Chronic Suppression of Periprosthetic Joint Infections with Oral Antibiotics Increases Infection-Free Survivorship

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Background: The clinical benefit of chronic suppression with oral antibiotics as a salvage treatment for periprosthetic joint infection is unclear. The purpose of this study was to compare infection-free prosthetic survival rates between patients who received chronic oral antibiotics and those who did not following irrigation and debridement with polyethylene exchange or two-stage revision for periprosthetic joint infection.

Methods: We reviewed the records on all irrigation and debridement procedures with polyethylene exchange and two-stage revisions performed at our institution from 1996 to 2010 for hip or knee periprosthetic joint infection. Of 625 patients treated with a total of 655 eligible revisions, ninety-two received chronic oral antibiotics for a minimum of six months and were eligible for inclusion in our study. These patients were compared with a matched cohort (ratio of 1:3) who did not receive chronic oral antibiotics.

Results: The five-year infection-free prosthetic survival rate was 68.5% (95% confidence interval [CI] = 59.2% to 79.3%) for the antibiotic-suppression group and 41.1% (95% CI = 34.9% to 48.5%) for the non-suppression group (hazard ratio [HR] = 0.63, p = 0.008). Stratification by the type of surgery and the infecting organism showed a higher five-year survival rate for the patients in the suppression group who underwent irrigation and debridement with polyethylene exchange (64.7%) compared with those in the non-suppression group who underwent irrigation and debridement with polyethylene exchange (30.4%, p < 0.0001) and a higher five-year survival rate for the patients in the suppression group who had a *Staphylococcus aureus* infection (57.4%) compared with those in the non-suppression group who had a *Staphylococcus aureus* infection (40.1%, p = 0.047).

Conclusions: Chronic suppression with oral antibiotics increased the infection-free prosthetic survival rate following surgical treatment for periprosthetic joint infection. Patients who underwent irrigation and debridement with polyethylene exchange and those who had a *Staphylococcus aureus* infection had the greatest benefit.

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

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Periprosthetic joint infection is a devastating complication of total knee and hip arthroplasty that is associated with substantial morbidity[1,2], mortality[3], and economic burden[4,5]. The risk of infection following total joint arthroplasty is approximately 1%[4,6,7]. Treatment guidelines for periprosthetic joint infection recommend irrigation and debridement with polyethylene exchange for acute infections caused by low-virulence pathogens around well-fixed implants and two-stage revision

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TABLE I Results of Univariate Analyses Comparing Baseline Characteristics Between Suppression and Non-Suppression Groups

Variable	Suppression Group (N = 92)	Non-Suppression Group (N = 276)	P Value
Charlson comorbidity index*	4 [3, 5]	4 [2, 5]	0.34
Age† *(yr)*	63.7 ± 11.7	64.2 ± 11.5	0.72
BMI† *(kg/m²)*	33.6 ± 9.2	33.2 ± 8.6	0.71
Sex†			0.90
Female	36 (39.1)	112 (40.6)	
Male	56 (60.9)	164 (59.4)	
Index surgery†			0.63
Irrigation and debridement with polyethylene exchange	54 (58.7)	152 (55.1)	
2-stage revision	38 (41.3)	124 (44.9)	
No. of previous revisions*	1 [0, 3]	1 [0, 2]	0.37
Pathogen†			0.33
S. aureus	44 (47.8)	114 (41.3)	
Non-*S. aureus*	48 (52.2)	162 (58.7)	
Joint†			0.94
Knee	71 (77.2)	210 (76.1)	
Hip	21 (22.8)	66 (23.9)	
Duration of symptoms* *(days)*	30 [7, 90]	14 [5, 45]	0.024
Duration of intravenous antibiotic therapy* *(wk)*	6 [6, 6]	6 [6, 6]	0.17
Previous joint infection anywhere†	41 (44.6)	130 (47.1)	0.76
Infecting organism class†			0.21
Virulent§	54 (58.7)	147 (53.2)	
Indolent#	31 (33.7)	55 (20.0)	
Fungal and acid-fast bacilli	0	1 (0.3)	
Miscellaneous and contaminants	5 (5.4)	22 (7.2)	
Multiple organisms†	18 (19.6)	35 (12.7)	0.13

*The values are given as the median with the 25th and 75th percentiles in brackets. †The values are given as the mean and standard deviation. ‡The values are given as the number of patients with the percentage in parentheses. §Includes *S. aureus,* Enterococcus, and gram-negative organisms. #Includes coagulase-negative Staphylococcus and Propionibacterium species.

for infections that are chronic, caused by a high-virulence pathogen, or around a loose component[8]. A two to six-week postoperative course of pathogen-specific intravenous antibiotic therapy is also recommended in both cases[9]. Despite optimal surgical and medical treatments, failure rates are still high, with five-year prosthetic survival rates ranging from 38.4%[10] to 64.7%[11].

Chronic antibiotic suppression is an unproven method that has been used in an attempt to increase the chance of retaining a functional prosthesis in certain patients, typically those who have undergone surgical treatment for periprosthetic joint infection but have a high risk of relapse and/or for whom the next surgical step would be limb-threatening. There are no clearly defined criteria for increased risk of relapse, although common factors include a history of multiple joint infections, immunosuppression, comorbidities that predispose to periprosthetic joint infection, and a virulent pathogen[9,12]. Candidates for chronic antibiotic suppression must also have the ability to tolerate side-effects.

The purpose of this study was to evaluate patients who underwent irrigation and debridement with polyethylene exchange or two-stage revision in order to (1) compare infection-free prosthetic survivorship between patients who did and those who did not undergo subsequent chronic oral antibiotic suppression; (2) analyze infection-free survivorship stratified by the type of surgery, infecting organism, and involved joint; and (3) determine factors associated with failure of chronic suppression with oral antibiotics and build a nomogram to preoperatively predict the probability of failure.

Materials and Methods

After institutional review board approval was obtained, we used a combination of Current Procedural Terminology (CPT)-4 and International Classification of Diseases, Ninth Revision (ICD-9) codes to identify all revision total knee and hip arthroplasties performed from 1996 to 2010 at a single institution. Of 10,411 procedures that were identified, 7111 that were done for indications other than periprosthetic joint infection, 2510 that were not either an irrigation and debridement with polyethylene exchange or a complete two-stage revision,

