutes for antibiotic agent in the model, and this did not explain the differences in observed effectiveness of the agents. The ORs, 95% CIs, and *P* values for all model terms are included in the eTable in Supplement.

The partial effect plots of the association between the antibiotic timing and SSI from the adjusted GAM are shown in Figure 2B. There was no significant association between timing and SSI for the overall or specialty-stratified models for orthopedic, colorectal, and vascular procedures. In adjusted overall and vascular GAMs, the estimated *df* for the splined timing were both less than 1.1, so their corresponding final models considered timing as a linear effect.

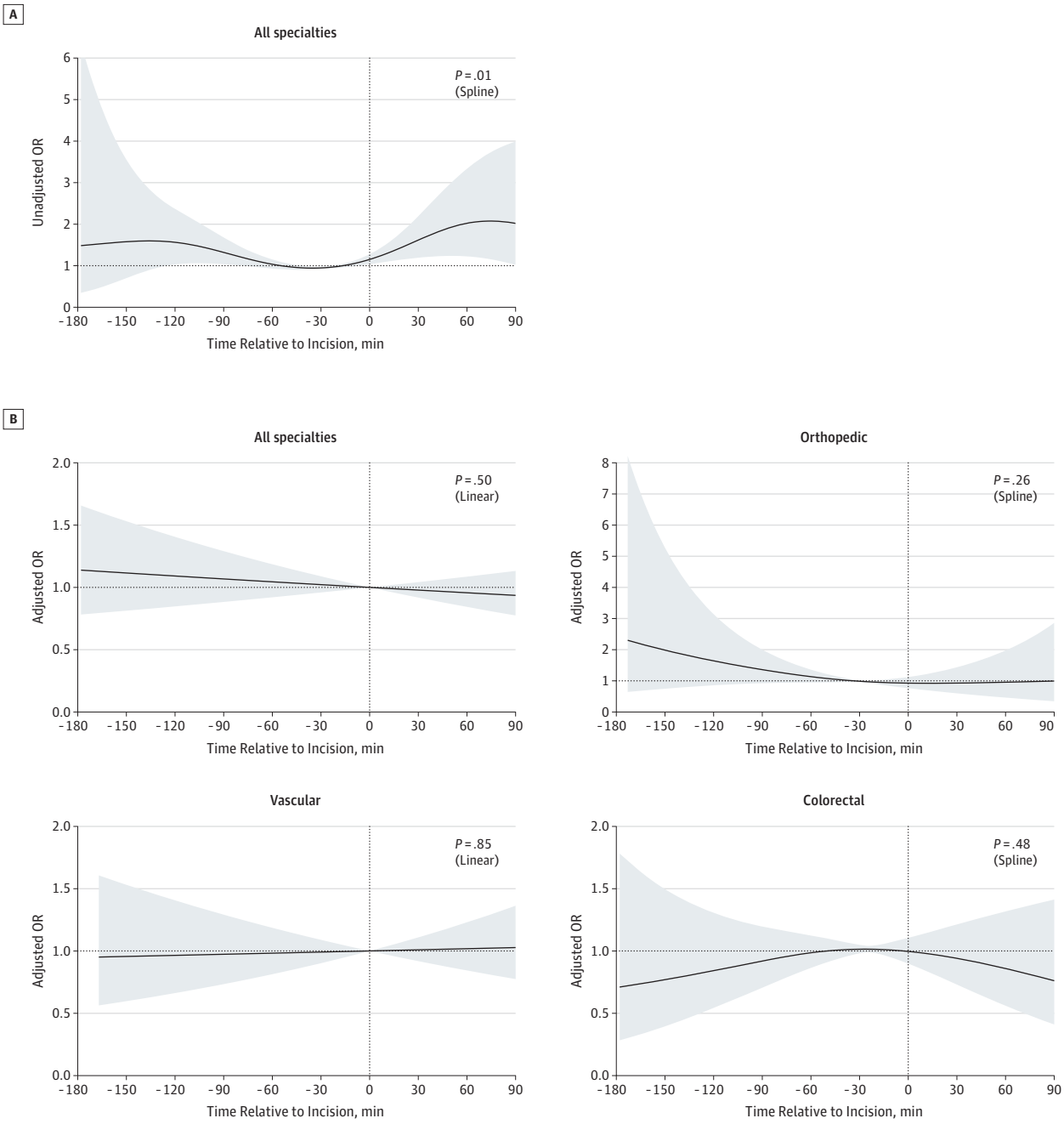
Sensitivity analyses including the 3779 cases with either a non-SCIP-approved antibiotic or a SCIP-approved antibiotic that was inappropriate for the procedure (Figure 1) did not demonstrate an association between prophylactic antibiotic timing and SSI (partial effect plots are shown in the eFigure in Supplement). The inclusion of VA facilities as random effects, organ-space infection in the composite SSI outcome, and the SCIP-INF-3 measure of timely discontinuation of antibiotics in the models did not significantly alter the association of antibiotic timing and SSI.

