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Complications - Infection

Extended Oral Antibiotics Increase Bacterial Resistance in Patients Who Fail 2-Stage Exchange for Periprosthetic Joint Infection

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ABSTRACT

Background: Although studies have demonstrated reductions in recurrent periprosthetic joint infection (PJI) with the administration of prolonged oral antibiotics at second-stage reimplantation, the potential for increasing bacterial resistance has not been studied. The purpose of this study was to determine if oral antibiotics at second-stage reimplantation increased the rate of antibiotic resistance in subsequent infections.

Methods: We retrospectively reviewed patients who underwent 2-stage exchange for chronic PJI from 2014 to 2019. We compared those who had received prolonged oral antibiotics at the time of stage 2 reimplantation with those who did not. The primary outcome was the presence of resistant organisms in any subsequent infection. The secondary outcome was the overall rate of recurrent PJI in the 2 groups. Multivariable analyses controlling for demographics and comorbid conditions were used.

Results: Of the 211 patients who underwent 2-stage exchange for PJI, 158 patients received prolonged oral antibiotics. The mean follow-up was 2.2 years. Recurrent PJI was diagnosed in 24 of 158 (15%) patients who received oral antibiotics compared with 11 of 53 (21%) patients who did not receive antibiotics ($P = .35$). PJI with resistant organisms was identified in 16 of 24 (67%) patients who received antibiotics compared with 0 of 11 (0%) patients who did not receive antibiotics ($P = .0001$).

Conclusions: Prolonged oral antibiotics following 2-stage exchange increase drug resistance to that antibiotic in subsequent PJI. We recommend further research in the area to refine antimicrobial protocols as we consider the risks and benefits of prolonged antibiotic treatment.

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Periprosthetic joint infection (PJI) is a devastating complication for patients undergoing hip and knee arthroplasty, associated with morbidity and high mortality rates [1]. Currently, the gold standard treatment for chronic PJI is a 2-stage exchange. The surgeon first removes the infected components and implants an antibiotic-impregnated spacer. After a minimum 6-week period of targeted antibiotic treatment, the patient returns to the operating room for the second stage of reimplantation. Although some studies report success rates ranging from 80% to 95% [2–4], others report a rate as low as 54% depending on how you define success [5].

A multicenter randomized controlled trial in 2017 demonstrated a reduced rate of repeat infection in patients who received a 3-month course of oral antibiotics following 2-stage exchange after chronic PJI of the hip or knee [6]. Of the 107 patients included in the initial analysis at 1-year follow-up, only 3 of 59 (5%) patients who received directed oral antibiotics failed secondary to infection compared with 9 of 48 patients (19%) in the control group (hazard ratio, 4.4; 95% confidence interval, 1.3-20; $P = .016$). The most recent update of this analysis demonstrated a 12.5% recurrence rate of PJI in patients who received oral antibiotics compared with 28.6% in the control group at a mean follow-up of 3.3 years ($P = .012$) [7]. Of note, the subsequent infections were mainly with different pathogens from the original infection, suggesting that the oral antibiotics were preventing new infections, not continuing to treat the prior infection. Although this study and others [8,9] support the

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efficacy of using oral antibiotics at the time of second-stage reimplantation, the potential side effect of creating bacterial resistance among these patients is unknown.

The purpose of the present study was to determine if oral antibiotics at the time of second-stage reimplantation increased the rate of antibiotic resistance in any subsequent infections. In addition, we determined if oral antibiotics reduced the overall rate of recurrent PJI in our patient population. Our hypothesis was that oral antibiotics at the time of stage 2 reimplantation would reduce our recurrent PJI rate but increase bacterial resistance among those patients with recurrent PJI after their 2-stage exchange.

Methods

This was a retrospective cohort study of 211 patients who underwent a 2-stage exchange for chronic PJI between January 1, 2014, and January 1, 2020, at a single institution. We selected this time frame to ensure a minimum of 1 year of follow-up after the second-stage surgery. Our institutional review board declared our study exempt, and no additional funding was received. We identified our patient population by looking for the Current Procedural Terminology codes 27134 or 27487 combined with 11982, followed by a chart review to confirm that the patient had undergone 2-stage exchange for PJI. Indications for 2-stage exchange at our institution include any chronic PJI, failed treatment of acute PJI, and other variables (eg, difficult to treat organism) at the discretion of the treating surgeon. Age, gender, body mass index, American Society of Anesthesiologists classification, smoking status, number and timing of previous surgeries, and certain medical comorbidities (rheumatoid arthritis, diabetes mellitus, chronic kidney disease, creatinine, and hemoglobin A_{1c}) were collected on all patients. Through manual chart review, we identified which patients received at least 2 weeks of oral antibiotics at the time of their second-stage reimplantation. At our institution, oral antibiotics at the time of second-stage reimplantation were not routinely provided until early 2017, after the results of the multicenter randomized clinical trial demonstrating their efficacy were published [6]. The decision to provide oral antibiotics after second-stage reimplantation was made by the attending arthroplasty surgeon. Any patients who received intravenous antibiotics at the time of second-stage reimplantation ($N = 1$) were excluded from the study.

