A commentary by James A. Keeney, MD, is linked to the online version of this article at jbjs.org.

Perioperative Antibiotic Prophylaxis in Total Joint Arthroplasty

A Single Dose Is as Effective as Multiple Doses

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Background: Recent surgical site infection prevention guidelines recommend that no additional prophylactic antibiotics be administered after the surgical incision is closed in clean-contaminated procedures. Although there is ample evidence to support this recommendation in non-arthroplasty surgery, there is concern about extending these guidelines to surgical procedures with an implant such as total joint arthroplasty (TJA). The aim of this study was to compare the efficacy of a single dose of prophylactic antibiotics with that of multiple doses of antibiotics for prevention of periprosthetic joint infection (PJI) in patients undergoing TJA.

Methods: A retrospective study of 20,682 primary TJAs carried out from 2006 to 2017 was performed. Patients who received a single dose of prophylactic antibiotics (n = 4,523) were compared with patients who received multiple doses of antibiotics (n = 16,159). A previously validated PJI risk score was assigned to each patient. Patients who developed PJI within 1 year were identified, and a multivariate logistic regression analysis was performed to control for potential confounders. Analyses using propensity score matching and regression adjustment were also performed.

Results: The overall PJI rate was 0.60% (27 of 4,523) for patients who received a single dose of antibiotics compared with 0.88% (142 of 16,159) for those who received multiple doses. There was no difference in the PJI rate between patients who received a single dose of antibiotics and those who received multiple doses in the univariate (adjusted odds ratio [OR] = 0.674, p = 0.064), multivariate (OR = 0.755, p = 0.205), or propensity score matched analysis (OR = 0.746, p = 0.277). Furthermore, multiple doses did not demonstrate any additional benefit for patients with a high preoperative risk of PJI (p = 0.136).

Conclusions: This study supports the notion that the administration of additional antibiotics following skin closure may not be required for primary TJA, regardless of the patient's preoperative risk of PJI. The findings of this large retrospective study highlight the need for a randomized, prospective study on which to base guidelines.

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

Perioperative antibiotic prophylaxis remains an important strategy for minimizing surgical site infection and periprosthetic joint infection (PJI) in patients undergoing total joint arthroplasty (TJA)[1,2]. The administration of prophylactic perioperative antibiotics is endorsed by all current guidelines[3-7]. While the optimal timing of initial prophylaxis has been well studied, the postoperative duration has not[1].

In 2002, the Centers for Disease Control and Prevention (CDC) joined with the Centers for Medicare & Medicaid Services to create the Surgical Infection Prevention guidelines, which eventually led to the Surgical Care Improvement Project (SCIP) in 2006. Many institutions have adopted the SCIP guidelines as best practice, and these guidelines include 3 measures: (1) prophylactic antibiotics given within 60 minutes

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before surgery (within 120 minutes for vancomycin or fluoroquinolones), (2) appropriate antibiotic selection based on procedure, and (3) discontinuation of antibiotics within 24 hours after surgery[8]. For TJA, most surgeons administer a prophylactic dose prior to incision and continue prophylaxis for 24 hours. This practice is supported by several guidelines, including those of the International Consensus on Periprosthetic Joint Infection and the Society for Healthcare Epidemiology of America[1,3]. We are aware of no evidence to suggest that continuing antibiotics past 24 hours is beneficial and, in fact, it may be detrimental as it may contribute to antimicrobial resistance[9,10], acute kidney injury[11], and/or *Clostridium difficile* infections[3]. On the basis of the aforementioned concerns, in 2017 the updated World Health Organization (WHO) and the CDC guidelines recommended against the administration of any antibiotics in the postoperative period for clean-contaminated surgery[4,5]. This proposed transition in the new CDC guidelines represents a dramatic shift in protocol for many arthroplasty surgeons. While there is evidence to suggest that postoperative antibiotics are unnecessary in non-orthopaedic procedures[1,4,5,12], there is limited evidence regarding the efficacy of a single dose for patients undergoing TJA. In addition, the recommendations of these guidelines rely primarily on studies in general surgery or outside of arthroplasty[13-16], which are not impacted by the mortality, morbidity, and economic burden of implant-related infections[17-19].

At our institution, we have been performing outpatient TJA over the past decade. Our patients are often discharged within hours after their surgery and may receive only a single dose of prophylactic antibiotics. The hypothesis of this study was that patients receiving a single dose of prophylactic antibiotics have a higher prevalence of 1-year PJI compared with those receiving multiple doses (24 hours of coverage).