Comment

To our knowledge, this is the largest study to date to evaluate the relationship between prophylactic antibiotic timing and subsequent SSI for major surgical procedures and the only study to assess timing as a continuous variable. We did not observe a significant relationship between timing and SSI in this contemporary national VA SCIP cohort, but we did observe a significant association between choice of antibiotic and SSI for orthopedic and colorectal procedures.

The empirical superiority of the 60-minute timing metric has yet to be substantiated. The evidence for this metric was based on antibiotic pharmacokinetics, including studies of antibiotic tissue concentration during surgery and a large cohort study.[1,2,18,19] The study by Classen et al[2] assessed the relationship between prophylactic antibiotic timing and SSI in a broad group of patients undergoing elective surgery and has several strengths, including prospective in-hospital assessment of SSI occurrence. However, of the 2847 patients in their cohort, only 44 (1.5%) developed an SSI. While they observed the lowest SSI rate in the group who received prophylactic antibiotics within 2 hours prior to incision, that rate was not significantly different from the group who received antibiotics in the perioperative period (≥3 hours after incision). The only significant differences were for the category of early, defined by antibiotics given 2 to 24 hours prior to surgical incision, and postoperative, defined by antibiotics given 3 to 24 hours after incision.

Figure 2. Association Between Timing of Prophylactic Antibiotics and Surgical Site Infection



Unadjusted (A) and adjusted (B) odds ratios (ORs) for the association between timing of prophylactic antibiotics and surgical site infection, with *P* values representing the significance of the association.Solid line indicates the OR estimate for surgical site infection; shaded area, 95% CI; dashed vertical line, incision time; and dashed horizontal line, an OR estimate of 1.0. Because spline fits for timing in the adjusted overall and vascular models were nearly linear (*df* < 1.1), final models considered timing as a linear effect.

Other studies have shown that the 60-minute window is not exclusively the most effective timing window and that infection rates among intervals within the 60-minute window are not equivalent.[5-9,20,21] Some studies suggest that antibiotics administered 0 to 30 minutes prior to incision are associated with higher SSI rates compared with antibiotics given 30 to 60 minutes before incision.[6,20] Conversely, another multicenter study of 4472 patients undergoing cardiac surgery, hysterectomy, or hip or knee arthroplasty reported an infection rate of 1.6% when the antibiotic was administered within 30 minutes prior to incision compared with 2.4% when administered between 31 and 60 minutes prior to incision (not statistically significant). Compared with the 60-minute preincision window, they observed higher SSI rates when antibiotics

Table 2. Frequency, Administration Time, and Surgical Site Infection Rates for Antibiotic Agents Stratified by Procedure Type

Antibiotic Class	No.	Time to Incision, Median (IQR), min	No. (%) Orthopedic (n = 20 528) Antibiotic	Orthopedic SSI[a]	Vascular (n = 5138) Antibiotic	Vascular SSI[a]	Colorectal (n = 5469) Antibiotic	Colorectal SSI[a]
Overall	32 459	28 (17-39)		298 (1.5)		467 (9.1)		705 (12.9)
Single antibiotic								
Cefazolin	21 862	28 (18-38)	16 816 (81.9)	231 (1.4)	4193 (81.6)	373 (8.9)	...	...
Clindamycin	1196	30 (19-40)	923 (4.5)	12 (1.3)	177 (3.4)	18 (10.2)	...	...
Vancomycin	2252	40 (23-60)	1641 (8.0)	39 (2.4)[b]	601 (11.7)	59 (9.8)	...	...
Cefoxitin	3216	23 (13-35)	...	...	...	...	3010 (78.3)	419 (13.9)
Cefotetan	911	25 (15-40)	...	...	...	...	795 (20.7)	113 (14.2)
Other[c]	41	25 (15-37)	...	...	...	...	40 (1.0)	7 (17.5)
Ampicillin/sulbactam	402	25 (16-36)	...	...	...	...	385 (7.0)	43 (11.2)
Ertapenem	360	28 (15-41)	...	...	...	...	360 (6.6)	46 (12.8)
Combination antibiotic								
Vancomycin + other[d]	1354	24 (13-36)	1148 (5.6)	16 (1.4)	164 (3.2)	17 (10.4)	37 (0.7)	5 (13.5)
Cefazolin + metronidazole	460	21 (10-36)	...	...	...	...	456 (8.3)	33 (7.2)[b]
Quinolone + anaerobic agent	335	18 (8-35)	...	...	...	...	332 (6.1)	28 (8.4)[e]
Clindamycin + gram-negative agent	70	16 (8-30)	...	...	...	...	54 (1.0)	11 (20.4)