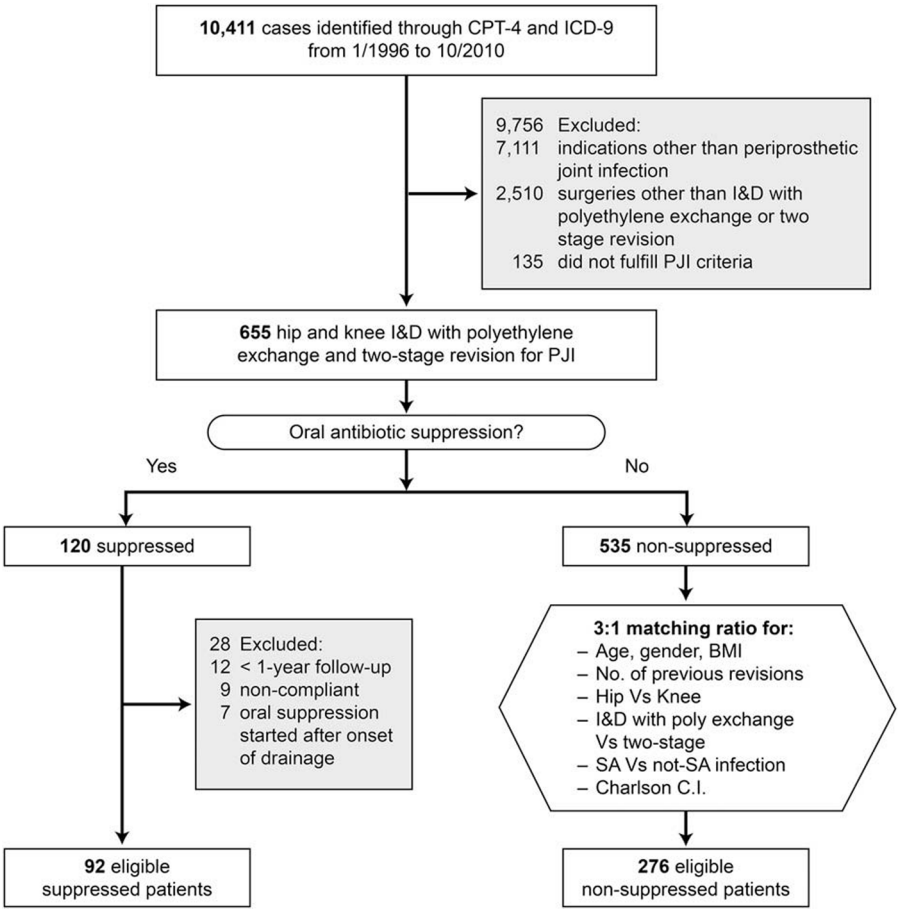

Fig. 1

Flowchart showing eligible cases of chronic antibiotic suppression and matched cases without suppression. I&D = irrigation and debridement, PJI = periprosthetic joint infection, SA = *S. aureus,* and C.I. = comorbidity index.

and 135 that were done for a condition that did not fulfill the criteria for periprosthetic joint infection[12] were excluded. This left 655 eligible procedures in 625 patients for the study (Fig. 1).

Of the 655 procedures, 379 were two-stage revisions (240 knees and 139 hips) and 276 were irrigation and debridement procedures with polyethylene exchange (207 knees and sixty-nine hips). Chart review and obituary database searches were performed. All cases were comanaged with the infectious diseases service at our hospital. Patients received broad-spectrum intravenous antibiotics following the first stage of the two-stage revision or following irrigation and debridement with polyethylene exchange. An organism-specific antibiotic regimen was started after culture results were obtained. One hundred and twenty patients received chronic antibiotic suppression, defined as treatment with oral antibiotics for a minimum of six months following the initial course of intravenous antibiotics. As we are aware of no current specific indication for chronic antibiotic suppression, the decision of whether to offer this treatment was individualized. Patients with intraoperative cultures that were positive for virulent pathogens received antibiotic suppression if they had a risk factor for reinfection (a history of multiple joint infections, previous failed surgery for periprosthetic joint infection, retained implants and/or immunosuppression). Patients with less virulent pathogens or negative cultures received antibiotic suppression if they had multiple risk factors for reinfection. The patients were contacted by telephone and questioned regarding compliance with the antibiotic therapy, additional joint surgery, joint pain, and drainage. Outcomes and death rates were recorded. Exclusion criteria included non-compliance (n = 9), less than one year of follow-up (n = 12), and initiation of oral antibiotic therapy after the onset of new drainage (n = 7). This resulted in ninety-two patients eligible for the study.

The non-suppression group was selected from the remaining pool of 505 patients in whom a total of 535 periprosthetic joint infections had been managed without chronic antibiotic suppression. In an effort to manage the inherent selection bias, the suppression-group patients were matched with similar, non-suppression-group patients. Propensity score matching was used for age, sex, body mass index (BMI), Charlson comorbidity index, number of previous operations on the affected joint, affected joint (hip or knee), type of surgery (irrigation and debridement with polyethylene exchange versus two-stage revision) preceding the antibiotic suppression, and infecting organism *(Staphylococcus aureus* versus non-*S. aureus).* Although the Charlson comorbidity index was developed to predict mortality within one year after hospital admission[13,14], it has been shown to be an independent predictor of periprosthetic joint infection in both the hip[15] and the knee[16]. Propensity scores were estimated on the scale of the log-odds based on the above variables with use of a logistic regression model. Patients in the suppression group were matched to those in the non-suppression group with the closest propensity scores without replacement in a ratio of 1:3 (suppression:non-suppression). The covariate balance resulting from propensity score matching was checked with use of standardized differences, variance ratios of propensity scores, and variance ratios of residuals orthogonal to propensity scores for each covariate. Balance was found to be adequate without restricting which patients were matched by enforcing a matching caliper.

The primary outcome variable was infection-free prosthetic survival, with additional surgery due to infection or death as the end points. All patients were included in the analysis even if the time to the outcome was less than one year. Further stratification on the basis of the affected joint, type of index surgery, and infecting organism was performed. Treatment failure was the outcome variable used to compare the patients in the suppression group for whom the

TABLE II Intravenous and Oral Antibiotic Regimens for the Suppression Group According to Pathogen*