Materials and Methods

Following institutional review board approval, a retrospective study was performed to identify all patients who underwent primary TJA from January 1, 2006, to June 31, 2017. We included all patients who underwent total knee arthroplasty (TKA) or total hip arthroplasty (THA) and received either a single dose or multiple doses (24 hours of coverage) of prophylactic antibiotics. Patients who underwent simultaneous bilateral TJA, had unclear information regarding antibiotic prophylaxis, received multiple types of antibiotics, or underwent prophylaxis other than with cefazolin or vancomycin were excluded. The final cohort included 20,682 patients (11,353 THAs and 9,329 TKAs), with 4,523 who received a single antibiotic dose and 16,159 treated with multiple doses (2 or 3 for 24 hours of coverage).

Data Collection

An electronic query was performed to obtain information on the dose and time of administration of perioperative antibiotics and to collect data on all important variables that influence PJI[20]. Patients who developed PJI were identified from a cross-reference query with a biannually maintained institutional PJI database of PJIs that fulfilled Musculoskeletal Infection Society (MSIS) criteria[21]. A manual chart review was then performed to verify data. A preoperative PJI risk score, derived with an established and validated risk calculator[20] (see Appendix), was assigned to all patients to allow for risk adjustment and control for potential confounders.

Antibiotic Dosage and Protocol

Antibiotics for 24 hours of coverage were ordered for all patients according to our institutional protocol, which consisted of a preoperative dose and 2 doses of cefazolin postoperatively (every 8 hours) or 1 dose of vancomycin postoperatively (at 12 hours). If patients met discharge criteria, they did not have to complete the 24 hours of antibiotic therapy before discharge.

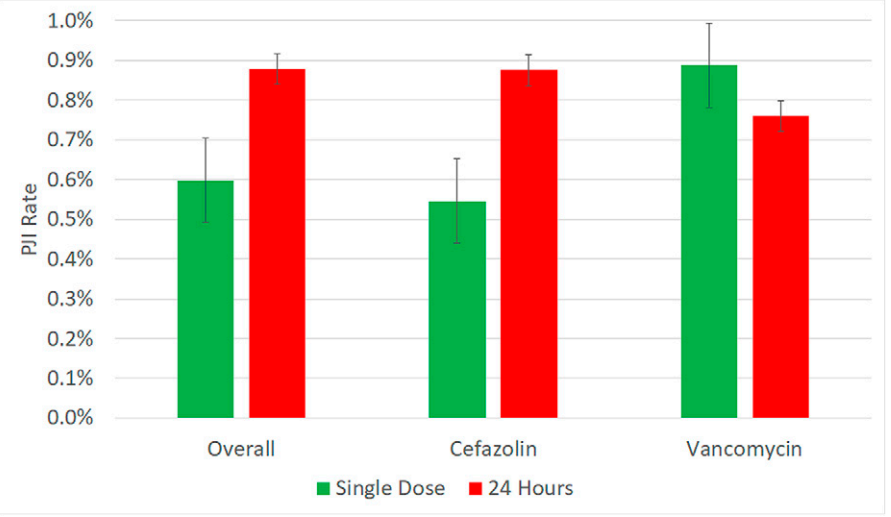

Fig. 1

PJI rates in patients treated with 1 dose compared with 24-hour antibiotic coverage, stratified by type of antibiotic. The error bars represent the standard error.

TABLE I Characteristics of Patients Treated with Single Versus Multiple Doses of Antibiotics

