Surgical Site Infection After Arthroplasty: Comparative Effectiveness of Prophylactic Antibiotics

Do Surgical Care Improvement Project Guidelines Need to Be Updated?

Brent Ponce, MD, Benjamin Todd Raines, MA, ATC, Rhiannon D. Reed, MPH, Catherine Vick, MS, Joshua Richman, MD, PhD, and Mary Hawn, MD, MPH

Investigation performed at the Center for Surgical, Medical Acute Care Research and Transitions, Birmingham Alabama VA Medical Center, Birmingham, and the Division of Orthopaedic Surgery, University of Alabama at Birmingham, Birmingham, Alabama

Background: Prophylactic antibiotics decrease surgical site infection (SSI) rates, and their timing, choice, and discontinuation are measured and reported as part of the Surgical Care Improvement Project (SCIP). The aim of this study was to assess the comparative effectiveness of the SCIP-approved antibiotics for SSI prevention.

Methods: This retrospective cohort study utilized national Veterans Affairs (VA) data on patients undergoing elective hip or knee arthroplasty from 2005 to 2009. Data on prophylactic antibiotics were merged with VA Surgical Quality Improvement Program data to identify patient and procedure-related risk factors for SSI. Patients were stratified by documented penicillin allergy. Chi-square and Wilcoxon rank-sum tests were used to compare SSI rates among patients receiving SCIP-approved prophylactic antibiotics.

Results: A total of 18,830 elective primary arthroplasties (12,823 knee and 6007 hip) were included. Most patients received prophylactic cefazolin as the sole agent (81.9%), followed by vancomycin as the sole agent (8.0%), vancomycin plus cefazolin (5.6%), and clindamycin (4.5%). Documented penicillin allergy accounted for 54.1% of cases involving vancomycin administration compared with 94.6% of cases involving clindamycin. The overall thirty-day SSI rate was 1.4%, and the unadjusted rate was 2.3% with vancomycin only, 1.5% with vancomycin plus cefazolin, 1.3% with cefazolin only, and 1.1% with clindamycin. Unadjusted analysis of penicillin-allergic patients revealed an SSI rate of 2.0% with vancomycin only compared with 1.0% with clindamycin ($p = 0.18$). For patients without penicillin allergy, the SSI rate was 2.6% with vancomycin only compared with 1.6% with vancomycin plus cefazolin ($p = 0.17$) and 1.3% with cefazolin only ($p < 0.01$).

Conclusions: Current SCIP guidelines address antibiotic timing but not antibiotic dosage. (The generally accepted recommendation for vancomycin is 15 mg/kg.) Although vancomycin is a narrower-spectrum antibiotic than either cefazolin or clindamycin, our finding of higher SSI rates following prophylaxis with vancomycin only may suggest a failure to use an appropriate dosage rather than an inequality of antibiotic effectiveness.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

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A commentary by Thomas J. Blumenfeld, MD, is linked to the online version of this article at jbjs.org.

Joint arthroplasty is a common procedure in the treatment of degenerative joint disease, effectively reducing pain and restoring function. Over the last twenty years, hip and knee arthroplasty rates have increased >150% in the United States, and between 2005 and 2030, it is anticipated that primary total knee arthroplasty will increase by 673% to roughly 3.48 million procedures annually and primary total hip arthroplasty will increase by 174% to 572,000 annually[1,2]. Periprosthetic joint infection occurs following 2% of total knee arthroplasties, which would result in nearly 70,000 prosthetic knee infections annually by 2030, in the United States[3]. The prevention of surgical site infections (SSIs) is a national priority and a major focus of the Surgical Care Improvement Project (SCIP)[4].

Prophylactic antibiotics effectively reduce SSI rates after hip and knee arthroplasty[5]. The SCIP antibiotic prophylaxis measures, established in 2005, represented an effort to reduce SSI rates in the Unites States. Prophylactic antibiotic choice, timing, and discontinuation are all measured and publicly reported as part of the SCIP. Despite widespread adoption of the SCIP directives, we are aware of no reported objective data reflecting a corresponding decrease in SSI rates[6,7]. Current SCIP guidelines for SSI prevention focus on three main efforts: (1) SCIP-inf-1 measures compliance with the recommendation for prophylactic antibiotic administration within sixty minutes prior to surgical incision, or within 120 minutes for vancomycin and fluoroquinolones (which have an extended infusion time); (2) SCIP-inf-2 assesses whether procedure-appropriate prophylactic antibiotics were administered; and (3) SCIP-inf-3 evaluates discontinuation of prophylactic antibiotics within twenty-four hours of the end time of the surgery[8]. One recently identified shortfall of antibiotic administration involves use of an adequate dosage based on patient weight[9]. Failure of SCIP guidelines to address adherence to use of a weight-based dosage, namely for vancomycin (15 mg/kg), may result in a disconnect between guideline adherence and SSI reduction.