Pathogen (No. of Patients)	IV Antibiotic Regimen [Adjunctive PO Antibiotic Regimen] (No. of Patients)	Chronic Suppressive Antibiotic Regimen (No. of Patients)
Methicillin-sensitive *Staphylococcus aureus* (31)	Oxacillin 2 g qid *or* q4h (14) Vancomycin 1 *or* 1.5 *or* 2 g bid *or* qd *or* q48h (8) Cefazolin 1 or 2 g tid (4) Imipenem 500 mg qid (1) Daptomycin 500 mg qd (1) Ceftriaxone 2 g qd (1) Ampicillin/sulbactam 2/1 g qid (1) Clindamycin 900 mg tid (1) Piperacillin/tazobactam 3/0.375 g tid (1)	Dicloxacillin 500 mg qid *or* tid *or* bid (11) Doxycycline 100 mg qid *or* bid *or* qd (7) Cephalexin 500 mg qid *or* tid *or* bid (6) Trimethoprim/sulfamethoxazole 160/800 mg bid (5) Minocycline 100 mg qd (1) Amoxicillin 500 mg tid (1) Clindamycin 300 mg bid (1)
Methicillin-resistant coagulase-negative staphylococci (21)	Vancomycin 1 *or* 1.25 *or* 1.5 g bid *or* qd (14) Daptomycin 500 *or* 650 mg qd (3) Oxacillin 2 g qid (1) Clindamycin 600 mg tid (1) Linezolid 600 mg bid (1) Tigecycline 50 mg bid (1)	Doxycycline 100 mg bid *or* qd (12) Rifampin 300 mg bid (2) Trimethoprim/sulfamethoxazole 160/800 mg bid *or* qd (4) Clindamycin 300 mg bid (2) Dicloxacillin 500 mg qid (2) Cephalexin 250 mg bid (1)
Methicillin-resistant *Staphylococcus aureus* (13)	Vancomycin 1 *or* 1.25 *or* 1.5 g bid *or* qd (8) Daptomycin 350 *or* 500 mg qd (2) Oxacillin 2 g qid (1) Linezolid 600 mg bid (1) Doxycycline 100 mg bid (1)	Doxycycline 100 mg qd (8) Trimethoprim/sulfamethoxazole 160/800 mg bid (3) Clindamycin 300 mg bid (1) Erythromycin 400 mg bid (1)
Methicillin-sensitive coagulase-negative staphylococci (12)	Vancomycin 1 *or* 1.25 *or* 1.5 g bid *or* qd (8) Oxacillin 1 *or* 2 g q4h *or* qid (2) Ceftriaxone 2 g qd (1) Daptomycin 600 mg qd (1) Linezolid 600 mg bid (1)	Doxycycline 100 mg bid *or* qd (8) Dicloxacillin 250 *or* 500 mg tid (3) Cephalexin 500 mg tid (1) Cefadroxil 500 mg bid (1)
Enterococci (5)	Ampicillin 2 g q4h (2) Penicillin 1 million U qid (1) Tigecycline 50 mg bid (1) Vancomycin 1 g qd (1)	Amoxicillin 500 mg tid (3) Doxycycline 100 mg bid (1) Ciprofloxacin 500 mg bid (1)
Viridans streptococci (5)	Ceftriaxone 2 g qd (2) Piperacillin/tazobactam 3/0.375 g qid (1) Clindamycin 900 mg tid (1) Cefazolin 1 g tid (1)	Amoxicillin 500 mg tid (2) Trimethoprim/sulfamethoxazole 160/800 mg bid (2) Moxifloxacin 400 mg qd (1) Doxycycline 100 mg bid (1)
Group-B streptococci (3)	Penicillin G 2 million U q4h (1) Ampicillin 2 g qid (1) Vancomycin 1 g bid (1)	Amoxicillin 500 mg tid (2) Dicloxacillin 250 mg tid (1)
Diphtheroid-like bacilli (2)	Vancomycin 1 g bid [ciprofloxacin 500 mg bid (1) *or* rifampin 300 mg PO bid (1)] (2)	Doxycycline 100 mg bid *or* qd (2)
Enterobacteriaceae (2)	Imipenem 500 mg qid [ciprofloxacin 750 mg bid] (1) Ciprofloxacin 750 mg bid (1)	Ciprofloxacin 750 mg bid (2)
Propionibacterium acnes (2)	Vancomycin 1 *or* 1.5 g bid *or* qd (2)	Doxycycline 100 mg bid *or* qd (2)
Pseudomonas aeruginosa (1)	Imipenem 500 mg qid [ciprofloxacin 750 mg bid] (1)	Ciprofloxacin 500 mg bid (1)
Staphylococcus lugdunensis (1)	Oxacillin 2 g q4h [rifampin 300 mg bid] (1)	Cephalexin 500 mg tid (1)
Ureaplasma species (1)	Ceftazidime 2 g qd (1)	Azithromycin 500 mg qd (1)
Negative culture (1)	Vancomycin 1 g bid (1)	Doxycycline 100 mg bid (1)

*IV = intravenously, PO = orally, qid = four times a day, q4h = every four hours, tid = three times a day, bid = twice a day, qd = every day, and q48h = every forty-eight hours. The number of pathogens adds up to more than the total number of ninety-two patients because some patients had polymicrobial infections. Also, the number of antibiotic regimens may add up to more than the total number of pathogens because some patients had multiple regimens at once.

TABLE III Intravenous Antibiotic Regimens for the Non-Suppression Group According to Pathogen*

Pathogen (No. of Patients)	IV Antibiotic Regimen [Adjunctive PO Antibiotic Regimen] (No. of Patients)
Methicillin-sensitive *Staphylococcus aureus* (61)	Oxacillin 2 g q4h *or* qid [rifampin 300 mg bid (9)] (25) Vancomycin 500 mg *or* 1 *or* 1.25 g bid *or* qd [rifampin 300 *or* 600 mg bid (2)] (16) Cefazolin 1 *or* 2 g bid *or* tid (9) Penicillin G 3 million U q4h [rifampin 300 mg bid (1)] (3) Daptomycin 600 mg qd (2) Piperacillin/tazobactam 3/0.375 g tid (1) Ceftriaxone 1 g qd (1) Amoxicillin 1 g tid (1) Linezolid 600 mg bid (1) Clindamycin 900 mg tid (1) Ampicillin/sulbactam 2/1 g qid (1) Doxycycline 100 mg bid (1)
Methicillin-resistant *Staphylococcus aureus* (53)	Vancomycin 500 mg *or* 1 *or* 1.25 *or* 1.5 g bid *or* qd *or* q48h *or* q72h [rifampin 300 mg bid (14)] (45) Piperacillin/tazobactam 3/0.375 g tid (3) Piperacillin 4 g tid (1) Ceftriaxone 1 g qd (1) Oxacillin 2 g q4h (1) Ampicillin 2 g qid (1) Linezolid 600 mg bid (1) Cefazolin 2 g tid (1)
Methicillin-sensitive coagulase-negative staphylococci (34)	Vancomycin 1 *or* 1.25 *or* 1.5 g bid *or* qd *or* q48h [rifampin 300 mg bid (4)] (29) Cefazolin 1 *or* 2 g tid (2) Oxacillin 2 g q4h (1) Daptomycin 600 mg qd (1) Piperacillin/tazobactam 3/0.375 g qid (1)
Methicillin-resistant coagulase-negative staphylococci (29)	Vancomycin 750 mg *or* 1 *or* 1.25 *or* 1.5 g bid *or* qd [rifampin 300 *or* 600 mg bid (2)] (24) Clindamycin 600 mg tid (2) Daptomycin 500 mg qd (2) Aztreonam 1 g q8h (1)
Diphtheroid-like bacilli (9)	Vancomycin 750 mg *or* 1 *or* 1.5 g bid *or* qd *or* q48h [ciprofloxacin 750 mg bid (6)] (8) Gentamycin 50 mg qd (1) [Ciprofloxacin 500 mg bid (1)] [Azithromycin 500 mg qd (1)]
Enterococci (8)	Vancomycin 1.5 g bid (4) Ampicillin 2 g qid (2) Piperacillin/tazobactam 3/0.375 g qid [ciprofloxacin 750 mg bid (1)] (2)
Pseudomonas aeruginosa (8)	Piperacillin/tazobactam 3/0.375 g qid *or* tid *or* bid [ciprofloxacin 500 mg bid (1)] (7) Daptomycin 570 mg qd [ciprofloxacin 500 mg bid] (1)
Viridans streptococci (6)	Penicillin G 3 million U q4h (2) Vancomycin 1 g bid *or* qd (2) Ampicillin 2 g qid (1) Ceftriaxone 1 g qd (1)
Group-B streptococci (6)	Vancomycin 1 g bid [rifampin 300 mg bid (1)] (2) Oxacillin 2 g q4h (1) Ceftriaxone 2 g qd (1) Penicillin G 3 million U tid (1)

continued

TABLE III (*continued*)