Variable	Single Dose (N = 4,523)	Multiple Doses (N = 16,159)	P Value
Demographics and habits			
Male sex*	2,183 (48.3)	720 (44.6)	<0.001
Age† *(yr)*	62.3 ± 11.0	63.3 ± 11.2	<0.001
Smoking history*	340 (7.5)	1,279 (7.9)	0.397
Joint (knee)*	1,679 (37.1)	7,650 (47.3)	<0.001
BMI† *(kg/m²)*	29.7 ± 5.5	30.0 ± 5.6	0.002
BMI class*			0.009
Underweight	33 (0.7)	86 (0.5)	
Normal weight	848 (18.7)	2,975 (18.4)	
Overweight	1,679 (37.1)‡	5,665 (35.1)‡	
Obese class I	1,207 (26.7)	4,405 (27.3)	
Obese class II	566 (12.5)‡	2,246 (13.9)‡	
Obese class III	190 (4.2)	782 (4.8)	
Comorbidities			
Preoperative PJI risk score†	35.0 ± 12.8	36.3 ± 14.1	<0.001
CCI†	0.3 ± 0.1	0.4 ± 0.9	<0.001
CCI >2*	68 (1.5)	471 (2.9)	<0.001
Diabetes mellitus*	460 (10.2)	2,174 (13.5)	<0.001
Chronic obstructive pulmonary disease*	421 (9.3)	1,928 (11.9)	<0.001
Congestive heart failure*	40 (0.9)	271 (1.7)	<0.001
Chronic kidney injury*	50 (1.1)	314 (1.9)	<0.001
Inflammatory arthritis*	121 (2.7)	503 (3.1)	0.141
Operative and admission			
Type of anesthesia (general)*	228 (5.0)	1,751 (10.9)	<0.001
Type of antibiotic*			<0.001
Vancomycin	675 (14.9)	3,026 (18.7)	
Cefazolin	3,848 (85.1)	12,133 (75.1)	
Surgical duration† *(min)*	73.4 ± 32.6	76.6 ± 30.1	<0.001
ASA classification*§			<0.001
I	146 (3.2)	550 (3.4)	
II	2,849 (63.0)‡	7,011 (43.4)‡	
III	1,482 (32.8)‡	8,439 (52.2)‡	
IV	15 (0.3)	68 (0.4)	
Length of stay† *(days)*	1.4 ± 2.0	2.5 ± 1.4	<0.001

*The values are given as the number with the percentage in parentheses. †The values are given as the mean and standard deviation. ‡A significant difference between groups. §ASA = American Society of Anesthesiologists.

Cefazolin was administered intravenously at a dose of 15 mg/kg before skin incision, unless the patient had an allergy to cephalosporins or penicillin, in which case 1 g of vancomycin was administered over 1 to 2 hours of infusion; this was generally completed 1 hour before skin incision. Antibiotic-impregnated cement was used for TKAs according to the surgeon's standard protocol, and all THAs were done without cement.

Treatment Outcomes

The primary end point was the development of PJI within 1 year. Secondary end points included acute kidney injury, an increase in serum creatinine concentration of 0.3 mg/dL within 48 hours or to >1.5 times the preoperative level, and development of a *C. difficile* infection. The types of organisms causing PJI and their resistance profiles were recorded.

Statistical Analysis

Univariate analyses were performed to compare demographics as well as perioperative variables between the groups treated with the 2 prophylaxis methods. Additionally, a multivariate logistic regression model was utilized to determine risk factors for PJI, with the variables examined including antibiotic duration, antibiotic type, antibiotic cement, surgical duration,

TABLE II Regression Analysis Assessing Independent Variables Associated with PJI, without Preoperative PJI Risk Score

	Overall			TKA			THA		
	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Antibiotic duration (single dose)	0.745	0.482-1.151	0.185	1.145	0.638-2.053	0.650	0.476	0.245-0.928	0.029
Antibiotic type (vancomycin)	0.718	0.385-1.392	0.708	1.462	0.844-2.538	0.175	0.773	0.416-1.439	0.417
Antibiotic-impregnated cement	0.865	0.520-1.440	0.576	0.847	0.507-1.416	0.526	—	—	—
VTE prophylaxis (aspirin)	0.785	0.565-1.091	0.15	0.676	0.406-1.127	0.133	0.927	0.594-1.449	0.741
Age	1.003	0.988-1.019	0.673	0.993	0.969-1.018	0.595	1.009	0.989-1.029	0.378
BMI	1.049	1.021-1.079	0.001	1.055	1.014-1.098	0.008	1.043	1.003-1.084	0.034
Sex (male)	1.864	1.345-2.583	<0.001	2.595	1.610-4.184	<0.001	1.405	0.898-2.199	0.137
Spinal anesthesia	0.511	0.342-0.763	0.001	0.472	0.274-0.815	0.007	0.574	0.313-1.052	0.072
Length of stay	1.106	1.042-1.172	0.001	1.199	1.087-1.321	<0.001	1.064	0.967-1.170	0.205
CCI	1.260	1.123-1.414	<0.001	1.233	1.034-1.471	0.020	1.273	1.090-1.485	0.002
Surgical duration in min	1.005	1.000-1.009	0.036	1.002	0.996-1.009	0.486	1.006	1.001-1.012	0.031
Joint (knee)	0.944	0.579-1.539	0.817	—	—	—	—	—	—