Despite the widespread adoption of routine antibiotic prophylaxis, the failure of SSI rates to decline has raised several questions. Controversy exists regarding the indications and effectiveness of SCIP-approved antibiotics compared with one another. One such debate focuses on the effectiveness of vancomycin as a prophylactic antibiotic, both in general and at institutions with an elevated MRSA (methicillin-resistant *Staphylococcus aureus*) prevalence (positive cultures in >25% of SSIs)[10,11]. The aim of the present study was to identify the comparative effectiveness of the SCIP-approved antibiotics for SSI prevention in patients undergoing elective hip and knee arthroplasty.

TABLE I Procedure Characteristics

	Total		Antibiotic Choice									SSI		
			Cefazolin Only		Vancomycin Only		Vancomycin + Cefazolin		Clindamycin					
	N	% of Cohort	N	%	N	%	N	%	N	%	P Value	N	%	P Value
ASA class											<0.0001			0.5
1 or 2	5805	30.8	4759	82.0	530	9.1	314	5.4	202	3.5		81	1.4	
3	12,529	66.5	10,256	81.9	934	7.5	725	5.8	614	4.9		173	1.4	
4	496	2.6	407	82.1	36	7.3	23	4.6	30	6.0		10	2.0	
Type											0.08			0.41
Hip	6007	31.9	4866	81.0	505	8.4	368	6.1	268	4.5		78	1.3	
Knee	12,823	68.1	10,556	82.3	995	7.8	694	5.4	578	4.5		186	1.5	
Knee subtype											0.64			0.5
Total	12,524	97.7	10,314	82.4	968	7.7	675	5.4	567	4.5		183	1.5	
Unicompartmental	299	2.3	242	80.9	27	9.0	19	6.4	11	3.7		3	1.0	

TABLE II SSI Rates According to Penicillin Allergy and Type of Antibiotic*

	Total	Cefazolin Only		Vancomycin		Vancomycin + Cefazolin		Clindamycin		P Value
		N	SSI *(%)*	N	SSI *(%)*	N	SSI *(%)*	N	SSI *(%)*	
Overall	18,830	15,422	1.3	1500	2.3	1062	1.5	846	1.1	0.02
No pen. allergy	16,446	14,722	1.3	685	2.6	994	1.6	45	2.2	0.03
Pen. allergy	2365	685	1.8	812	2.0	68	0.0	800	1.0	0.3

*Information regarding penicillin allergy was not available for nineteen patients.

TABLE III Multivariate Model of Predictors of SSI After Arthroplasty

Variable	Unadjusted OR	Adjusted OR*	Adjusted 95% CI
Smoking	1.57	1.57	1.21-2.03
Prophylactic antibiotic			
Cefazolin	Ref.	Ref.	
Clindamycin	0.80	0.79	0.41-1.55
Vancomycin	1.72	1.73	1.20-2.49
Vancomycin plus cefazolin	1.14	1.12	0.67-1.87

*Model adjusted only for the factors shown. C-statistic = 0.568.

Materials and Methods

We performed a retrospective cohort study utilizing national Veterans Affairs (VA) data on patients from ninety-four hospitals undergoing elective primary hip or knee arthroplasty from 2005 to 2009. The study protocol was reviewed and approved by the local VA institutional review board, with waiver of informed consent.

Data Sources

Data from both the SCIP and the Veterans Affairs Surgical Quality Improvement Program (VASQIP) were used. The Veterans Health Administration Office of Information and Analytics External Peer Review Program contracts with the West Virginia Medical Institute to collect VA hospital SCIP measures. The process began in 2005 according to guidelines set forth by the Joint Commission on Accreditation of Healthcare Organizations and the Centers for Medicare & Medicaid Services. Frequent assessment of the abstracted information is performed to ensure reliability[12]. The VASQIP was started in 1991 to analyze risk-adjusted thirty-day postoperative morbidity and mortality data in the VA Healthcare System[13,14]. The VASQIP collects demographics, preoperative risk and laboratory data, operative data, and thirty-day postoperative morbidity and mortality outcomes on a majority of the patients undergoing major surgery in the VA Healthcare System. Clinical nurse reviewers, trained in clinical medicine and quality assurance, complete in-depth training on the data collection procedures and detailed definitions of each of the variables. A recent study of the quality of the data at a sample of VA medical centers showed that VASQIP data are highly reliable[15].

Study Cohort

Patients undergoing elective hip arthroplasty (CPT [Current Procedural Terminology] codes 27130 or 27132) or elective knee arthroplasty (CPT 27440, 27441, 27442, 27443, 27446, or 27447) were eligible for inclusion in the sample[16]. Patients who had an ASA (American Society of Anesthesiologists) grade of 5 (n = 2); had a wound classification other than clean (n = 200); or underwent emergency arthroplasty (e.g., for hip fracture) (n = 720), partial hip arthroplasty (n = 526), or revision arthroplasty (n = 132) were excluded.