Our primary outcome was the presence of resistant organisms in any subsequent infection in the same joint, comparing those who had received extended oral antibiotics at the time of second-stage reimplantation to those who had not. We identified all patients who underwent repeat surgery for any reason on the same joint and did manual chart review to determine the type of repeat surgery, diagnosis of recurrent PJI, and the resistance pattern of any cultured pathogens. We examined both the first repeat surgery and the first recurrent PJI and report the results separately. For most patients, these are the same event, but a subset of patients first had repeat surgery for a noninfectious complication and subsequently developed a recurrent PJI. Positive cultures were classified as resistant organism, sensitive organism, or unknown (if no susceptibility data). Resistance was defined as any organism with intermediate or higher level of resistance to the oral antibiotic prescribed at the time of second-stage reimplantation. Because nearly all the patients in the antibiotic group received doxycycline, for those patients who did not receive antibiotics after stage 2, we classified their pathogens as sensitive/resistant based on sensitivity/resistance to doxycycline (or tetracycline). For polymicrobial infections, they were classified as resistant if at least one cultured organism was tested against a tetracycline and found to have intermediate or higher resistance. Culture negative infections included those with no organisms found, single colony growth on only one culture, or organisms isolated in broth only from only one culture. Finally, we compared resistance in our patient population to the local antibiogram.

Secondary outcomes included recurrent PJI, time to first repeat surgery, and time to recurrent PJI. We classified recurrent PJI in any patient who underwent surgery for suspected PJI and was subsequently treated with a prolonged course of antibiotics, as this is a clinically meaningful outcome and indicated that their treating physicians considered them to have a recurrent PJI. We included all such cases as recurrent PJI in our analyses and report how many of them met Musculoskeletal Infection Society (MSIS) criteria for PJI.

Demographics and cultures from subsequent surgeries were compared between patients who received oral antibiotics and those who did not use *t*-tests, chi-squared, and Fisher's exact tests. Wilcoxon rank-sum tests were used to compare time to subsequent surgery, as it was not normally distributed. Statistical analysis was performed using SAS 9.4 (Cary, NC).

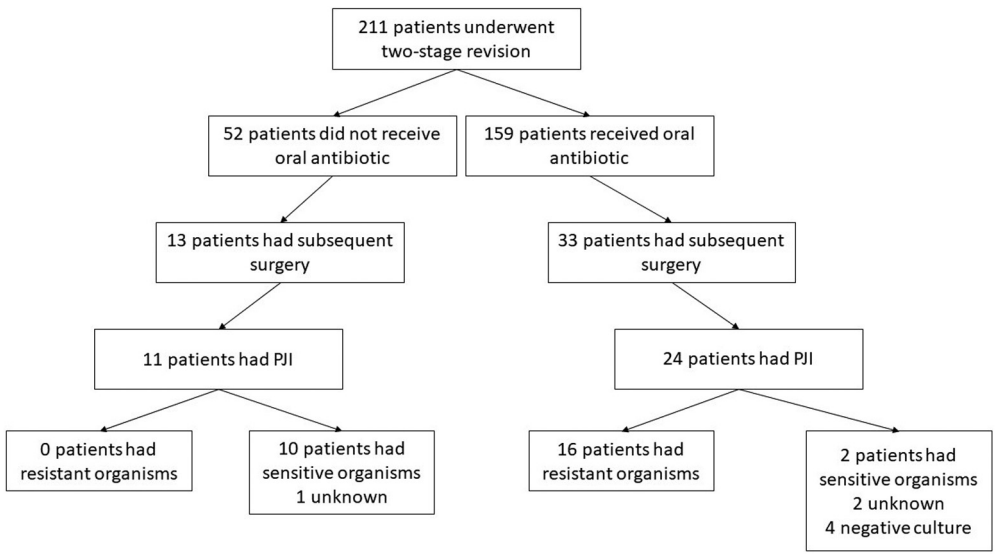

Fig. 1. Flow chart of patients.

Results

Of the 211 patients who underwent 2-stage exchange for PJI, 158 patients received oral antibiotics at the time of second-stage reimplantation (Fig. 1). The mean follow-up was 2.2 years (standard deviation 1.7). Demographic variables were similar between the 2 groups (Table 1). The most common antibiotics used in this cohort were doxycycline (N = 135), quinolones (N = 9), beta-lactams (N = 11), and trimethoprim-sulfamethoxazole (N = 4). One patient received minocycline, and one patient received both ciprofloxacin and cefadroxil. The percentage of patients who received oral antibiotics each year increased with time: 23% in 2014, 29% in 2015, 63% in 2016, 97% in 2017, 95% in 2018, and 100% in 2019. Of patients who received >2 weeks of antibiotics immediately following their second-stage procedure, 124 (78.5%) received >12 weeks, 27 (17.1%) received 4-12 weeks, and 7 (4.4%) received 2-4 weeks. Forty-six patients underwent subsequent surgery on the same joint, and 35 patients were diagnosed with recurrent PJI. Of these 35 patients, 29 met the 2018 MSIS criteria [10] for definite PJI by virtue of 2 positive cultures, and another 3 patients met 2018 MSIS criteria by points. The remaining 3 cases were clinically consistent with PJI but had missing laboratory data and so did not meet MSIS criteria (eg, no erythrocyte sedimentation rate or C-reactive protein checked preoperatively).