TABLE III Regression Analysis Assessing Independent Variables Associated with PJI, Using Preoperative PJI Risk Score

	Overall			TKA			THA		
	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Antibiotic duration (single dose)	0.755	0.489-1.166	0.205	1.186	0.662-2.123	0.567	0.476	0.245-0.927	0.029
Antibiotic type (vancomycin)	1.049	0.698-1.577	0.817	1.412	0.816-2.445	0.217	0.773	0.416-1.433	0.413
Age	0.997	0.982-1.011	0.632	0.983	0.96-1.007	0.164	1.005	0.987-1.024	0.592
Antibiotic-impregnated cement	0.902	0.541-1.505	0.694	0.902	0.538-1.511	0.695	—	—	—
VTE prophylaxis (aspirin)	0.814	0.586-1.132	0.222	0.741	0.447-1.228	0.245	0.933	0.595-1.463	0.762
Spinal anesthesia	0.561	0.374-0.84	0.005	0.489	0.283-0.845	0.01	0.650	0.353-1.199	0.168
Length of stay	1.090	1.025-1.16	0.006	1.198	1.086-1.321	<0.001	1.037	0.931-1.156	0.508
Surgical duration	1.005	1.001-1.010	0.018	1.003	0.996-1.01	0.415	1.007	1.002-1.013	0.012
Preoperative PJI risk score (per point)	1.025	1.018-1.031	<0.001	1.024	1.015-1.033	<0.001	1.026	1.017-1.035	<0.001

TABLE IV Comparison of Single and Multiple-Dose Antibiotics Using Propensity Score Analysis

	Propensity Score Matching (1:1)						Regression Adjustment Using Propensity Score on Total Sample					
	With Preoperative PJI Risk Score			With CCI			With Preoperative PJI Risk Score			With CCI		
	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value
TJA	0.746	0.438-1.267	0.277	0.671	0.406-1.147	0.149	0.763	0.494-1.179	0.224	0.774	0.501-1.196	0.249
THA	0.508	0.236-1.091	0.083	0.498	0.223-1.015	0.055	0.478	0.245-0.933	0.030	0.489	0.251-0.957	0.037
TKA	0.927	0.515-2.427	0.776	1.058	0.504-2.222	0.881	1.209	0.682-2.146	0.516	1.217	0.685-2.160	0.503

anesthesia, venous thromboembolism (VTE) prophylaxis, age, body mass index (BMI), sex, joint, length of hospital stay, and comorbidities. A multivariate analysis was also performed using a PJI risk score that was assigned based on a PJI risk calculator developed in a previous study that determined the relative weight of 17 risk factors for PJI[20]. Propensity score matching was performed in 2 ways: (1) 1:1 without replacement using an exact match for joint and a nearest-neighbor matching technique for all other covariates and (2) regression adjustment with propensity score analysis of the total

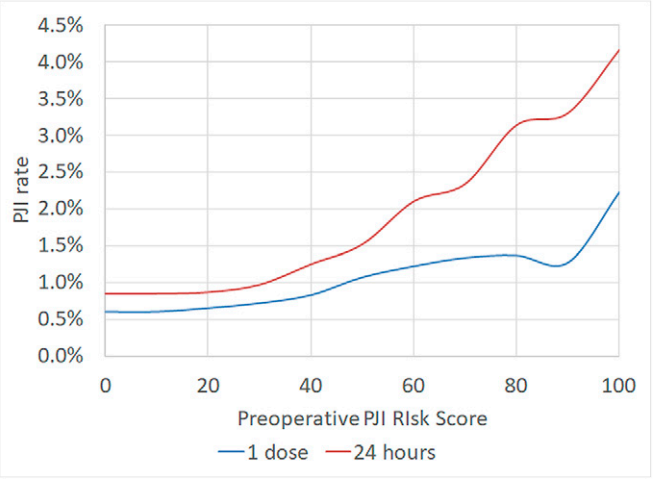

Fig. 2

PJI rates in patients treated with 1 dose compared with 24-hour antibiotic coverage according to PJI risk score.

sample (see Appendix)[22]. All analyses were performed with and without the PJI calculator. All statistical analyses were performed using R 2.15.1 (R Foundation for Statistical Computing), and an alpha level of 0.05 was used to evaluate significance.