Study Variables

The independent variable of interest was the choice of prophylactic antibiotic. The dependent variable of interest was the occurrence of a superficial or deep incisional SSI within thirty days postoperatively as reported by the VASQIP, which follows the Centers for Disease Control and Prevention definition[14]. Superficial and deep incisional SSIs were combined to create a composite SSI outcome variable.

The prophylactic antibiotic agents were (1) cefazolin as the sole agent, (2) vancomycin as the sole agent, (3) vancomycin plus cefazolin, and (4) clindamycin. Patients receiving any non-SCIP-approved antibiotic or combination were excluded.

Patient-level covariates known to predict the occurrence of SSIs were obtained from the VASQIP. These included demographics; lifestyle variables (e.g., tobacco and alcohol use); and cardiovascular, pulmonary, renal, hepatobiliary, nutritional, and immune comorbidities (with the latter defined as regular administration of oral or parenteral corticosteroid medication in the thirty days prior to admission for a chronic medical condition)[15]. Surgery characteristics considered in the study included the type of arthroplasty (hip or knee), ASA status, and duration of the operation (from incision to surgery end time).

Statistical Analyses

Unadjusted testing for associations among patient characteristics, prophylactic antibiotic choice, and SSI was performed with use of chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Patients were stratified by documented penicillin allergy, and SSI rates were compared between patients receiving vancomycin only and other SCIP-approved prophylactic agents with use of chi-square tests. Multivariate backward stepwise logistic regression was performed to determine predictors of SSI. A facility-level analysis was also performed, calculating Pearson correlation coefficients and excluding VA hospitals that contributed fewer than ten cases.

Source of Funding

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TABLE IV Multivariate Model of SSI Predictors Including All Clinically Relevant Demographics

Variable	Unadjusted OR	Adjusted OR*	Adjusted 95% CI
Clindamycin vs. cefazolin only	0.80	0.85	0.39-1.87
Vancomycin only vs. cefazolin only	1.72	1.77	1.15-2.73
Vanc. plus cefazolin vs. cefazolin only	1.14	1.15	0.69-1.93
Age, per yr	0.98	0.99	0.97-1.00
Female sex	1.17	1.09	0.64-1.85
Penicillin allergy	0.91	0.94	0.59-1.49
Smoker	1.57	1.48	1.11-1.96
BMI in kg/m^2			
18-25.0 vs. <18	0.81	0.82	0.52-1.30
25.1-30.0 vs. <18	0.77	0.79	0.56-1.13
>30.0 vs. <18	0.84	0.82	0.59-1.12
Non-insulin-dependent vs. no diabetes	1.12	1.14	0.81-1.61
Insulin-dependent vs. no diabetes	1.45	1.45	0.90-2.33
COPD†	1.04	0.97	0.64-1.47
ASA 3 vs. 1 or 2	0.99	1.03	0.78-1.37
ASA 4 or 5 vs. 1 or 2	1.45	1.62	0.81-3.21
Knee vs. hip	1.12	1.20	0.91-1.57

*Adjusted for all factors shown above. C-statistic = 0.593. †COPD = chronic obstructive pulmonary disease.

Results

A total of 18,830 elective primary arthroplasties (12,823 knee and 6007 hip) performed at ninety-four VA facilities were included in the cohort. The majority of patients received cefazolin only (15,422, 81.9%), followed by vancomycin only (1500, 8.0%), vancomycin plus cefazolin (1062, 5.6%), and clindamycin (846, 4.5%). A documented penicillin allergy accounted for only 54.1% of patients receiving vancomycin but 94.6% of those receiving clindamycin.

Antibiotic administration was generally timely; 3.0% of doses were early, 95.4% were on time, and only 1.6% were late. The rate of appropriate timing was 95.1% for cefazolin only, 99.2% for vancomycin plus cefazolin, 97.1% for vancomycin only, and 94.4% for clindamycin ($p < 0.0001$).

Analysis of patient-level variables revealed that only patient age was significantly associated with both the type of antibiotic selected ($p < 0.001$) and SSI rate ($p < 0.01$). Patient factors significantly associated with antibiotic choice were age, sex, race, penicillin allergy, body mass index (BMI), diabetes, and chronic obstructive pulmonary disease. The only patient factor other than age that was significantly associated with SSI rate was tobacco use ($p < 0.001$), but the association of tobacco use with antibiotic choice did not reach significance ($p = 0.08$) (see Appendix). An analysis of procedure-level variables is presented in Table I.

A total of 264 SSIs (1.4%) were observed within thirty days of the arthroplasties (see Appendix). The unadjusted overall SSI rate was 2.3% with vancomycin as the sole prophylactic agent, 1.5% with vancomycin plus cefazolin, 1.3% with cefazolin only, and 1.1% with clindamycin (chi-square $p = 0.02$). Unadjusted analysis of the patients with a documented penicillin allergy (n = 2365, 12.6%) revealed an SSI rate of 2.0% with vancomycin prophylaxis only compared with 1.0% with clindamycin (chi-square $p = 0.18$). For the patients without a penicillin allergy (n = 16,446, 87.3%), the SSI rate was 2.6% with vancomycin only compared with 1.6% with vancomycin plus cefazolin ($p = 0.17$) and 1.3% with cefazolin only ($p < 0.01$) (Table II).