Pathogen (No. of Patients)	IV Antibiotic Regimen [Adjunctive PO Antibiotic Regimen] (No. of Patients)
Escherichia coli (5)	Vancomycin 1 g bid [ciprofloxacin 500 mg bid (2)] (2) Ertapenem 1 g qd [metronidazole 250 mg tid] (1) [Levofloxacin 750 mg qd (1)] [Ciprofloxacin 500 mg bid (1)]
Unspecified β-hemolytic streptococci (5)	Vancomycin 1 *or* 1.5 g qd (3) Clindamycin 900 mg tid (1) Penicillin G 4 million U tid (1)
Klebsiella pneumoniae (4)	Tigecycline 50 mg bid (2) Piperacillin/tazobactam 3/0.375 g tid (1) Daptomycin 570 mg qd [ciprofloxacin 500 mg bid] (1)
Propionibacterium acnes (3)	Vancomycin 1 g qd (2) Ampicillin 2 g tid (1)
Serratia marcescens (3)	Vancomycin 1 g bid [ciprofloxacin 750 mg bid (1)] (3) Gentamycin 50 mg qd (2)
Peptostreptococcus species (3)	Oxacillin 2 g qid [rifampin 300 mg bid] (1) Vancomycin 1.25 g bid (1) Cefazolin 2 g bid (1)
Streptococcus pneumoniae (2)	Vancomycin 1.25 g bid (1) Linezolid 300 mg bid (1)
Group-C streptococci (2)	Vancomycin 1 g bid (2)
Group-A streptococci (1)	Vancomycin 1 g bid (1)
Group-G streptococci (1)	Ampicillin 2 g qid (1)
Enterobacteriaceae (1)	Ceftriaxone 1 g qd (1)
Bacteroides fragilis (1)	Metronidazole 250 mg tid (1)
Candida parapsilosis (1)	[Fluconazole 400 mg qd (1)]
Proteus mirabilis (1)	Ceftazidime 1 g qd (1)
Morganella morganii (1)	Ciprofloxacin 400 mg qd (1)
Staphylococcus lugdunensis (1)	Oxacillin 2 g q4h [rifampin 600 mg qd] (1)
Negative culture (32)	Vancomycin 1 *or* 1.5 g bid *or* qd *or* q48h [rifampin 300 mg bid (1) or ciprofloxacin 500 mg bid (1)] (12) Cefazolin 1 g tid (7) Oxacillin 2 g q4h [rifampin 300 mg bid (1)] (2) Daptomycin 450 mg qd (2) Vancomycin 1 g bid [ciprofloxacin 500 mg bid] (1) Piperacillin/tazobactam 3/0.375 g tid (1) Ticarcillin/clavulanate 3/0.1 g qd (1) Ciprofloxacin 400 mg qd (1) Doxycycline 100 mg bid (1) Penicillin G 4 million U q4h (1) Clindamycin 900 mg tid (1) Ceftriaxone 2 g qd (1) [Levofloxacin 500 mg qd (1)]

*IV = intravenously, PO = orally, q4h = every four hours, qid = four times a day, bid = twice a day, qd = every day, tid = three times a day, q48h = every forty-eight hours, q72h = every seventy-two hours, and q8h = every eight hours. The number of pathogens adds up to more than the total number of 276 patients because some patients had polymicrobial infections. Also, the number of antibiotic regimens may add up to more than the total number of pathogens because some patients had multiple regimens at once.

TABLE IV Cox Proportional Hazards Model Estimates of Survival, with Adjustment for Matching Covariates

Variable	HR	95% CI	P Value
Chronic suppressive antibiotics	0.48	0.34-0.67	<0.001
No. of previous revisions	1.12	1.04-1.21	0.005
Non-*S. aureus* infection	0.69	0.51-0.94	0.018
Age (per year)	1.01	1.00-1.03	0.11
Hip joint	0.86	0.59-1.24	0.42
Charlson comorbidity index (per index point)	1.02	0.92-1.14	0.67
Male sex	1.05	0.78-1.40	0.76
BMI (per index point)	1.00	0.99-1.02	0.92

suppression failed with those for whom it did not fail. Failure was defined, as described by Diaz-Ledezma et al.[17], as (1) subsequent surgical intervention for infection after the index procedure; (2) persistent fistula, drainage, or joint pain at the last follow-up visit; or (3) death related to the periprosthetic joint infection. Any unresolved drainage at the last follow-up visit was considered a failure. Pain was considered to indicate a failure only when it was severely debilitating and prevented any kind of walking at the time of the last follow-up. Because we could not determine the causes of most deaths, we considered death within one year after the surgery as the cutoff point for failure; this was based on the findings of Zmistowski et al.[3], who showed that the highest differential mortality between septic and aseptic revisions occurred within one year.

The Fisher exact test or Pearson chi-square test was used for categorical data, whereas the Wilcoxon rank sum test or Welch two-sample t test was used for continuous data. Infection-free survival was estimated by using the Kaplan-Meier method. Hazard ratios (HRs) for comparison between the suppression and non-suppression groups were calculated with use of Cox proportional hazards regression models, with adjustment for variables that were previously used for matching. Subset analyses were performed by selecting the matched groups in which all subjects belonged to the subset of interest. This was done to preserve the matching characteristics of the original data, and the propensity score balance was rechecked within these subsets to verify that this had been accomplished. A log-rank test was used to compare prosthetic survival between the suppression and non-suppression groups in the subset cohorts. Further modeling was performed with Cox proportional hazards models to verify the effect of chronic antibiotic therapy across the different subsets. This model compared the benefits of suppression between the subsets of infecting organism (methicillin-resistant *S. aureus* [MRSA] versus methicillin-sensitive *S. aureus* [MSSA] versus non-*S. aureus*), affected joint (hip versus knee), and type of surgery (irrigation and debridement with polyethylene exchange versus two-stage revision).

Failures within the suppression group were modeled as a function of clinically relevant variables, with use of a penalized logistic regression model[18]. As a result of a low ratio of events to parameters, this model included only three variables and used a ridge-type penalty to correct for possible overfitting. A significance level of 5% was used, and analyses were done with use of R software (version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria). The penalized model was fit with use of rms (regression modeling strategies) in the R package[19].

Source of Funding

This study was internally funded by our institution.

Results

The baseline characteristics of the suppression and non-suppression groups are depicted in Table I.

The mean duration of follow-up (and standard deviation) was 69.1 ± 38.2 months (range, 2.2 to 168.3 months) in the suppression group and 41.6 ± 40.2 months (range, less than one to 183 months in the non-suppression group). Sixty-two (67.4%) of the patients in the suppression group and 186 (67.4%) of those in the non-suppression group had had previous revisions (mean, 2.7 ± 1.4 and 2.4 ± 1.7 previous revisions, respectively) for any cause. With the exception of two knees and one hip (all in the non-suppression group), which had a resection arthroplasty, all knees were treated with static spacers and all hips were treated with articulated spacers at the time of explantation. The time interval between removal and reimplantation was variable, averaging 21.1 ± 9.7 weeks (range, 6.6 to 46.3 weeks) in the suppression group and 15 ± 8 weeks (range, 3.1 to 45.6 weeks) in the non-suppression group. The median duration of postoperative intravenous therapy with antibiotics was six weeks in both groups. The mean duration of oral antibiotic suppression was 63.5 ± 38.3 months (range, six to 165.1 months). The specific antibiotic regimens are depicted in Tables II and III.