Literature Review

A systematic review of the literature was conducted through MEDLINE (PubMed), the Cochrane database, Google Scholar, and Embase. The search term "single dose antibiotic" AND "arthroplasty" OR "infection" returned 513 possible articles. Abstracts were reviewed to identify articles comparing single and multiple doses of antibiotic prophylaxis surrounding TJA. Full-text articles, including their references, were then reviewed to determine study design, duration of follow-up, sample size, antibiotic regimen, and results.

Results

The overall rates of PJI were 0.60% (27 of 4,523) and 0.88% (142 of 16,159) for the patients who received a single dose and multiple doses of antibiotics, respectively (Fig. 1). In the univariate analysis, there was no significant difference in the overall PJI rate between the 2 groups, but there was a trend toward a lower PJI risk among patients who received a single dose (p = 0.09). Patients who received a single dose of antibiotics had different baseline characteristics, including a shorter length of stay, a lower BMI, and fewer comorbidities (Table I). In the multivariate analysis, after controlling for potential confounders, there was no difference in PJI rate between the single and multiple-dose groups without adjustment with the preoperative risk calculator (adjusted odds ratio [OR] = 0.745, 95% confidence interval [CI] = 0.482 to 1.151, p = 0.185) or with such adjustment (adjusted OR = 0.755, 95% CI = 0.489 to 1.166, p = 0.205) (Tables II and III). Propensity score matching using the preoperative PJI risk score demonstrated no increase in the PJI rate with a single dose in the analysis of all TJAs together (adjusted OR = 0.746, 95% CI = 0.438 to 1.267, p = 0.277) or when the group was stratified into hips and knees (Table IV). When stratified by joint, there was no difference between single and multiple doses in the propensity score 1:1 match analysis for hips or knees (Table IV). In the multivariate analysis with propensity score regression adjustment, patients who received a single dose demonstrated a decreased PJI rate in the THA group (Table IV). However, in the propensity score matched analysis using the PJI risk score, there were no differences in either the THA group (OR = 0.508, 95% CI = 0.236 to 1.091, p = 0.083) or the TKA group (OR = 0.927, 95% CI = 0.515 to 2.427, p = 0.776).

Furthermore, there was no significant difference in the PJI rate between patients treated with vancomycin and those who received cefazolin (p = 0.991). However, patients who received a single dose of cefazolin demonstrated a trend toward lower rates of PJI compared with those who received 24 hours

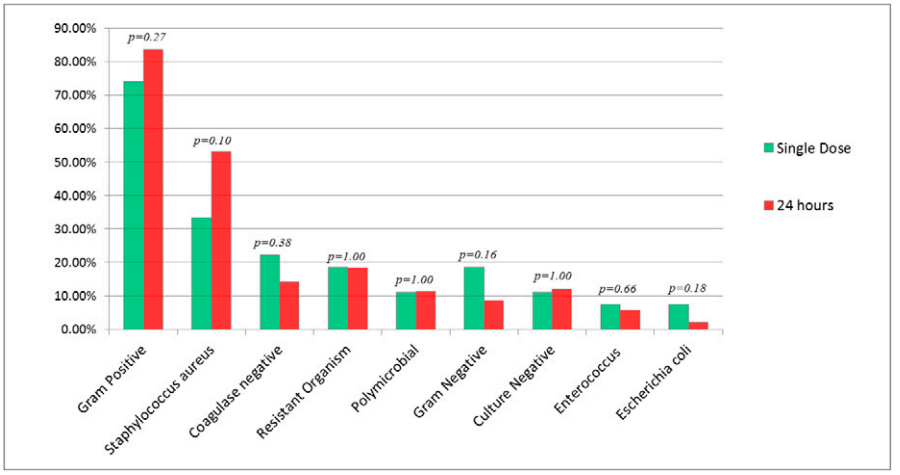

Fig. 3

Organism prevalence of PJIs stratified by duration of antibiotic treatment.

