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Effect of Antibiotic Spacer Dosing on Treatment Success in Two-Stage Exchange for Periprosthetic Joint Infection

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ABSTRACT

Introduction: In two-stage exchange for periprosthetic joint infection (PJI), adding antibiotics to cement spacers is the standard of care; however, little is known about optimal dosage. There is emphasis on using >3.6 g of total antibiotic, including ≥2.0 g of vancomycin, per 40 g of cement, but these recommendations lack clinical evidence. We examined whether recommended antibiotic spacer doses affect treatment success.

Methods: This was a retrospective review of 202 patients who underwent two-stage exchange for PJI from 2004 to 2020 with at least 1-year follow-up. Patients were separated into high (>3.6 g of total antibiotic per 40 g of cement) and low-dose spacer groups. Primary outcomes were overall and infectious failure.

Results: High-dose spacers were used in 80% (162/202) of patients. High-dose spacers had a reduced risk of overall (OR, 0.37; $P = 0.024$) and infectious (OR, 0.35; $P = 0.020$) failure for infected primary arthroplasties, but not revisions. In multivariate analysis, vancomycin dose ≥2.0 g decreased the risk of infectious failure (OR, 0.31; $P = 0.016$), although not overall failure (OR, 0.51; $P = 0.147$).

Conclusion: During two-stage exchange for PJI, spacers with greater than 3.6 g of total antibiotic may reduce overall and infectious failure for infected primary arthroplasties. Furthermore, using at least 2.0 g of vancomycin could independently decrease the risk of infectious failure.

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Periprosthetic joint infection (PJI) is one of the most devastating and costly complications after total joint arthroplasty.[1,2] The standard of care for chronic PJI in North America is two-stage exchange arthroplasty, where implants are explanted and replaced with an antibiotic spacer. The spacer is designed to elute antibiotics locally from its cement substrate and stays in place during a course of systemic antibiotics; then it is removed with new implants implanted at a later date.[3,4] Reported success rates for this procedure are variable, historically ranging from 65% to 100%,

although more recent studies suggest we may be overestimating success in two-stage exchange for PJI, especially when not accounting for patients who never make it to the second stage.[5-8]

The addition of thermally stable antibiotics to cement spacers, such as aminoglycosides or vancomycin, allows for the local delivery of high-concentration antibiotics that can exceed levels obtained by systemic antibiotics alone.[9] However, the choice and dose of antibiotics used in spacers during two-stage exchange varies widely.[10] Experts and professional societies recommend the use of high-dose antibiotic cement spacers, defined as greater than 3.6 g of antibiotic per 40 g bag of cement, but these recommendations are based off in vitro studies and lack supporting clinical evidence.[10-12] Others have recommended at least 2.0 g of vancomycin and 2.4 g of an aminoglycoside per 40 g bag of cement, but again, these suggestions have no clinical data to support them.[3,10] Furthermore, antibiotic elution from the spacer varies depending on the viscosity of the cement used, with higher viscosity cement demonstrating superior elution characteristics.[13]

Understanding how antibiotic spacer dosing affects clinical outcomes has important implications for increasing the likelihood of success in two-stage exchange and minimizing the potential for adverse effects, such as acute kidney injury (AKI).[14] Our primary question is whether commonly recommended antibiotic doses in cement spacers affect overall or infectious treatment failure. We secondarily seek to evaluate their effect on reimplantation, mortality, and readmission for acute renal injury or failure.

Methods

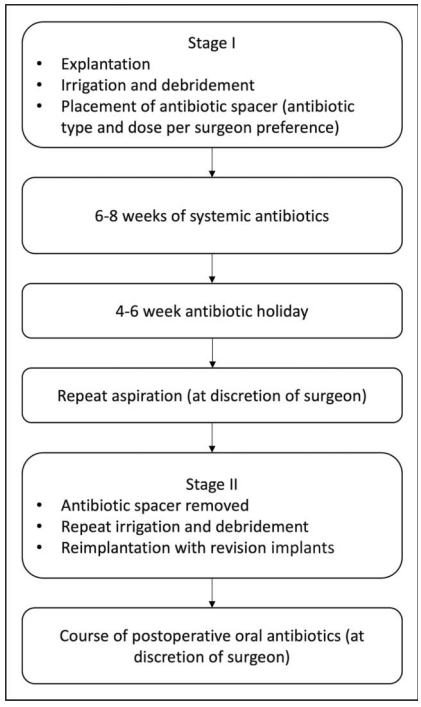
This was a retrospective review conducted at a single institution for all patients who underwent two-stage exchange arthroplasty from 2004 to 2020 for PJI based on the definition created by the Musculoskeletal Infection Society (MSIS).[15] The study attained institutional review board exemption. Exclusion criteria were patients with a megaprosthesis, those with a fungal infection, those who did not have information on specific antibiotic spacer dosing, and those with a history of prior PJI with spacer placement. Patients with a history of surgical site infection or PJI who only underwent irrigation and débridement were included. All patients were required to have a minimum of 1-year follow-up after initial spacer placement. After exclusion of 58 cases based on these criteria, the final cohort included a total of 202 PJIs. The cohort comprised 56 primary total hip arthroplasties, 79 primary total knee arthroplasties, 27 revision total hip arthroplasties, and 40 revision total knee arthroplasties.