The five-year infection-free prosthetic survival rate was 68.5% (95% confidence interval [CI] = 59.2% to 79.3%) for the antibiotic-suppression group compared with 41.1 % (95% CI = 34.9% to 48.5%) for the non-suppression group (HR = 0.63, p = 0.008) (Fig. 2). The Cox proportional hazards model showed

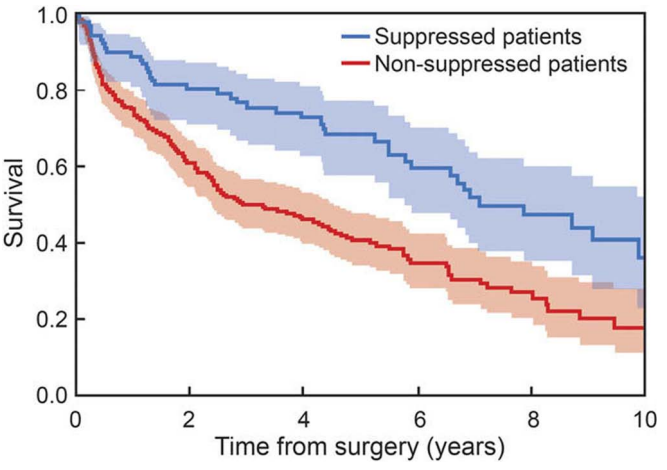

Fig. 2

Kaplan-Meier infection-free prosthetic survival curves for suppression and non-suppression patient groups. The blue line represents the suppression group, and the red line represents the non-suppression group; the shaded areas surrounding the lines represent the 95% CI.

TABLE V Comparisons of the Effects of Suppression Across Groups Stratified by Infecting Organism, Affected Joint, and Type of Surgery

Subset Interaction	HR	95% CI
Methicillin-sensitive *S. aureus* vs. non-*S. aureus*	0.83	0.3-2.27
Methicillin-resistant *S. aureus* vs. non-*S. aureus*	0.42	0.11-1.63
Methicillin-resistant vs. methicillin-sensitive *S. aureus*	0.50	0.12-2.08
Hip vs. knee	0.33	0.09-1.2
Irrigation and debridement with polyethylene exchange vs. 2-stage revision	1.40	0.55-3.57

that a higher number of previous revisions predicted a decreased survival rate (HR = 1.12 [95% CI = 1.04 to 1.21]; p = 0.005) and a non-*S. aureus* infection predicted an increased survival rate (HR = 0.69 [95% CI = 0.51 to 0.94]; p = 0.018) (Table IV).

Stratification by the type of index surgery showed that, in the group that underwent irrigation and debridement with polyethylene exchange, the patients treated with chronic antibiotic suppression had an increased five-year infection-free survival rate (64.7% [95% CI = 49.7% to 77.3%]) compared with the non-suppression group (30.4% [95% CI = 22.4% to 39.6%]; p < 0.0001). There was no difference in survival between the suppression and non-suppression groups following two-stage revision (p = 0.14) (Fig. 3).

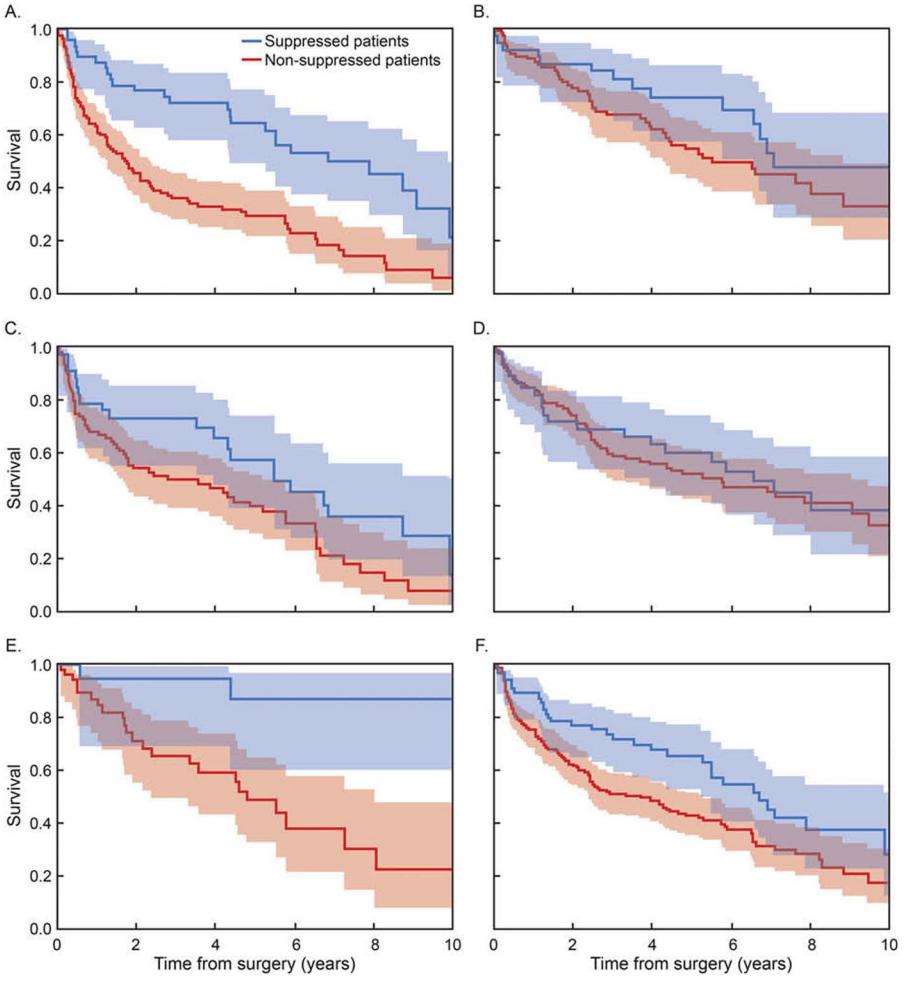

Fig. 3

Kaplan-Meier infection-free prosthetic survival curves for subset cohorts. The blue line represents the suppression group, and the red line represents the non-suppression group; the shaded areas surrounding the lines represent the 95% CI. **Fig. 3-A** Individuals who underwent irrigation and debridement with polyethylene exchange (p < 0.0001 for the difference between the suppression and non-suppression groups). **Fig. 3-B** Individuals who underwent a two-stage revision (p = 0.14). **Fig. 3-C** Individuals with an *S. aureus* infection (p = 0.047). **Fig. 3-D** Individuals with a non-*S. aureus* infection (p = 0.62). **Fig. 3-E** Individuals with an infection in the hip (p = 0.001). **Fig. 3-F** Individuals with an infection in the knee (p = 0.01).