Resistant organisms were isolated at first subsequent surgery in 11 of 33 (33%) patients who received oral antibiotics compared with 0 of 13 patients who did not receive antibiotics ($P = .0004$; Table 2). Negative culture results occurred in 14 of 33 (42%) patients who received antibiotics compared with 2 of 13 (15%) patients who did not receive antibiotics ($P = .0004$). Four patients, 2 in each subgroup, did not have any susceptibility analysis done on the culture organisms and were categorized as unknown. Cultures were not sent in 6 patients at the time of subsequent surgery.

Recurrent PJI at any time point was diagnosed in 24 of 158 (15%) patients who received oral antibiotics compared with 11 of 53 (21%) patients who did not receive antibiotics, although this was not statistically significant ($P = .35$; Table 3). Resistant organisms were identified in 16 of the 24 (67%) patients who received antibiotics and were diagnosed with recurrent PJI, compared with 0 of the 11 (0%) patients who did not receive antibiotics and developed recurrent PJI ($P = .0001$). The identified pathogen at the time of repeat failure was different than the pathogen found at stage 1 in nearly all cases, with only 2 patients (one who received oral antibiotics and one who did not) having a repeat infection with the same species of bacteria (Table 4). The median time to revision was 3.2 months (interquartile range 1.8-11.7) in patients who received antibiotics compared with 5.7 months (interquartile range 1.1-51.3) in patients who did not receive antibiotics, although there was high variability in both groups ($P = .74$; Fig. 2).

Table 1
Demographics.

Patient Demographics	Total (n = 211)	No Antibiotic (n = 53)	Oral Antibiotic (n = 158)	*P* Value
	n (%)	n (%)	n (%)	
Gender				
Female	113 (53.6)	31 (58.5)	82 (51.9)	.4050
Male	98 (46.5)	22 (41.5)	76 (48.1)	
Smoking				
Current	14 (6.6)	5 (9.4)	9 (5.7)	.4515
Former	80 (37.9)	17 (32.1)	63 (39.9)	
Never	117 (55.5)	31 (58.5)	86 (54.4)	
Joint				
Hip	104 (49.3)	29 (54.7)	75 (47.5)	.3610
Knee	107 (50.7)	24 (45.3)	83 (52.5)	
RA	41 (19.4)	10 (18.9)	31 (19.6)	.9047
Diabetes	68 (32.2)	24 (45.3)	44 (27.9)	.0188
CKD	37 (17.5)	12 (22.6)	25 (15.8)	.2586
	Mean (SD)	Mean (SD)	Mean (SD)	*P* Value
Age	61.4 (11.0)	61.0 (11.1)	61.5 (11.1)	.8100
BMI	32.9 (8.4)	32.4 (8.1)	33.1 (8.5)	.5754
ASA	2.6 (0.6)	2.5 (0.6)	2.6 (0.6)	.4283
Years between index surgery and stage 2	4.8 (6.8)	4.2 (8.3)	5.0 (6.2)	.5637
Number of prior surgeries	3.4 (1.7)	3.3 (1.3)	3.4 (1.8)	.7111
Creatinine	1.1 (0.5)	1.2 (0.6)	1.1 (0.4)	.1486
A1c (only had for 90 patients)	6.1 (1.2)	6.0 (0.6)	6.1 (1.3)	.7114

ASA, American Society of Anesthesiologists; BMI, body mass index; CKD, chronic kidney disease; RA, rheumatoid arthritis; SD, standard deviation.

Table 2
Resistant Organisms at First Subsequent Surgery.

Resistant Organism Group	No Antibiotic (n = 53)	Oral Antibiotic (n = 158)	*P* Value
	n (%)	n (%)	
Total number of patients who had subsequent surgery	13 (24.5)	33 (20.9)	.5784
Negative culture	2 (15.4)	14 (42.4)	.0004
Positive culture: sensitive organism	7 (53.9)	2 (6.1)	
Positive culture: resistant organism	0	11 (33.3)	
Unknown	2 (15.4)	2 (6.1)	
No samples	2 (15.4)	4 (12.1)	
	Median (IQR)	Median (IQR)	*P* Value
Time to first subsequent surgery (mo)	3.3 (0.5-14.4)	3.1 (1.7-10.1)	.6452
Negative culture (mo)	0.5 (0.4-0.7)	1.7 (2.4-9.1)	.0658
Positive culture: sensitive organism (mo)	5.7 (1.2-14.4)	15.6 (15.1-16.0)	.2242
Positive culture: resistant organism (mo)	–	3.3 (1.2-10.1)	N/A
Unknown (mo)	25.9 (0.5-51.3)	2.3 (1.9-2.8)	1.0000
No samples (mo)	11.1 (0.1-22.2)	7.4 (3.2-9.8)	1.0000

IQR, interquartile range.