Multivariate logistic regression modeling identified only two independent predictors of SSI, current smoking (unadjusted odds ratio [OR] = 1.57; adjusted OR = 1.57, 95% confidence interval [CI] = 1.21 to 2.03) and the use of vancomycin as the sole prophylactic agent (compared with cefazolin only) (unadjusted OR = 1.72; adjusted OR = 1.73, 95% CI = 1.20 to 2.49). The SSI rates with clindamycin and with vancomycin plus cefazolin did not differ significantly from those with cefazolin only (Table III). Inclusion of additional patient-level variables in this model did not improve the c-statistic, demonstrating no significant association between those factors and infection (Table IV).

Hospital-level analysis revealed that the use of vancomycin only ranged from 0.0% to 97.0%, with hospital use of any vancomycin (vancomycin only or in combination with cefazolin) ranging from 0.0% to 100.0%. Hospital vancomycin use, both overall and as a single prophylactic agent, was not strongly correlated with the infection rate for the procedures at the hospital ($R^2 = 0.026$), suggesting that variations in the rate of vancomycin use do not satisfactorily explain

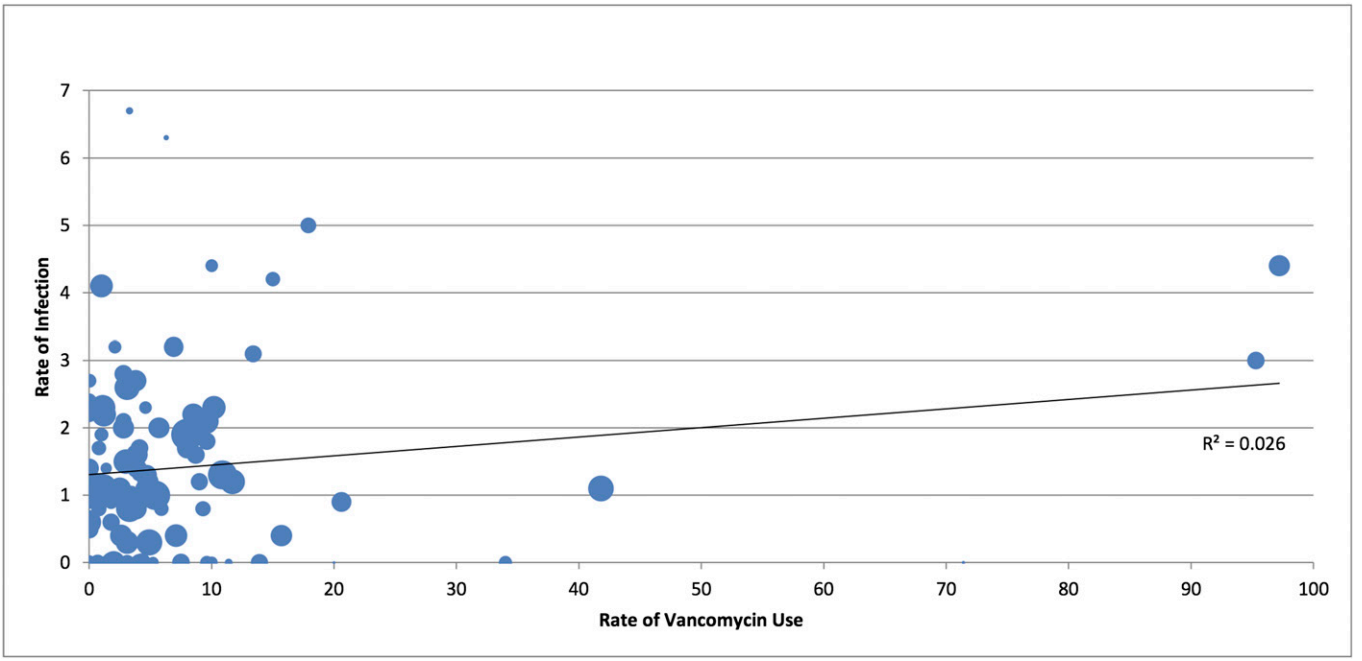

Fig. 1

Figs. 1 through 4 Facility-level analysis of the use of a specific antibiotic (%) versus the facility infection rate (%). Each individual data point represents one facility; VA hospitals that contributed fewer than ten cases were excluded. R^2 represents the Pearson correlation coefficient. **Fig. 1** Facility use of vancomycin only versus infection rate.