TABLE VI Results of Univariate Analyses Comparing Baseline Characteristics Between Patients for Whom Chronic Oral Antibiotic Suppression Did Not Fail and Those for Whom It Failed

Variable	No Failure (N = 60)	Failure (N = 32)	P Value
Age at revision* *(yr)*	64.92 ± 12.5	61.34 ± 9.81	0.13
Sex†			
Male	34 (56.7)	22 (68.8)	
Female	26 (43.3)	10 (31.3)	
BMI* *(kg/m²)*	32.37 ± 9.01	35.83 ± 9.25	0.09
Index surgery†			>0.99
Irrigation and debridement with polyethylene exchange	35 (58.3)	19 (59.4)	
2-stage revision	25 (41.7)	13 (40.6)	
Duration of intravenous antibiotic therapy‡ *(wk)*	6 [6, 6]	6 [6, 6]	0.26
Duration of symptoms‡ *(days)*	30 [6, 77.5]	28 [13.25, 83.75]	0.23
Onset of infection†			0.70
Early	24 (40.0)	12 (37.5)	
Late	36 (60.0)	20 (62.5)	
Joint†			0.012
Knee	41 (68.3)	30 (93.8)	
Hip	19 (31.7)	2 (6.3)	
No. of previous revisions*	1.47 ± 1.55	2.41 ± 1.9	0.02
Infecting organism class†			0.76
Virulent§	35 (58.3)	19 (59.4)	
Indolent#	19 (31.7)	12 (37.5)	
Fungal and acid-fast bacilli	0	0	
Miscellaneous and contaminants	4 (6.7)	1 (3.1)	
Multiple organisms†	10 (16.7)	9 (28.8)	0.27
Pathogen†			0.93
S. aureus	28 (46.7)	16 (50.0)	
Non-*S. aureus*	32 (53.3)	16 (50.0)	
Duration of antibiotic suppression* *(mo)*	65.31 ± 37.01	59.87 ± 41.26	0.53
Charlson comorbidity index*	4.00 ± 1.48	3.66 ± 1.64	0.33
American Society of Anesthesiologists score‡	3 [3, 3]	3 [2.75, 3]	0.89
Smoker†	4 (6.7)	3 (9.4)	0.69
Diabetes†	15 (25.0)	11 (34.4)	0.48
Inflammatory arthropathy†	10 (16.7)	1 (3.1)	0.089
Malignancy†	7 (11.7)	2 (6.3)	0.49
Steroid use†	9 (15.0)	2 (6.3)	0.32
Heart disease†	47 (78.3)	24 (75.0)	0.92

*The values are given as the mean and standard deviation. †The values are given as the number of patients with the percentage in parentheses. ‡The values are given as the median with the 25th and 75th percentiles in brackets. §Includes *S. aureus,* Enterococcus, and gram-negative organisms. #Includes coagulase-negative Staphylococcus and Propionibacterium species.

Stratification by the affected joint showed a significant increase in the infection-free survival rate in the suppression group, compared with the non-suppression group, both after revision for a hip infection (87.2% [95% CI = 60.2% to 96.8%] compared with 49.0% [95% CI = 32.9% to 65.4%]; p = 0.001) and after revision for a knee infection (65.8% [95% CI = 53.0% to 76.7%] compared with 43.2% [95% CI = 35.4% to 51.4%]; p = 0.01).

Stratification by the infecting organism showed that, when the pathogen was *S. aureus,* the five-year infection-free survival rate in the suppression group (57.4% [95% CI = 39.2% to 73.8%]) was increased compared with that in the non-suppression group

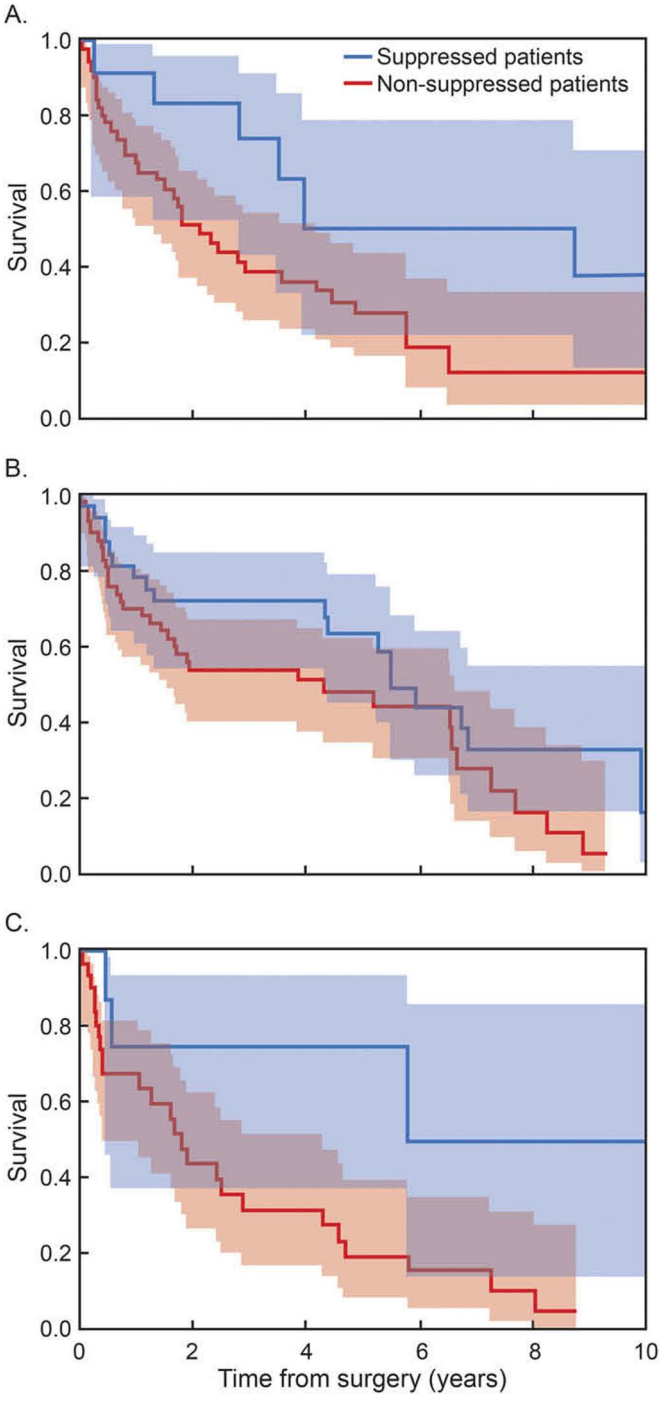

Fig. 4

Kaplan-Meier infection-free prosthetic survival curves for subsets with MRSA (**Fig. 4-A**), MSSA (**Fig. 4-B**), and gram-negative (**Fig. 4-C**) infection. The blue line represents the suppression group, and the red line represents the non-suppression group; the shaded areas surrounding the lines represent the 95% CI. Suppressive antibiotics increased the five-year infection-free prosthetic survival rate for patients with MRSA infection, with a survival rate of 50.8% (95% CI = 22.2% to 78.9%) in the suppression group and 28.2% (95% CI = 16.5% to 43.8%) in the non-suppression group (p = 0.05). There was no difference in the infection-free survival rate between the suppression group with MSSA infection (63.6% [95% CI = 45.1% to 78.8%]) and the non-suppression group with MSSA infection (48.1% [95% CI = 34.4% to 62.1%]; p = 0.09). The suppression-group patients with gram-negative infection had an increased infection-free survival rate (74.7% [95% CI = 36.7% to 94.1%]) compared with the non-suppression group with gram-negative infection (20.3% [95% CI = 10.6% to 39.2%]; p = 0.04).

(40.1% [95% CI = 29.6% to 51.6%]; p = 0.047). There was no difference in survival between the suppression and non-suppression groups when the patients had a non-*S. aureus* infection (p = 0.62). The results of additional stratification, by whether the patient had MRSA, MSSA, or gram-negative infection, are shown in Figure 4, although this analysis did not preserve the original matching quality between the suppression and non-suppression groups.