Discussion

The treatment of chronic PJI involves significant patient morbidity and presents a challenge to the treating surgeon [1]. Two-stage exchange is a costly intervention with success rates reported as low as 54% [5]. A multicenter trial demonstrated significant reduction in recurrent PJI rate in patients who received a 3-month oral antibiotic course after the second-stage reimplantation surgery, which led many surgeons to adjust their treatment

Table 3
Rate of Recurrent PJI.

Resistant Organism Group	No Antibiotic (n = 53)	Oral Antibiotic (n = 158)	*P* Value
	n (%)	n (%)	
Number of patients with recurrent PJI	11 (20.8)	24 (15.2)	.3459
Negative culture	0	4 (16.7)	<.0001
Positive culture: sensitive organism	10 (90.9)	2 (8.3)	
Positive culture: resistant organism	0	16 (66.7)	
Unknown	1 (9.1)	2 (8.3)	
	Median (IQR)	Median (IQR)	*P* Value
Time to recurrent PJI (mo)	5.7 (1.1-51.3)	3.2 (1.8-11.7)	.7378

IQR, interquartile range.

Table 4
Summary of Patients Who Underwent Repeat Surgery on the Same Joint After 2-Stage Exchange for PJI.

Joint	Original Infecting Organism (Susceptibility, to Tetracyclines Unless Otherwise Specified)	IV Antibiotics	Antibiotic at Stage 2	Time to First Repeat Surgery (mo)	Microbiology at First Repeat Surgery (Susceptibility, to Tetracyclines Unless Otherwise Specified)	Time to First Recurrent PJI (mo)	Microbiology of Recurrent PJI (Susceptibility, to Tetracyclines Unless Otherwise Specified)	Surgery Details and Current Status
Hip	*Gemella morbillorum* (unk.)	Daptomycin	None	7.0	MRSA (S)	7.0	MRSA (S)	s/p hardware removal with positive culture, short course antibiotics
Hip	Coagulase-negative Staphylococci (S)	Vancomycin	Doxycycline	8.7	Negative			s/p conversion to constrained liner
Hip	*Staphylococcus epidermidis* (unk.)	Vancomycin	Doxycycline	2.1	Negative			s/p conversion to constrained liner
Knee	Unknown (outside hospital)	Unknown (outside hospital)	Doxycycline	2.8	Coagulase-negative Staphylococci (unk.)	4.2	*Staphylococcus epidermidis* (R)	s/p modular component exchange of hinge, not on antibiotics
Knee	*Staphylococcus epidermidis* (S)	Vancomycin	Doxycycline	15.4	MSSA (S)	15.4	MSSA (S)	s/p AKA
Knee	Culture negative	Vancomycin	Doxycycline	3.1	Negative			s/p femoral revision for periprosthetic femur fracture
Hip	*Finegoldia magna* (S)	Penicillin	Doxycycline	4.1	*Staphylococcus epidermidis* (R)	4.1	*Staphylococcus epidermidis* (R)	s/p repeat 2-stage, on chronic doxycycline
Knee	Proteus mirabilis, Finegoldia magna (unk.)	PO Flagyl and Levaquin	Doxycycline	0.9	Negative	2.9	*Corynebacterium spp.* (R)	s/p multiple I&D and eventually AKA
Hip	MRSA (S)	Vancomycin	Doxycycline	12.1	Negative			s/p conversion to dual mobility