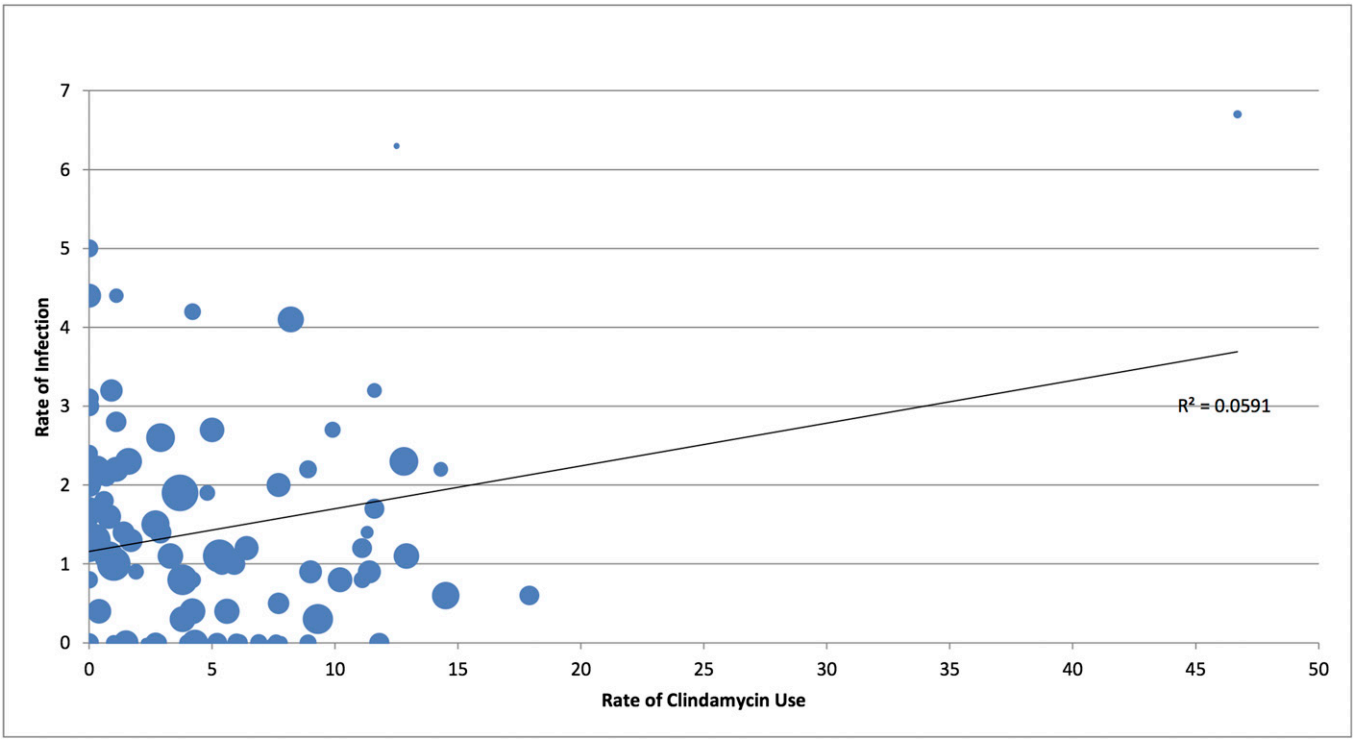

Fig. 2

Facility use of clindamycin versus infection rate.