Abbreviations: IQR, interquartile range; SSI, surgical site infection; ellipses, antibiotic was not appropriate for surgical procedure.

[a] Percentage represents the SSI rate for the antibiotic class.

[b] Significant difference in SSI rate for the procedure group at α = .01.

[c] Includes cefonicid, cefprozil, and cefuroxime.

[d] Other indicates other Surgical Care Improvement Project–approved prophylactic antibiotic.

[e] Significant difference in SSI rate for the procedure group at α = .05.

Table 3. Relative Contribution of Model Covariates for Surgical Site Infection Risk[a]

Variable	Overall $\chi^2 - df$	Overall Rank	Orthopedic $\chi^2 - df$	Orthopedic Rank	Vascular $\chi^2 - df$	Vascular Rank	Colorectal $\chi^2 - df$	Colorectal Rank
Total	362.7		14.0		79.0		77.4	
Specialty	233.2[b]	1	...	...	...	...	...	...
Antibiotic timing	−0.5	15	1.2	5	−1.0	14	0.1	11
Antibiotic agent	17.6[b]	5	5.1[b]	2	−2.1	15	18.0[b]	2
Operative duration	31.7[b]	2	−0.6	9	9.2[b]	5	26.3[b]	1
Age	30.0[b]	3	4.9	3	14.8[b]	2	11.1[b]	4
Diabetes	19.4[b]	4	1.4	4	20.5[b]	1	1.0	10
Wound class	9.9[b]	6	...	...	13.9[b]	3	2.4	6
Dyspnea	8.9[b]	7	1.0	6	−0.5	11	11.8[b]	3
ASA class	6.2[b]	8	−1.9	14	10.0	4	2.3	7
Work RVUs	2.1	9	−0.8	11	4.5	7	2.2	8
COPD	2.0	10	−1.0	13	0.5	9	1.3	9
Emergent case	1.3	11	−0.9	12	−0.9	13	4.1[b]	5
Alcohol use	1.3	12	−0.4	8	7.7[b]	6	−0.4	12
Smoker	0.8	13	6.9[b]	1	−0.8	12	−0.9	14
Penicillin allergy	−0.1	14	−0.6	10	3.0[b]	8	−0.9	13
Steroid use	−1.0	16	−0.3	7	0.1	10	−1.0	15

Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; RVUs, relative value units; ellipses, covariates not included in model.

[a] $\chi^2 - df$ is the χ^2 estimate minus the *df* for the model term. Rank is the relative contribution of the model term to the overall surgical site infection risk.

[b] Covariate is significant ($P < .05$).

were administered after incision (OR = 2.20; 95% CI, 1.03-4.66) but not prior to 60 minutes.[8] Our partial effect plots confirm that giving antibiotics closer to the time of incision appears to be an equally effective practice. The variability in antibiotic timing importance among these reports and our study confirms that the relationship between timing and SSI

is highly dependent on the selection of timing intervals, the antibiotic agent, and the surgical population studied.