Hip	Enterobacter cloacae (unk.)	Piperacillin-Tazobactam	None	0.4	Negative	0.8	Polymicrobial (S)	s/p repeat 2-stage exchange, not on antibiotics
Hip	*Corynebacterium striatum/simulans* (R)	Vancomycin	None	22.5	No samples			s/p trochanter plate removal
Knee	*Prevotella bivia* (unk.)	Ceftriaxone	None	5.8	MSSA (S)	5.8	MSSA (S)	s/p I&D poly exchange, on chronic doxycycline
Knee	Culture negative		None	3.3	*Staphylococcus epidermidis* (S)	3.3	*Staphylococcus epidermidis* (S)	s/p I&D poly exchange of DFR, on doxycycline, now deceased
Hip	Culture negative	Vancomycin	Doxycycline	1.2	Negative	1.9	Polymicrobial (R)	s/p I&D, head liner exchange, and conversion to constrained liner, not on antibiotics
Hip	Unknown (outside hospital)	Daptomycin	None	1.3	Coagulase-negative Staphylococci (S)	1.3	Coagulase-negative Staphylococci (S)	s/p I&D modular exchange, s/p conversion to constrained liner, on chronic doxycycline
Hip	MRSA (S)	Vancomycin	None	0.7	Negative			s/p I&D of surgical wound
Hip	*Staphylococcus epidermidis* (S)	Vancomycin	Doxycycline	0.5	Negative			s/p revision for fixation of migrated ETO fragment
Knee	Coagulase-negative Staphylococci (S)	Vancomycin	Doxycycline	6.5	*Staphylococcus epidermidis* (R)	6.5	*Staphylococcus epidermidis* (R)	s/p I&D modular exchange, on chronic doxycycline
Hip	Unknown (outside hospital)	Vancomycin	Doxycycline	0.8	No samples	1.2	Polymicrobial (R)	s/p resection arthroplasty
Knee	MSSA (S)	Cefazolin	Doxycycline	10.5	No samples	32.5	*Streptococcus bovis* (R)	s/p I&D modular exchange, s/p total femur, s/p 2 stage of total femur, on chronic suppression
Knee	Coagulase-negative Staphylococci (S)	Vancomycin	None	14.6	*Staphylococcus lugdunensis* (S)	14.6	*Staphylococcus lugdunensis* (S)	s/p AKA
Knee	*Staphylococcus epidermidis* (unk.)	Vancomycin	None	52.0	Group G *Streptococcus* (unk.)	52.0	Group G *Streptococcus* (unk.)	s/p I&D modular exchange, not on antibiotics
Hip	Coagulase-negative Staphylococci (S)	Cefazolin	None	0.5	*Hafnia spp.* (unk.)	62.7	Polymicrobial (S)	s/p repeat 2-stage exchange, on chronic TMP-sulfa
Hip	Polymicrobial (R)	Daptomycin	Doxycycline	2.4	Negative	2.7	Negative	s/p multiple I&D with proximal body exchange, on fluconazole for 1 y
Hip	*Candida albicans*	PO doxycycline	Doxycycline (and fluconazole)	10.7	Negative	10.7	Negative	s/p repeat 2-stage exchange, on doxycycline
Hip	*Staphylococcus lugdunensis* (S)	Nafcillin	None	0.1	No samples	1.2	Coagulase-negative Staphylococci (S)	s/p repeat 2-stage exchange, not on chronic antibiotics
Knee	Coagulase-negative Staphylococci (R)	Vancomycin	Doxycycline	0.7	*Staphylococcus epidermidis* (R)	0.7	*Staphylococcus epidermidis* (R)	s/p I&D and femoral revision, on chronic doxycycline