TABLE V Results of Systematic Review of Literature on Single Versus Multiple Doses of Antibiotics for TJA*

Authors (Year)	Study Design/ Population/ Duration of Follow-up	No. of Patients	Antibiotic Treatment	Outcomes	Conclusions
Heydemann and Nelson[33] (1986)	RCT/THA and TKA/ 1 yr	211	Single dose: 1 g nafcillin or cefazolin (n = 103); 48 hr: 1 g nafcillin or cefazolin Q6H (n = 108)	Deep infection: 0 in either group	Reducing doses may decrease complications and costs while preserving antimicrobial coverage
Ritter et al.[34] (1989)	RCT/primary THA and TKA/1 yr	196	2 intraop. doses: 1,500 mg and 750 mg cefuroxime (n = 98); 24 hr: 750 mg cefuroxime Q8H after 1,500 mg and 750 mg intraop. (n = 98)	Deep infection: 0 in either group	Isolated intraop. prophylaxis may be sufficient
Wymenga et al.[28] (1992)	RCT/THA and hemiarthroplasty/ mean, 13 mo	2,651	Single dose: 1.5 g cefuroxime (n = 1,327); multiple doses: 2 doses 750 mg cefuroxime after 1.5 g intraop. (n = 1,324)	Joint sepsis: 0.8% (11 patients) in single-dose group, 0.5% (6 patients) in 2-dose group; wound infection: 1.9% (25 patients) in single-dose group, 2.3% (31 patients) in 2-dose group	No significant difference seen between groups. Authors recommended continuation of 3-dose regimen until larger study with longer follow-up can be performed
Suter et al.[25] (1994)	RCT/primary THA/ 2 yr	496	Single dose: 400 mg teicoplanin (n = 250); 2 doses: cefamandole (2 g preop. and 1 g postop.) (n = 246)	Infected superficial hematoma: 0 in teicoplanin group, 1.6% (4 patients) in cefamandole group; 0 deep infections	Single dose as effective as multiple doses for preventing surgical site infections
Periti et al.[26] (1999)	RCT/THA and TKA/ 1 yr	826	Single dose: 400 mg teicoplanin (n = 410); 24 hr: cefazolin (2 g preop., then 1 g Q6H) (n = 416)	Wound infection: 1.5% (6 patients) in single-dose group, 1.7% (7 patients) in 24-hr group	Single preop. dose allows prophylaxis comparable with that provided by multiple doses
Tang et al.[32] (2003)	Retrospective review/primary THA and TKA/2 yr	1,367	Single dose: 1 g cefazolin (n = 1,152); 16 hr: 750 mg cefuroxime Q8H (n = 215)	Superficial infection: 1.6% (19 patients) in single-dose group, 2.8% (6 patients) in 16-hr group, p = 0.26; deep infection: 1.0% (12 patients) in single-dose group, 1.4% (3 patients) in 16-hr group, p = 0.72	Single and multiple postop. doses offer significantly similar prophylaxis and infection rates
Engesaeter et al.[31] (2003)	Retrospective register review/ primary THA in Norwegian register/ 0-14 yr; 10-yr revision rates	14,465	Groups 1-4: 1 day with 1-4 doses (unclear timing of doses); group 5: 2 days; group 6: 3 days†	Revision: risk lower when systemic prophylaxis given 4× on day of surgery than when 1, 2, or 3 doses given; revision for infection: less likely when systemic prophylaxis given 4× on day of surgery compared with other groups, but this was not significant	Primary THA showed improved results when antibiotics were given both systemically and in cement and when prophylaxis provided 4× on day of surgery
van Kasteren et al.[30] (2007)	Retrospective review/primary THA/ 1 yr	1,922	Single dose (n = 649); 24 hr (n = 808); >24 hr (n = 433); unknown duration (n = 32)‡	Infection: 2.5% (16 patients) in single-dose group, 3.2% (26 patients) in 24-hr group, 1.4% (6 patients) in >24-hr group	Multiple doses do not significantly reduce infection risk
Kanellakopoulou et al.[27] (2009)	RCT/primary THA and TKA/2 yr	568	Single dose: 10 mg/kg teicoplanin (n = 256); 4-6 days: multiple different antibiotics at different doses (n = 312)	Infection: 0.78% (2 patients) in single-dose group, 3.5% (11 patients) in multiple-dose group, p = 0.025	Single dose of teicoplanin significantly reduces infection risk compared with multiple doses of broad-spectrum antibiotics
Present study (2019)	Retrospective review/primary THA and TKA/1 yr	20,682	Single dose: cefazolin 15 mg/kg or 1 g vancomycin (n = 4,523); 3 doses: 15 mg/kg cefazolin Q8H or 2 doses 1 g vancomycin Q12H (n = 16,159)	Infection: 0.60% (27 patients) in single-dose group, 0.88% (142 patients) in multiple-dose group	No significant difference between single and multiple doses of antimicrobials

*Single dose = single preoperative dose. †Cephalothin, cefuroxime, cloxacillin, or dicloxacillin was used as prophylaxis. ‡Various antibiotics were used at unknown doses.

of coverage with cefazolin (p = 0.054); this was not the case for patients treated with vancomycin (p = 0.732) (Fig. 1).