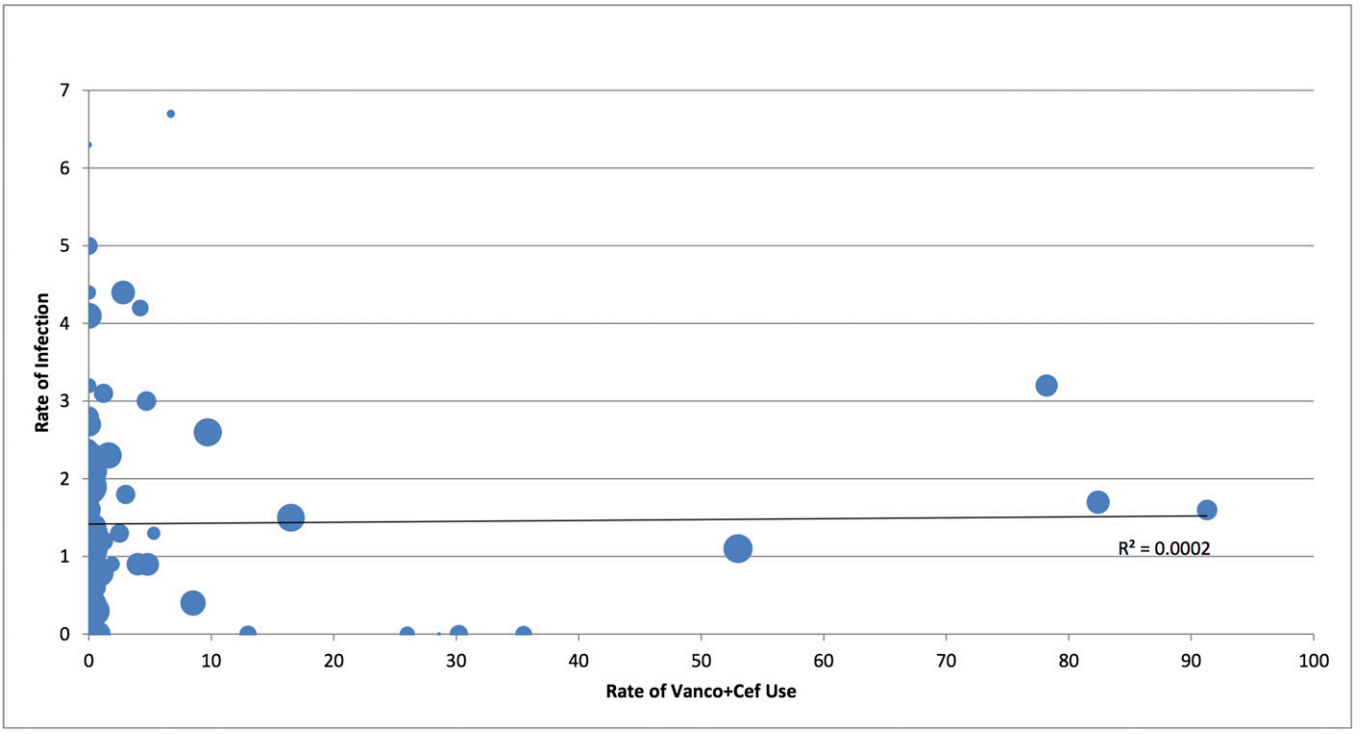

Fig. 3

Facility use of vancomycin plus cefazolin versus infection rate.

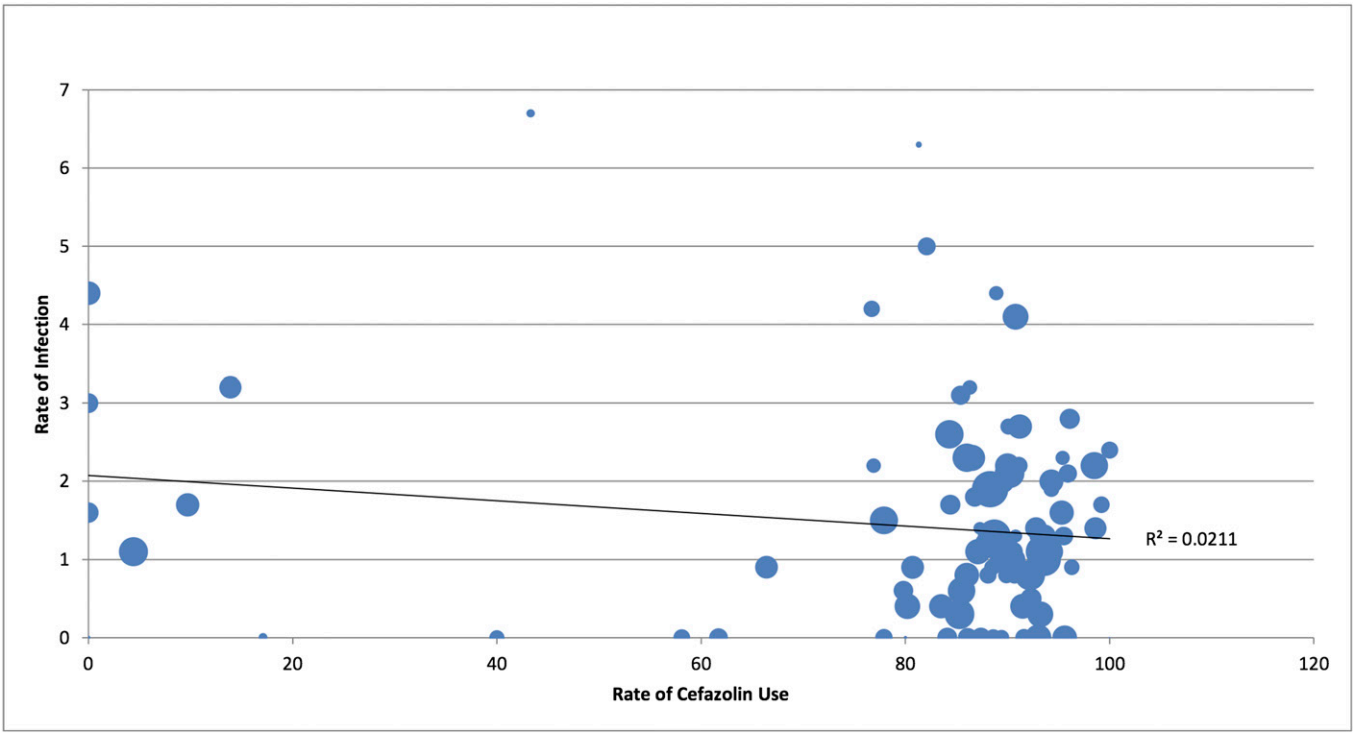

Fig. 4
Facility use of cefazolin only versus infection rate.

variations in facility infection rates (Fig. 1). Comparable analyses were conducted for clindamycin (Fig. 2, $R^2 = 0.059$), vancomycin plus cefazolin (Fig. 3, $R^2 = 0.0002$), and cefazolin only (Fig. 4, $R^2 = 0.0211$), with only clindamycin showing a stronger, but still poor, correlation with hospital infection rates.