(*continued on next page*)

Table 4 (*continued*)

Joint	Original Infecting Organism (Susceptibility, to Tetracyclines Unless Otherwise Specified)	IV Antibiotics	Antibiotic at Stage 2	Time to First Repeat Surgery (mo)	Microbiology at First Repeat Surgery (Susceptibility, to Tetracyclines Unless Otherwise Specified)	Time to First Recurrent PJI (mo)	Microbiology of Recurrent PJI (Susceptibility, to Tetracyclines Unless Otherwise Specified)	Surgery Details and Current Status
Hip	MRSA (S)	Vancomycin	None	0.5	MRSA (S)	0.5	MRSA (S)	s/p repeat 2-stage exchange, s/p resection arthroplasty
Hip	*Staphylococcus capitis/caprae* (S)	Cefazolin	Doxycycline	9.3	No samples			s/p hardware removal
Knee	*Enterobacter cloacae* (sensitive to quinolones)	Vancomycin	Levofloxacin	28.9	*Staphylococcus epidermidis* (R to levofloxacin)	28.9	*Staphylococcus epidermidis* (R to levofloxacin)	s/p AKA
Knee	Coagulase-negative Staphylococci (R)	Vancomycin	None	63.4	MSSA (S)	63.4	MSSA (S)	s/p repeat 2-stage exchange, not on antibiotics
Hip	*Staphylococcus capitis/caprae* (S)	Vancomycin	Doxycycline	1.2	*Staphylococcus epidermidis* (R)	1.1	*Staphylococcus epidermidis* (R)	s/p I&D with femoral component revision, on chronic clindamycin
Hip	*Corynebacterium striatum/simulans* (R)	Daptomycin and Zosyn	Doxycycline	1.7	Polymicrobial (R)	1.7	Polymicrobial (R)	s/p repeat 2-stage exchange, on chronic tedizolid
Knee	*Streptococcus mitis* (intermediate to penicillin)	Ceftriaxone	Amoxicillin	19.6	*Streptococcus mitis* (intermediate to penicillin)	19.6	*Streptococcus mitis* (intermediate to penicillin)	s/p I&D modular exchange, s/p AKA
Hip	*Staphylococcus epidermidis* (S)	Vancomycin	Doxycycline	2.5	Negative	2.5	Negative	s/p repeat spacer, has not been reimplanted
Hip	Pseudomonas aeruginosa	Cefepime and Vancomycin	Doxycycline	5.6	No samples			s/p conversion to constrained liner
Knee	MSSA (S)	Vancomycin	Doxycycline	1.6	*Staphylococcus epidermidis* (R)	1.6	*Staphylococcus epidermidis* (R)	s/p I&D modular exchange with extensor mechanism reconstruction, on chronic TMP-sulfa
Knee	*Enterobacter cloacae* (unk.)	Cefepime and Vancomycin	Doxycycline	3.3	*Staphylococcus epidermidis* (R)	3.3	*Staphylococcus epidermidis* (R)	s/p I&D ×3, then repeat 2-stage exchange, not on chronic suppression
Knee	*Corynebacterium striatum/simulans* (R)	Vancomycin and Levofloxacin	Doxycycline	13.0	Negative	13.0	Negative	s/p I&D modular exchange, s/p AKA
Knee	*Staphylococcus epidermidis* (R)	Vancomycin	Doxycycline	2.0	Negative			s/p revision for failure of compress device
Hip	Culture negative	Ceftriaxone	Doxycycline	16.3	*Staphylococcus caprae* (S)	16.3	*Staphylococcus caprae* (S)	s/p I&D with modular exchange, on chronic doxycycline
Knee	Culture negative	Vancomycin and Ceftriaxone	Doxycycline	1.7	Negative	3.1	Group B *Streptococcus* (unk.)	s/p I&D with extensor mechanism reconstruction, on amoxicillin for undetermined duration
Hip	*Enterococcus faecalis* (R)	Ampicillin	Doxycycline	0.9	Polymicrobial (R)	0.9	Polymicrobial (R)	s/p I&D, on chronic doxycycline
Knee	Culture negative	Vancomycin	Doxycycline	9.2	Negative			s/p ORIF periprosthetic distal femur fracture
Knee	*Anaerococcus vaginalis* (unk.)	Penicillin	Doxycycline	1.9	Coagulase-negative Staphylococci (unk.)	1.9	Coagulase-negative Staphylococci (unk.)	s/p I&D modular exchange, not on chronic antibiotics
Knee	*Cutibacterium acnes* (S)	Cefazolin	Doxycycline	10.2	*Staphylococcus epidermidis* (R)	10.2	*Staphylococcus epidermidis* (R)	s/p repeat 2-stage exchange, not reimplanted

I&D, irrigation and debridement; AKA, above knee amputation; DFR, distal femoral replacement.

approach to PJI [6,7]. Unfortunately, the increased use of antibiotics may lead to antibiotic resistance, which was not evaluated in any of the previous studies. Therefore, we performed a retrospective review of patients who underwent 2-stage exchange to determine if oral antibiotics at the time of second-stage reimplantation led to the development of drug-resistant organisms in any subsequent recurrent PJIs.

Our data demonstrate that putting patients on oral antibiotics after their second-stage exchange for PJI increases the risk that any subsequent PJI in those patients will be with organisms resistant to the antibiotic used. At the time of first subsequent surgery for any reason following 2-stage exchange, 11 of 33 (33%) patients who received oral antibiotics had infection with a resistant organism. When we looked at all time points going forward, 24 patients who received antibiotics eventually developed recurrent PJI, and 16 of those recurrent infections were with organisms resistant to the antibiotic given after stage 2. There were no doxycycline-resistant organisms found in patients who did not receive oral antibiotics at the time of second-stage reimplantation.

The results of our study are consistent with previous literature demonstrating a lower rate of recurrent PJI in patients who receive antibiotics at second-stage reimplantation [7–9]. In our cohort, 15% of patients who received antibiotics at second-stage reimplantation developed recurrent PJI compared with 21% of patients who did not receive antibiotics. Although this was not statistically significant ($P = .35$), our results may be subject to selection bias as the higher risk patients may have been more likely to receive antibiotics; therefore, the trend in our data may be underestimated. These results are consistent with the updated results of the multicenter