When we stratified by preoperative PJI risk score, we found no difference in the PJI rate between patients who received a single dose and those who received multiple doses of antibiotics; this was the case across all preoperative PJI risk scores, including those indicating high risk (Fig. 2). When the analysis was confined to patients with a score in the 80th percentile (55.46) or higher, the study still did not show any difference between single and multiple antibiotic doses in terms of PJI rate among all TJAs (1.08% compared with 1.81%, p = 0.136), THAs only (1.19% compared with 2.20%, p = 0.260), or TKAs only (0.92% compared with 1.6%, p = 0.260). Variables that did show an independent association with PJI in the multivariate analysis were higher BMI, male sex, longer length of hospital stay, longer surgical duration, non-spinal anesthesia administration, higher Charlson comorbidity index (CCI), or higher preoperative PJI risk score (Tables II and III).

Patients who received multiple doses of antibiotics demonstrated a trend (p = 0.068) toward higher rates of acute kidney injury (104 of 16,121, 0.6%) compared with patients administered a single dose (15 of 3,921, 0.4%). *C. difficile* infections were infrequent in both groups (0.05% compared with 0.3%, p = 0.629). No differences in the organism profiles of the PJIs were observed between dose groups (Fig. 3).

Literature Review

The literature review identified 9 studies comparing the outcomes of single and multiple doses of antibiotic prophylaxis for TJA (Table V); 3 had a Level of Evidence of III and 6 were Level I. The studies in the literature were frequently underpowered, and there were large differences among them in terms of antibiotic types, dosages, and regimens of administration, making cross-comparison impossible. No studies analyzed the utility of the number of doses on the basis of PJI risk or medical comorbidities. A conclusion based on 1 dose versus 24 hours of antibiotics is thus difficult to make on the basis of those studies. Teicoplanin and cefuroxime were the most commonly used antibiotics in the single and multiple-dose groups, respectively. The Level-I studies included a total of 2,466 and 2,530 arthroplasties in the single and multiple-dose groups. The largest single-dose cohort reported was 1,327 TJAs in the Level-I studies compared with 1,152 in the retrospective Level-III studies. In the largest Level-I study, the authors noted that the sample size was inadequate to detect a clinically relevant difference between groups. In both the prospective and the retrospective studies, single and multiple antibiotic doses offered similar protection against PJI.

Discussion

Recent guidelines for prevention of surgical site infection from the CDC and WHO recommend a single dose of perioperative antibiotic prophylaxis for patients undergoing clean-contaminated surgical procedures[23]. Although we can comprehend the rationale for efforts to reduce antibiotic use, the new recommendation for perioperative antibiotic prophylaxis is largely based on literature related to non-arthroplasty procedures. Thus, it is not known if the use of an implant during TJA poses an additional risk for infection, and this uncertainty can justify extending the antibiotic prophylaxis to 24 hours, which is the routine practice currently[24].

The literature on this topic has multiple shortcomings (Table V). First, teicoplanin, which is currently unavailable in the United States, was used in 3 Level-I studies[25-27]. Second, the largest Level-I study, conducted by Wymenga et al., included 2,651 patients[28]. Although the authors reported no difference in infection rate, they noted the insufficient power of their study and recommended continued use of multiple doses until a larger study could be performed. This highlights the largest shortcoming encountered in all of the prospective studies in the literature, in which the average cohort size was 416 patients (range, 98 to 1,327 patients). Given that the rate of PJI after primary TJA is approximately 1%, 3,500 patients per group are required for a study to be appropriately powered to detect noninferiority between dose groups; as noted, this was not reached in any of the arthroplasty studies that we reviewed. In an attempt to support the decision to use single-dose antibiotic prophylaxis, Thornley et al. combined 4 randomized controlled trials (RCTs) in a meta-analysis, but they were unable to show that additional postoperative antibiotics decreased the rate of surgical site infection[29]. The authors reported that the "overall quality of the evidence was very low" and highlighted the need for a larger randomized, prospective study[29]. Several retrospective studies performed more recently[30-32] were inconsistent regarding antibiotic utilization; used small, often subtherapeutic, doses (1 g rather than 2 g of cefazolin); and/or used inconsistent definitions of "infection" that are not in agreement with current MSIS guidelines.