Discussion

The potential causes of SSIs are multiple and have varying degrees of importance. With increasing concerns regarding health-care costs and the increased costs associated with revision surgery, infection following joint replacement is of increasing interest with regard to quality measurement and resource utilization. The findings in the present study highlight a few key points. First, the rate of surgical infections within the first thirty days after surgery was higher when vancomycin was used as the sole prophylactic antibiotic. Second, the choice of vancomycin was not entirely explained by a documented penicillin allergy. Third, SCIP guidelines fail to address adherence to use of a weight-based antibiotic dosage.

The explanation for the higher SSI rate with vancomycin is likely multifactorial. Growing concerns regarding the comparative effectiveness of vancomycin focus on appropriate dosage, spectrum coverage, and organism selection. Concerns regarding the potential adverse effects of vancomycin may have precluded use of an effective dosage. It has become a more common practice to give a "standardized" 1-g dose of vancomycin instead of the appropriate 15 mg/kg. Catanzano et al. recently showed that up to 80% of patients undergoing elective total joint and spine surgery who receive vancomycin are underdosed when given a standard 1-g dose preoperatively instead of 15 mg/kg[9]. A 1-g dose would be appropriate only for those weighing <67 kg (<147 lb). Finally, vancomycin is a narrower-spectrum antibiotic compared with both cefazolin and clindamycin.

Prior studies have revealed conflicting findings regarding the efficacy of vancomycin in reducing SSIs[9-11,17,18]. In a 2010 prospective study, the suggestion was made that vancomycin as the sole agent may not be as effective as other SCIP-approved prophylactic antibiotics[11]. More recently, Smith et al. found a lower rate of joint infections when the routine prophylactic antibiotic was changed from cefazolin to vancomycin[10]. The authors of another study found no significant difference in SSI rates with vancomycin plus cefazolin compared with cefazolin only[18]. AAOS (American Academy of Orthopaedic Surgeons) information statements have recommended vancomycin for patients with β-lactam allergy, for patients with known colonization with MRSA, at facilities with recent MRSA outbreaks, or at facilities having a notable MRSA prevalence of 10% to 20%[17,19]. Limitations in prior studies include a single study site, small sample sizes, and multifactorial approaches to reducing SSIs that make it difficult to establish the antibiotic choice as the reason for a change in the SSI rate. Further studies are needed to determine whether use of an appropriate dose of vancomycin only or vancomycin in combination with cefazolin is the better strategy.

Nearly one-half of the patients receiving vancomycin did not have a penicillin allergy; thus, other reasons for selecting vancomycin as the prophylactic antibiotic were also

present. A number of variables drive practice style and preference with regard to prophylactic antibiotic choice, and these can be divided into three main categories: patient-specific factors, hospital factors, and surgeon preference. Patient-specific factors may include variables such as comorbidities, prior SSI or MRSA status, procedure nature (primary or revision), and wound classification. All of these patient-specific factors impact the perceived risk of infection. Hospital-level factors may include hospital adherence to SCIP protocols, facility SSI and MRSA rates, and the availability of specific prophylactic antibiotics. Finally, surgeon preference may be driven by prior SSI rate, familiarity with recent evidence on the efficacy of prophylactic antibiotics, and postgraduate training. Regardless of the particular patient, hospital, or surgeon factors involved, the use of vancomycin may reflect concern regarding an elevated risk of MRSA infection.

The potential dosage issue regarding vancomycin may point to a larger concern regarding what defines "compliance" with SCIP guidelines. Current guidelines focus on antibiotic timing (involving both the preoperative administration and the postoperative discontinuation) and whether the antibiotic choice is appropriate for the procedure. However, SCIP guidelines fail to address use of a proper dosage of the antibiotic[8]. AAOS guidelines do address use of a proper dosage, highlighting the potential need for SCIP guidelines to be modified for orthopaedic procedures[17-19].