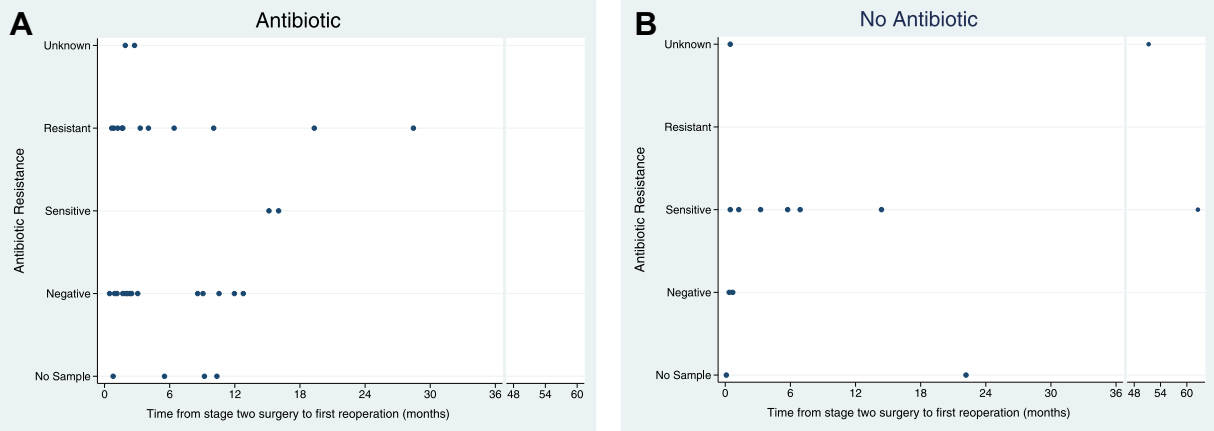

Fig. 2. Time from stage 2 surgery to first reoperation by antibiotic resistance for patients who received an oral antibiotic (A) and patients who did not (B).

randomized controlled trial with 2-year follow-up, which demonstrated 13% of patients who received antibiotics failed due to further infection compared with 29% of patients who did not receive antibiotics ($P = .012$) [7].

Determining the effect of a particular episode of antimicrobial treatment on subsequent drug resistance is not straightforward. Many of our patients have chronic conditions that expose them to health care settings, procedures, and antibiotics, any of which can put them at increased risk for acquiring drug-resistant pathogens. For this reason, we looked at microbiologic data from the first subsequent surgery, reasoning that these data would be less confounded by patients undergoing multiple operations and inpatient hospital stays before their diagnosis of recurrent PJI. Of the 33 patients who were treated with antibiotics and had subsequent surgery, we identified a drug-resistant infection at the first surgery in 11 patients (33.3%). Fourteen of 33 (42.4%) patients who received oral antibiotics at second-stage surgery had negative cultures compared with only 2 of 13 (15.4%) in the group who did not receive antibiotics. When we use PJI diagnosis as the endpoint, an additional 5 patients (16 in total) developed a drug-resistant PJI. These 5 patients had further surgery and hospital admissions between their first subsequent surgery and the surgery when diagnosed with PJI that may contribute to drug resistance. However, it is plausible that the oral antibiotic caused more negative cultures initially, but eventually a drug-resistant PJI declared itself (Fig. 2).

Staphylococcus epidermidis resistant to doxycycline was isolated in 8 of the 24 patients with recurrent PJI who received doxycycline after second-stage reimplantation (Fig. 3). This change in susceptibility profile is not explained by a change in our local antibiogram, as >85% of our coagulase-negative staphylococci remain susceptible to doxycycline. Most likely, the use of doxycycline causes these patients to become colonized with doxycycline-resistant *S. epidermidis*, which subsequently causes infection. This hypothesis is supported by the fact that nearly all recurrent infections were with a different organism. Although losing the use of a single antibiotic may seem unimportant, doxycycline is one of the safest and best tolerated antibiotics for long-term use. Because many patients with recurrent PJI are ultimately put on indefinite oral "suppression," losing doxycycline creates significant challenges. Coagulase-negative staphylococci are one of the most common causes of PJI [11], and they are frequently resistant to beta-lactams, clindamycin, and trimethoprim-sulfamethoxazole, leaving doxycycline and linezolid as the only oral antibiotics with reliable activity against these bacteria [12–14]. As long-term use of linezolid can lead to neuropathy and cytopenia, doxycycline is often the drug of choice for long-term suppression in these patients.

It is certainly possible that the risk of becoming colonized with resistant organisms is particularly high with doxycycline and would be lower with a different antibiotic. Intriguingly, the one patient with recurrent PJI who had received levofloxacin ended up getting infected with levofloxacin-resistant (but doxycycline-sensitive) *Staphylococcus epidermidis* (Table 4). Data from other institutions that have, for example, chosen to give trimethoprim-sulfamethoxazole as prophylaxis after second-stage revision could show whether the same problem exists (ie, their patients have a higher rate of subsequent infection with organisms resistant to trimethoprim-sulfamethoxazole).

Our article has several limitations. With the retrospective design of the study, there are inherent selection biases in the treatment we chose for each patient. This bias is particularly relevant when we analyze our rate of recurrent PJI, as before 2017, high-risk patients were more likely to receive oral antibiotics following 2-stage exchange; after 2017, oral antibiotics at the time of second-stage reimplantation became routine for all patients. Second, Yang et al. described adverse events in 6 of a total 43 patients who received doxycycline that led to discontinuation in 4 patients [7]. We did not adjust for patient adherence with antibiotic treatment. Third, the use of vancomycin powder is variable between the 5 surgeons who cared for patients in this study, and we could not reliably control for this with our retrospective data. Fourth, the patients who did not receive antibiotics had longer period of follow-up, which could inflate the rate of PJI; however, all patients had a minimum of 1-year follow-up, and the mean follow-up time was >2 years. Fifth, 4 patients did not have susceptibility data, and 6 patients did not have cultures from their first subsequent surgery. Three of the 6 patients without cultures taken at their first subsequent surgery ultimately developed a recurrent PJI. Finally, as this study used a sample size of convenience, taking all available cases, it was underpowered to detect a significant difference in the rate of subsequent PJI.