We observed significant differences in risk-adjusted SSI rates for several SCIP-approved antibiotics. Vancomycin as a sole agent was associated with higher SSI rates. It is unclear whether the selection of vancomycin is an indicator of patients at higher risk for SSI; however, the higher rate was observed when vancomycin was used alone but not in combination with another SCIP-approved antibiotic. This is in contrast to a prior study that found higher rates of SSI when vancomycin was used in combination rather than as a single agent.[8] We also observed a protective effect with cefazolin and quinolone in combination with anaerobic agents for colorectal surgery. Similar findings of decreased infections with these combinations as well as ertapenem have been reported for a large multicenter study of colorectal surgery.[22] Furthermore, a randomized controlled trial comparing ertapenem and cefotetan reported lower rates of SSI for ertapenem compared with cefotetan (adjusted OR = 0.41; 95% CI, 0.28-0.61).[23] Studies are needed to determine whether the lack of antibiotic redosing or bacterial resistance patterns led to differences in antibiotic effectiveness.

Our study has several strengths, including assessing timing as a continuous variable, detailed patient- and procedure-level data, and assessment of SSI out to 30 days after the surgical procedure.[24] Furthermore, the antibiotic timing and SSI outcome data were assessed by 2 independent programs, limiting the chance for bias.

The study sample primarily comprises older male patients, limiting the generalizability to women, and we were not able to assess cardiac procedures. Intraoperative redosing of antibiotics has been shown to be important for longer procedures,[5] and we were not able to assess whether redosing occurred. Our cohort is large in absolute terms, with the highest SSI rates observed for antibiotics administered more than 120 minutes prior to incision; however, this group was a small proportion of the cohort. Given current high adherence to the timely antibiotic measure, it is likely that all observational studies will share this limitation.[8]

Conclusions

Timing of prophylactic antibiotic administration is not significantly associated with SSI occurrence. While adherence to the timely prophylactic antibiotic measure is not bad care, there is little evidence to suggest that it is better care. Future endeavors for reducing SSI should robustly correlate with improved outcomes and include studies to refine recommended antibiotic choice and redosing.

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Author Affiliations: Birmingham Center for Surgical and Medical Acute Care Research and Transitions, Birmingham Veterans Administration Hospital, Birmingham, Alabama (Hawn, Richman, Vick, Deierhoi, Graham); Section of Gastrointestinal Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama (Hawn, Richman, Deierhoi); Colorado Health Outcomes Program, University of Colorado, Aurora, Colorado (Henderson); Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, Colorado (Henderson); Department of Surgery, Veterans Affairs Boston Health Care System, Boston University and Harvard Medical School, Boston, Massachusetts (Itani).

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Study concept and design: Hawn, Vick, Henderson, and Itani.
Acquisition of data: Vick, Deierhoi, Graham, and Henderson.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Hawn, Richman, Vick, and Deierhoi.
Critical revision of the manuscript for important intellectual content: Hawn, Richman, Vick, Graham, Henderson, and Itani.
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REFERENCES

1. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis*. 2006;43(3):322-330.

2. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med*. 1992;326(5):281-286.

3. Khuri SF, Daley J, Henderson W, et al; National VA Surgical Quality Improvement Program. The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. *Ann Surg*. 1998;228(4):491-507.

4. Khuri SF, Daley J, Henderson W, et al. Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. *J Am Coll Surg*. 1997;185(4):315-327.

5. Miliani K, L'Hériteau F, Astagneau P; INCISO Network Study Group. Non-compliance with recommendations for the practice of antibiotic prophylaxis and risk of surgical site infection: results of a multilevel analysis from the INCISO Surveillance Network. *J Antimicrob Chemother*. 2009;64(6):1307-1315.

6. Weber WP, Marti WR, Zwahlen M, et al. The timing of surgical antimicrobial prophylaxis. *Ann Surg*. 2008;247(6):918-926.

7. Walz JM, Paterson CA, Seligowski JM, Heard SO. Surgical site infection following bowel surgery: a retrospective analysis of 1446 patients. *Arch Surg*. 2006;141(10):1014-1018.

8. Steinberg JP, Braun BI, Hellinger WC, et al; Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) Study Group. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. *Ann Surg*. 2009;250(1):10-16.

9. van Kasteren ME, Manniën J, Ott A, Kullberg BJ, de Boer AS, Gyssens IC. Antibiotic prophylaxis and

the risk of surgical site infections following total hip arthroplasty: timely administration is the most important factor. *Clin Infect Dis*. 2007;44(7):921-927.

10. The Joint Commission; Centers for Medicare and Medicaid Services. *Specifications Manual for National Hospital Inpatient Quality Measures: Measure Information: Surgical Care Improvement Project (SCIP): Version 3.3*. Oakbrook Terrace, IL: The Joint Commission, Centers for Medicare & Medicaid Services; 2011.