Although the results of the present study suggest that SSI prophylaxis with vancomycin only is associated with a higher SSI rate, the reason(s) for this association remains to be understood. A number of points would need to be addressed to confirm that vancomycin is less effective in SSI prevention compared with other SCIP-approved antibiotics. First, SCIP measures should include a weight-based dosage guideline. Second, the knowledge gap regarding SSI predictors in patients undergoing elective arthroplasty must be bridged. To date, a number of studies have identified an array of SSI predictors following arthroplasty: hematoma formation, persistent postoperative drainage, systemic corticosteroid use, wound discharge, greater BMI, diabetes, and an ASA class of ≥3 resulting from a combination of "specific comorbidities."[20-23] However, all of these studies lack inclusiveness, investigating a very limited scope of variables. Of all of the independent variables analyzed in the present study, only increased age and smoking were associated with higher SSI rates after arthroplasty. The present study confirms the previously reported elevated risk of SSI in smokers and, given the elective nature of this procedure, smoking cessation interventions should be considered for active smokers[24,25]. We are aware of only one previous study involving a thorough evaluation of the association between patient comorbidities and the risk of periprosthetic joint infection after hip or knee arthroplasty. That study by Bozic et al., published in 2012, evaluated twenty-nine comorbid conditions and indicated that rheumatologic disease, obesity, coagulopathy, and preoperative anemia had the strongest association with periprosthetic joint infection within ninety days after total hip arthroplasty (a time period three times as long as that in the present study)[26]. In contrast, we were not able to identify a similar spectrum of comorbidities associated with the thirty-day SSI rate. Given that the patient cohort in the study by Bozic et al. was twice as large as that in the present study, it may be that those comorbidities are indeed associated with SSI but that the cohort size of nearly 20,000 patients in the present study was still not sufficient to demonstrate the significance of the associations.

The present study has a number of strengths. First, the data used for the analysis were obtained from validated sources that are assessed frequently for data accuracy and precision[15]. Second, the tracking and the extraction of antibiotic choice and infection rate were done by separate individuals and entities, thus removing the potential for bias. Third, to the best of our knowledge after a thorough search of the literature, this is the only study of SSI after arthroplasty that included an analysis of the majority of the prophylactic antibiotics approved for orthopaedic procedures by the SCIP. Finally, this was a multicenter study, drawing from ninety-four facilities throughout the United States.

The study also has several limitations. First, the cohort consisted primarily of older, male patients with multiple comorbidities, limiting the generalizability of the results to female, healthier, and younger patients undergoing similar procedures. Second, neither the microbiology data for the SSIs diagnosed in the individual patients nor the hospital biogram data were available for analysis. These are of importance as different prophylactic antibiotic regimens have been associated with specific causative organisms in SSIs. Furthermore, specific antibiotic regimens, based on this association, appear to drive regional organism susceptibility and resistance[27]. Without knowing the biogram data, we cannot determine what effect organism susceptibility to other prophylactic antibiotics had on choosing vancomycin as the prophylactic agent. However, the number of institutions included in the study ameliorates this limitation. Third, we were unable to reliably assess certain variables involving antibiotic dosage[6]. Although administration of a second dose of prophylactic antibiotics is important for longer procedures, we were unable to assess whether redosing occurred in the study cohort. Furthermore, as previously mentioned, patient weight values were not available and we were therefore unable to assess the proportion of patients who would have been underdosed if given the "standardized" 1-g vancomycin dose. The analyses also did not take into account whether the antibiotic was discontinued within twenty-four hours after surgery; however, we demonstrated previously that adherence to this specific measure is not associated with reduced SSI occurrence. Fourth, both deep and superficial SSIs were combined into a composite SSI category on the basis of the VASQIP data. This was done because of concerns regarding misclassification bias during retrospective chart review and because the low event rates precluded reliable estimates of the individual infection types. Furthermore, we are unaware of any studies suggesting that the role of prophylactic antibiotics is more or less

important in prevention of superficial compared with deep SSIs, and such a composite end point has been used in our previous work[28]. The fifth limitation is the difficulty in performing subgroup analyses because of the limited cohort size and the low overall SSI event rates. Finally, the VASQIP data were limited to SSIs within the first thirty days and precluded identification of infections presenting after this window.

Appendix

eA Tables summarizing the cohort characteristics are available with the online version of this article as a data supplement at jbjs.org. ■

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Brent Ponce, MD
Division of Orthopaedic Surgery,
University of Alabama at Birmingham,
1313 13th Street South, Suite 203,
Birmingham, AL 35205-5327.
E-mail address: bponce@uabmc.edu

Benjamin Todd Raines, MA, ATC
Rhiannon D. Reed, MPH
Joshua Richman, MD, PhD
Mary Hawn, MD, MPH
Center for Surgical,
Medical Acute Care Research and Transitions,
Birmingham Alabama VA Medical Center,
700 South 19th Street,
Birmingham, AL 35233.
E-mail address for B.T. Raines: raines@uab.edu.
E-mail address for R.D. Reed: Rhiannon.Deierhoi@va.gov.
E-mail address for J. Richman: jrichman@uabmc.edu.
E-mail address for M. Hawn: mhawn@uabmc.edu

Catherine Vick, MS
2409 Shallowford Lane,
Chapel Hill, NC 27517

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