The benefit of chronic antibiotic suppression compared across different subsets was non-significant for the entire model (p = 0.22) and at every interaction (Table V).

Thirty-two patients (34.8%) in the suppression group and 115 (41.7%) in the non-suppression group met the criteria for failure of treatment. Comparisons between the patients for whom chronic antibiotic suppression failed and those for whom it did not fail are depicted in Table VI. Failures had a lower association with hip infection than with knee infection (HR = 0.10, p = 0.013) and were associated with a higher number of prior revisions (HR = 2.83, p = 0.026) (Table VII).

Discussion

With the rates of total knee and hip arthroplasties performed in the United States expected to increase by 673% and 174%, respectively, from 2005 to 2030[20], strategies to avoid limb-threatening outcomes and high mortality rates associated with periprosthetic joint infection are needed. In the current study, we examined how chronic suppressive antibiotics affect infection-free prosthetic survival rates after surgical intervention for periprosthetic joint infection. The five-year infection-free survival rate in the suppression group was 68.5% compared with 41.1% in the non-suppression group (p = 0.008). The increased survival rate in the suppression group is consistent with the findings in another study, which showed a three-year success rate of 78% after treatment of 112 periprosthetic joint infections with debridement, antibiotics, and implant retention[21]. Other studies documenting the management of periprosthetic joint infection with antibiotics and prosthesis retention have demonstrated both positive[22,23] and negative[24] outcomes; however, subsequent chronic suppression with oral antibiotics was not consistently used.

Stratification by the type of surgery and infecting organism showed that the patients who benefited the most from chronic suppressive antibiotic therapy were those who underwent irrigation and debridement with polyethylene exchange and those with *S. aureus* infection. The benefit of suppression following irrigation and debridement with polyethylene exchange has already been documented and is in accordance with findings in the current literature[25-27]. Persistence of a latent infection is common

TABLE VII Penalized Regression Model Estimates of Factors Associated with Treatment Failure

Variable	HR	95% CI	P Value
No. of previous revisions*	2.83	1.14-7.03	0.026
BMI†	1.45	0.68-3.10	0.33
Hip infection	0.10	0.02-0.61	0.013

*Effect for a three-unit change. †Effect for a 12.7-unit change.

in patients with retained implants and thus antibiotic suppression seems to be a reasonable alternative that avoids the need for a more invasive two-stage revision. Antibiotic suppression following two-stage procedures did not seem to affect prosthetic survival. The current study also showed that, among the patients who had *S. aureus* infection, those who underwent postoperative suppression had a higher infection-free survival rate than those who did not receive postoperative suppression. This conflicts with the findings in the study by Brandt et al.[28], in which suppression did not influence the outcome of surgical treatment of periprosthetic joint infections caused by *S. aureus.* Possible explanations for this discrepancy are the newer, more efficacious antibiotic regimens used in the present study, the longer course of intravenous antibiotics postoperatively (six weeks versus four weeks in the study by Brandt et al.), and differences in the end points that were used. Furthermore, it has been suggested that *S. aureus* survives in the intracellular environment[29], which may account for its higher recurrence rate and thus the need for a long-term oral antibiotic regimen. Finally, chronic antibiotic therapy did not seem to influence infection-free survival after revisions for non-*S. aureus* infections. This was probably due to the greater success attained with the surgery and by the increased susceptibility of these pathogens to intravenous agents used in the first six weeks after surgery. Numerous studies have shown the efficacy of chronic suppression even of non-*S. aureus* infections[25-27], but the absence of a control group in those studies precludes any definite conclusions from being reached.

TABLE VIII Findings in Previous Studies of Chronic Antibiotic Suppression

Study	No.	Mean Duration of Follow-up *(mo)*	Mean Duration of Antibiotic Suppression (Range) *(mo)*	Previous Surgical Treatment	Failure Criteria	No. *(%)* of Successful Cases
Johnson and Bannister[30] (1986)	25 knees	15.6	15.6 (1.2-59)	Excision of sinus tract, debridement, exchange arthroplasty	Persistent discharge, joint pain	2 (8%)
Goulet et al.[27] (1988)	19 hips	49.2	45 (2-120)	Incision and drainage (11), no prior surgery (8)	Removal or revision of prosthesis, increasing symptoms of infection	9 (47%)
Tsukayama et al.[31] (1991)	8 knees, 5 hips	37.6	24.5 (6-48)	Surgical debridement	Prosthesis removal for recurrent infection	3 (23%)
Segreti et al.[25] (1998)	12 knees, 6 hips	60	48.9 (4-103)	Surgical debridement	Persistence of symptoms of infection (pain, drainage, etc.)	15 (83%)
Rao et al.[26] (2003)	19 knees, 15 hips, 2 elbows	61.5	52.6 (6-128)	Surgical debridement	Development of progressive pain, loosening of implant, or drainage	31 (86%)
Current study	71 knees, 21 hips	69.6	63.47 (6-165)	Irrigation and debridement with polyethylene exchange (54), 2-stage revision (38)	Additional surgery due to infection, persistent drainage or joint pain, death within 1 yr	60 (65%)

The multivariate models constructed for our study confirmed the overall benefit of chronic antibiotic therapy. However, this analysis was not able to determine the subset from which this benefit was mostly derived, probably because of the limited number of events in each subset and overfitting of the data within the model.

The 34.8% failure rate for the ninety-two patients who received chronic antibiotic therapy for a minimum of six months was higher than the rates in the most recently published studies[25,26]. Segreti et al.[25] reviewed the cases of eighteen patients who had undergone surgical debridement and six to eight weeks of intravenous antibiotics followed by prolonged antibiotic suppression. At five years, only three had persistent symptoms of infection. Rao et al.[26] prospectively examined thirty-six patients who had undergone the same protocol of surgical debridement and four to six weeks of intravenous antibiotics prior to antibiotic suppression. The failure rate was 13.9% (five of the thirty-six patients) after 4.4 years of follow-up. Possible explanations for the higher failure rates observed in the present study include the higher prevalence of invasive pathogens (47.8% of the infections were caused by *S. aureus* compared with 38.9% in the other studies[25,26]) and the inclusion of deaths within the first year after treatment as failures. Older studies on chronic antibiotic suppression[27,30,31] showed higher failure rates, probably as a result of less efficient antibiotic regimens (Table VIII). In our study, patients for whom suppressive antibiotic treatment failed had had more prior joint revisions. The association of a higher number of previous revisions with increased failure rates is in accordance with the findings in other studies[32,33]. We also found that patients with knee periprosthetic joint infection had a higher rate of failure than those with hip infection. In a review of 9245 cases, Pulido et al.[6] reported an increased prevalence of periprosthetic joint infection after total knee arthroplasty than after total hip arthroplasty. This does not explain why knees have an inferior response to treatment of periprosthetic joint infection, but it provides some evidence of an increased susceptibility to periprosthetic joint infection in knees.

Our study was limited by its sample size. This is a common limitation of studies of chronic antibiotic suppression for periprosthetic joint infection because it is a last-resort treatment for an infrequent complication of joint arthroplasty. The small sample size compromised the ability of the multivariate analyses stratified by the infecting organism, affected joint, and type of surgery to provide results similar to those in the survivorship analysis. In addition, sampling bias was an inherent limitation of our study when the suppression group was compared with the non-suppression group. In an effort to overcome this bias, propensity score matching with a 3:1 matching ratio was done for eight variables. Also, the retrospective nature of the study precluded the use of standardized surgical techniques and antibiotic regimens. Finally, the six subset cohorts had lower-quality propensity score matching than the cohort as a whole. This was the case because the matching was designed to produce good matches for all subjects rather than within subsets.