Conclusion

Prolonged oral antibiotics after 2-stage exchange increase drug resistance to that antibiotic in subsequent PJI. Although we found a non-significant trend toward reduction in the rate of recurrent PJI with the use of prolonged oral antibiotics, we recommend further

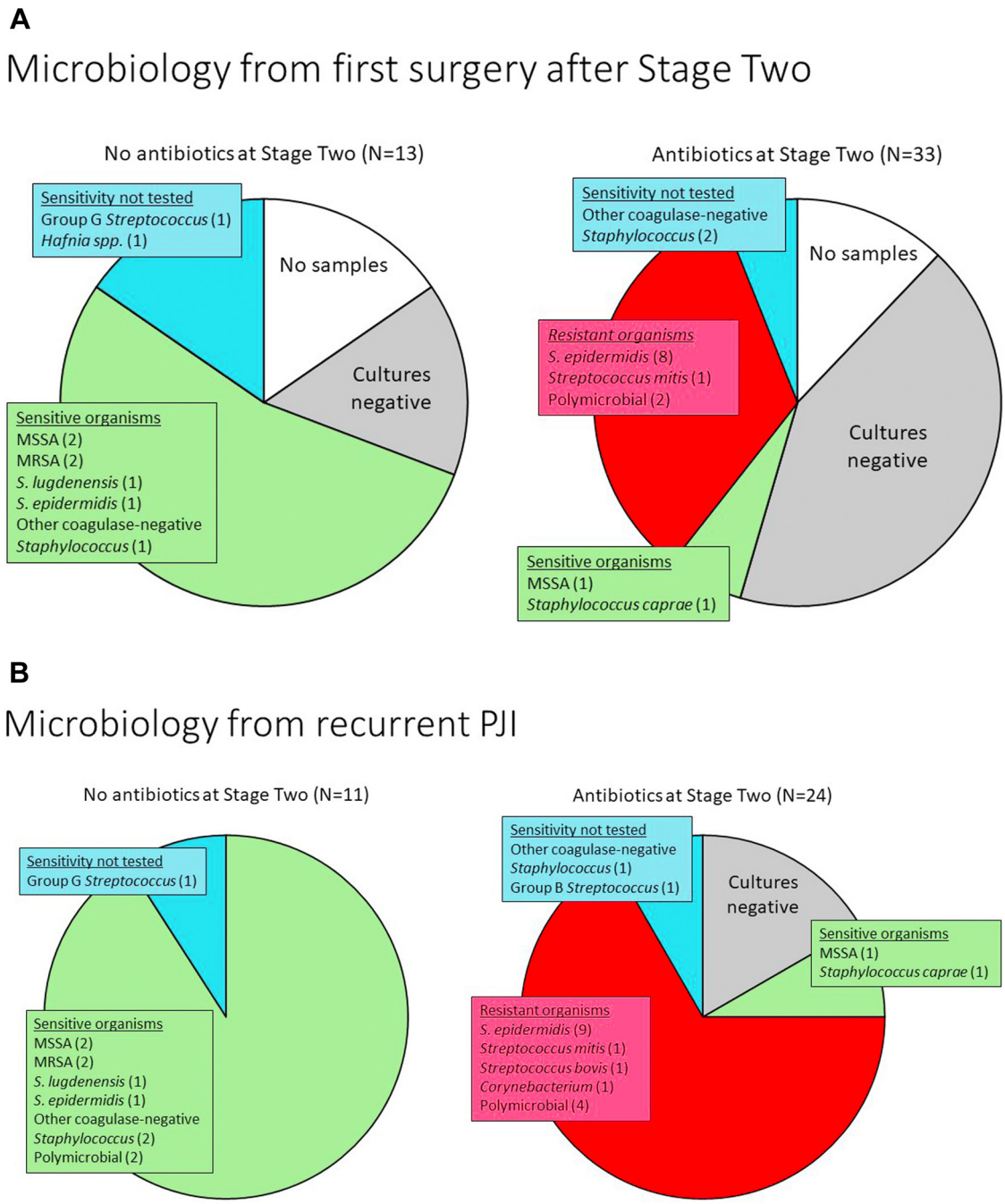

Fig. 3. Microbiology from first surgery after Stage 2 (A) and microbiology from recurrent PJI (B).

research in the area to refine antimicrobial protocols as we consider the risks and benefits of prolonged antibiotic treatment.

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