11. Khuri SF, Daley J, Henderson W, et al. The National Veterans Administration Surgical Risk Study: risk adjustment for the comparative assessment of the quality of surgical care. *J Am Coll Surg*. 1995;180(5):519-531.

12. Davis CL, Pierce JR, Henderson W, et al. Assessment of the reliability of data collected for the Department of Veterans Affairs national surgical quality improvement program. *J Am Coll Surg*. 2007;204(4):550-560.

13. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR; Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. Guideline for Prevention of Surgical Site Infection, 1999. *Am J Infect Control*. 1999;27(2):97-132.

14. Neumayer L, Hosokawa P, Itani K, El-Tamer M, Henderson WG, Khuri SF. Multivariable predictors of postoperative surgical site infection after general and vascular surgery: results from the patient safety in surgery study. *J Am Coll Surg*. 2007;204(6):1178-1187.

15. Harrell FE Jr. *Regression Modeling Strategies With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York, NY: Springer; 2001.

16. Halekoh U, Højsgaard S, Yan J. The R package geepack for Generalized Estimating Equations. *J Stat Softw*. 2006;15(2):1-11.

17. Wood SN. Thin plate regression splines. *J R Stat Soc Series B Stat Methodol*. 2003;65(1):95-114. doi:10.1111/1467-9868.00374.

18. Polk HC Jr, Lopez-Mayor JF. Postoperative wound infection: a prospective study of determinant factors and prevention. *Surgery*. 1969;66(1):97-103.

19. Burke JF. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. *Surgery*. 1961;50:161-168.

20. Garey KW, Dao T, Chen H, et al. Timing of vancomycin prophylaxis for cardiac surgery patients and the risk of surgical site infections. *J Antimicrob Chemother*. 2006;58(3):645-650.

21. Lallemand S, Thouverez M, Bailly P, Bertrand X, Talon D. Non-observance of guidelines for surgical antimicrobial prophylaxis and surgical-site infections. *Pharm World Sci*. 2002;24(3):95-99.

22. Hendren S, Fritze D, Banerjee M, et al. Antibiotic choice is independently associated with risk of surgical site infection after colectomy: a population-based cohort study [published online October 10, 2012]. *Ann Surg*. doi:10.1097/SLA.0b013e31826c4009.

23. Itani KM, Wilson SE, Awad SS, Jensen EH, Finn TS, Abramson MA. Ertapenem vs cefotetan prophylaxis in elective colorectal surgery. *N Engl J Med*. 2006;355(25):2640-2651.

24. Bilimoria KY, Cohen ME, Ingraham AM, et al. Effect of postdischarge morbidity and mortality on comparisons of hospital surgical quality. *Ann Surg*. 2010;252(1):183-190.

Invited Commentary

Timing May Not Be Everything

Leigh Neumayer, MD, MS

Ideally, any metric (especially a publicly reported one) should be reliable and valid. If it is a process measure, there should be a long track record of reports confirming that adherence to the measure is associated with significantly better results than nonadherence to the measure. Using large, validated, reliable data sets and sophisticated statistical analyses, Hawn et al[1] have furthered their work showing little relationship between adherence to the publicly reported "quality" measure of the right antibiotic within 60 minutes of incision and improved outcomes. In this analysis, multiple statistical methods were used to tease out any potential associations. While there was a small association between antibiotic timing and surgical site infection in unadjusted analyses, the difference disappeared when the models were adjusted for patient, procedure, and antibiotic variables. This article is not a call to abandon prophylactic antibiotics when indicated, as most studies have shown a significant reduction in postoperative surgical site infections with their use (when compared with no antibiotics). However, it does once again strongly suggest that the current publicly reported measures are not associated with improved outcomes. As surgeons, we should work with federal and local agencies to define metrics that are more robustly associated with better outcomes for our patients.

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Author Affiliation: Department of Surgery, University of Utah, Salt Lake City.

Corresponding Author: Dr Neumayer, Department of Surgery, Huntsman Cancer Hospital, 1950 Circle of Hope, Room N6335, Salt Lake City, UT 84112 (leigh.neumayer@hsc.utah.edu).

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REFERENCE

1. Hawn MT, Richman JS, Vick CC, et al. Timing of surgical antibiotic prophylaxis and the risk of surgical site infection [published online March 20, 2013]. *JAMA Surg*. 2013;148(7):649-657.