In summary, chronic suppression with oral antibiotics resulted in superior infection-free survival rates after surgical treatment for periprosthetic joint infection compared with those observed without suppression. Patients who underwent irrigation and debridement with polyethylene exchange and those with *S. aureus* infection showed the greatest benefit. Knee infection and a greater number of prior revisions were identified as variables associated with treatment failure. ■

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References

1. Darouiche RO. Treatment of infections associated with surgical implants. N Engl J Med. 2004 Apr 1;350(14):1422-9.

2. Bozic KJ, Ries MD. The impact of infection after total hip arthroplasty on hospital and surgeon resource utilization. J Bone Joint Surg Am. 2005 Aug;87(8):1746-51.

3. Zmistowski B, Karam JA, Durinka JB, Casper DS, Parvizi J. Periprosthetic joint infection increases the risk of one-year mortality. J Bone Joint Surg Am. 2013 Dec 18;95(24):2177-84.

4. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty. 2008 Oct;23(7):984-91. Epub 2008 Apr 10.

5. Klouche S, Sariali E, Mamoudy P. Total hip arthroplasty revision due to infection: a cost analysis approach. Orthop Traumatol Surg Res. 2010 Apr;96(2):124-32.

6. Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. Clin Orthop Relat Res. 2008 Jul;466(7):1710-5. Epub 2008 Apr 18.

7. Phillips JE, Crane TP, Noy M, Elliott TS, Grimer RJ. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey. J Bone Joint Surg Br. 2006 Jul;88(7):943-8.

8. Parvizi J, Adeli B, Zmistowski B, Restrepo C, Greenwald AS. Management of periprosthetic joint infection: the current knowledge: AAOS exhibit selection. J Bone Joint Surg Am. 2012 Jul 18;94(14):e104.

9. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013 Jan;56(1):e1-25. Epub 2012 Dec 6.

10. Buller LT, Sabry FY, Easton RW, Klika AK, Barsoum WK. The preoperative prediction of success following irrigation and debridement with polyethylene exchange for hip and knee prosthetic joint infections. J Arthroplasty. 2012 Jun;27(6):857-64.e1-4. Epub 2012 Mar 6.

11. Sabry FY, Buller L, Ahmed S, Klika AK, Barsoum WK. Preoperative prediction of failure following two-stage revision for knee prosthetic joint infections. J Arthroplasty. 2014 Jan;29(1):115-21. Epub 2013 May 23.

12. Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. Bone Joint J. 2013 Nov;95-B(11):1450-2.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

14. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol. 1994 Nov;47(11):1245-51.

15. Soohoo NF, Farng E, Lieberman JR, Chambers L, Zingmond DS. Factors that predict short-term complication rates after total hip arthroplasty. Clin Orthop Relat Res. 2010 Sep;468(9):2363-71.

16. SooHoo NF, Lieberman JR, Ko CY, Zingmond DS. Factors predicting complication rates following total knee replacement. J Bone Joint Surg Am. 2006 Mar;88(3):480-5.

17. Diaz-Ledezma C, Higuera CA, Parvizi J. Success after treatment of periprosthetic joint infection: a Delphi-based international multidisciplinary consensus. Clin Orthop Relat Res. 2013 Jul;471(7):2374-82. Epub 2013 Feb 26.

18. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996 Feb 28;15(4):361-87.

19. Harrel FE Jr. rms: regression modeling strategies. R package version 4.0-0. 2013. http://CRAN.R-project.org/package=rms. Accessed 2014 June 25.

20. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am. 2007 Apr;89(4):780-5.

21. Byren I, Bejon P, Atkins BL, Angus B, Masters S, McLardy-Smith P, Gundle R, Berendt A. One hundred and twelve infected arthroplasties treated with 'DAIR' (debridement, antibiotics and implant retention): antibiotic duration and outcome. J Antimicrob Chemother. 2009 Jun;63(6):1264-71. Epub 2009 Mar 31.

22. Aboltins CA, Page MA, Buising KL, Jenney AW, Daffy JR, Choong PF, Stanley PA. Treatment of staphylococcal prosthetic joint infections with debridement, prosthesis retention and oral rifampicin and fusidic acid. Clin Microbiol Infect. 2007 Jun;13(6):586-91. Epub 2007 Feb 28.

23. Mont MA, Waldman B, Banerjee C, Pacheco IH, Hungerford DS. Multiple irrigation, debridement, and retention of components in infected total knee arthroplasty. J Arthroplasty. 1997 Jun;12(4):426-33.

24. Deirmengian C, Greenbaum J, Lotke PA, Booth RE Jr, Lonner JH. Limited success with open debridement and retention of components in the treatment of acute Staphylococcus aureus infections after total knee arthroplasty. J Arthroplasty. 2003 Oct;18(7)(Suppl 1):22-6.

25. Segreti J, Nelson JA, Trenholme GM. Prolonged suppressive antibiotic therapy for infected orthopedic prostheses. Clin Infect Dis. 1998 Oct;27(4):711-3.

26. Rao N, Crossett LS, Sinha RK, Le Frock JL. Long-term suppression of infection in total joint arthroplasty. Clin Orthop Relat Res. 2003 Sep;(414):55-60.

27. Goulet JA, Pellicci PM, Brause BD, Salvati EM. Prolonged suppression of infection in total hip arthroplasty. J Arthroplasty. 1988;3(2):109-16.

28. Brandt CM, Sistrunk WW, Duffy MC, Hanssen AD, Steckelberg JM, Ilstrup DM, Osmon DR. Staphylococcus aureus prosthetic joint infection treated with debridement and prosthesis retention. Clin Infect Dis. 1997 May;24(5):914-9.

29. Drancourt M, Stein A, Argenson JN, Zannier A, Curvale G, Raoult D. Oral rifampin plus ofloxacin for treatment of Staphylococcus-infected orthopedic implants. Antimicrob Agents Chemother. 1993 Jun;37(6):1214-8.

30. Johnson DP, Bannister GC. The outcome of infected arthroplasty of the knee. J Bone Joint Surg Br. 1986 Mar;68(2):289-91.

31. Tsukayama DT, Wicklund B, Gustilo RB. Suppressive antibiotic therapy in chronic prosthetic joint infections. Orthopedics. 1991 Aug;14(8):841-4.

32. Sherrell JC, Fehring TK, Odum S, Hansen E, Zmistowski B, Dennos A, Kalore N; Periprosthetic Infection Consortium. The Chitranjan Ranawat Award: fate of two-stage reimplantation after failed irrigation and débridement for periprosthetic knee infection. Clin Orthop Relat Res. 2011 Jan;469(1):18-25.

33. Bejon P, Berendt A, Atkins BL, Green N, Parry H, Masters S, McLardy-Smith P, Gundle R, Byren I. Two-stage revision for prosthetic joint infection: predictors of outcome and the role of reimplantation microbiology. J Antimicrob Chemother. 2010 Mar;65(3):569-75. Epub 2010 Jan 6.