We believe that the issue of perioperative antibiotic prophylaxis for patients undergoing TJA needs to be addressed by a randomized, prospective study of a large cohort of patients. In fact, the American Association of Hip and Knee Surgeons (AAHKS) recently funded such a study to examine this issue. While we await the outcome, many hospitals have "requested" arthroplasty surgeons to limit prophylactic antibiotics to a single dose for patients undergoing TJA in an effort to comply with the guidelines.

In the present study, we did not find that multiple doses of perioperative antibiotics provided any additional benefits to patients undergoing TJA. This finding is in line with those of a few prior studies[25,26,28,30,32], albeit of much smaller cohorts of patients, of the same issue. Although the majority of the prior studies demonstrate no difference in infection rate[25,26,28,30,32-34], the equivocal results may be attributed to a lack of power given the relative rarity of PJI. One concern about outpatient TJA is that patients do not receive sufficient antibiotic dosages compared with patients who stay in the hospital longer. This study suggests that outpatient surgery may be safe and the benefit of inpatient surgery may be limited because the

reduced number of doses with outpatient surgery does not increase the risk of PJI.

The CDC and WHO used available evidence, mainly outside orthopaedics, to support their recommendation that a single dose of prophylactic antibiotic may be adequate for clean elective surgery, which includes TJA[4,23]. Several studies outside of arthroplasty have demonstrated that prolonged antibiotic prophylaxis does not add benefit in clean elective procedures[13-16]. In a systematic review of prospective RCTs across multiple surgical disciplines, McDonald et al. found no significant reduction in surgical site infection by the use of multiple doses of prophylactic antibiotics compared with a single dose (OR = 1.06, 95% CI = 0.89 to 1.25)[14].

If the efficacy of a single dose of antibiotics is proven to be equivalent to that of multiple doses, the former has multiple advantages over the latter. One obvious benefit is a reduction in cost; cefazolin and vancomycin cost $12 and $30 per dose at our institution. Considering the number of TJAs performed yearly, this becomes a major health-care cost. Another main concern relates to antibiotic stewardship and the emergence of antimicrobial resistance with the liberal use of antibiotics[10,35]. The CDC has estimated that at least 2 million people become infected with bacteria resistant to antibiotics, resulting in 23,000 deaths annually[10], and the WHO has identified antimicrobial resistance as 1 of the 3 greatest threats to human health[35]. Other issues regarding administration of multiple doses of antibiotics include the potential for systemic toxicity and opportunistic infections, such as pseudomembranous colitis[9,36-39].

Our study has several limitations. First, it was retrospective and may have been affected by the inherent data limitations of that study design. Second, the cohort receiving single-dose antibiotic prophylaxis had significantly different baseline characteristics compared with the group receiving multiple doses, which is indicative of selection bias. We attempted to control for these potential confounders by using a multivariate regression analysis, employing a validated PJI risk score, and utilizing propensity score analysis. However, it is possible that the healthier population of the single-dose group may have led to an underestimation of the rate of PJI in that group, which may explain the lack of a difference in the results compared with the multiple-dose group and the trend toward lower rates of PJI in the single-dose group. Third, PJI was assessed within 1 year after the TJA, and it is feasible that infection after 1 year could be influenced by the perioperative antibiotic. Finally, because of the relative rarity of PJI, this study may have been subject to type-II error even with the large numbers of patients included.

Despite the aforementioned limitations, this study detected no reduction of PJI risk with multiple doses of prophylactic antibiotics, compared with a single dose, for primary elective TJA in the largest cohort of patients in a study of this issue; this was the case even for patients at higher risk for PJI. Therefore, this study supports the recent changes in current guidelines that recommend a single dose of antibiotics for patients undergoing clean surgery, including TJA. Unfortunately, the body of literature prospectively comparing the administration of single and multiple-dose antibiotic prophylaxis for TJA remains limited. Combining the findings of this retrospective study and the literature review highlights the need for a well-powered, randomized, prospective trial to confirm or refute the use of single-dose antibiotic prophylaxis for TJA.

Appendix

eA Details regarding PJI definition, assessment of preoperative PJI risk, and propensity score matching; figures and tables demonstrating the standard differences before and after matching with and without the propensity score; and a table showing the prevalence of comorbidities by dose group and PJI rate by comorbidity and dose group are available with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/F97). ■

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