Patients were separated into high and low-dose groups based on the definition of high-dose antibiotic spacers as containing greater than 3.6 g of total antibiotic per 40 g of cement.[12]

Surgical Technique

Our treatment protocol is demonstrated in Figure 1. For all patients, a thorough synovectomy and débridement with at least 9 L of fluid was performed. Additional antimicrobial irrigation solutions were used at the discretion of the treating surgeon. An antibiotic spacer was placed. The choice and dose of the antibiotic used in the spacer was based on surgeon preference. The decision to use an articulating or static spacer was also based on surgeon discretion. Articulating spacers were fashioned by hand, made from preformed molds, or included prosthetic implants comprising metal and/or polyethylene. Among articulating spacers, 69% (78/113) contained metal and/or polyethylene components. A total of 6 to 8 weeks of systemic antibiotics was administered based on the culture results and recommendations by an infectious disease consultant. In

Figure 1



Flowchart showing a summary of the treatment protocol for periprosthetic joint infection.

addition, the serum erythrocyte sedimentation rate and C-reactive protein were trended. An antibiotic holiday period of 4 to 6 weeks was routinely used before reimplantation, during which time clinical symptoms were monitored. Repeat aspiration during this period was based on the decision of the surgeon because there was no institutional protocol to determine timing of reimplantation. Repeat débridement was performed at the time of reimplantation, and revision implants were used. Administration of extended postoperative oral antibiotics was the decision of the treating surgeon.

Outcome Variables

A retrospective chart review was conducted to obtain surgical details, including type and dose of antibiotic used in spacers, cement type, dates and clinical course of any subsequent surgeries after initial spacer placement, need for amputation, hospital readmissions for AKI or acute renal failure, mortality, organism culture information, and use of extended postoperative oral antibiotics which was defined as use for ≥3 months after reimplantation. For preloaded antibiotic cement, the type and dose of the preloaded antibiotic was included in calculations of the antibiotic dose. Antibiotic-resistant organisms included vancomycin-resistant *Enterococcus* and methicillin resistant *Staphylococcus aureus*. An electronic query of the medical record was also conducted to extract details on age, sex, body mass index, comorbidities, tobacco use, alcohol use, and drug use. Patients were classified as A, B, or C hosts according to the McPherson classification for systemic host grade.[16]

Primary and Secondary Outcomes

The primary outcomes were overall treatment failure and treatment failure for infectious reasons. Overall treatment success was based on a recent definition from the MSIS.[17] Tier 1 or 2 were defined as a success while Tier 3 or 4 were defined as failure, which included patients who were not reimplanted, died, or underwent any unplanned revision surgeries (Table 1). Treatment failure for infection included any repeat irrigation and débridement, spacer exchange, or amputation. Secondary outcomes included mortality, failure to undergo reimplantation, and readmission for AKI or acute renal failure. Subanalyses were run for infected primaries, infected revisions, high-viscosity cement spacers, and low-viscosity cement spacers.

Statistical Analysis

All statistical analyses were conducted using SPSS (Version 21.0, IBM). Continuous variables were evaluated using Student *t*-test or Mann-Whitney *U* tests as

Table 1. Treatment Success Definition

Success	Tier 1	Infection control with no continued antibiotic therapy
	Tier 2	Infection control with the patient on suppressive antibiotic therapy
Failure	Tier 3	Need for revision surgery and/or revision and/or spacer retention (assigned to subgroups A, B, C, D, E, and F based on the type of revision surgery)
	A	Aseptic revision at >1 yr from initiation of PJI treatment
	B	Septic revision (including débridement, antibiotics, and implant retention [DAIR]) at >1 year from initiation of PJI treatment (excluding amputation, resection arthroplasty, and arthrodesis)
	C	Aseptic revision at ≤1 yr from initiation of PJI treatment
	D	Septic revision (including DAIR) at ≤1 year from initiation of PJI treatment (excluding amputation, resection arthroplasty, and arthrodesis)
	E	Amputation, resection arthroplasty, or arthrodesis
	F	Retained spacer
	Tier 4	Death (assigned to subgroups A or B)
	A	Death <1 yr from initiation of PJI treatment
	B	Death >1 yr from initiation of PJI treatment

PJI = periprosthetic joint infection

appropriate. Categorical variables were assessed using a Fisher exact test or chi square test, and odds ratios were calculated.

Univariate analyses were conducted to compare demographic and other perioperative variables. Individual vancomycin and aminoglycoside doses were used as predictive variables in univariate analyses. Cutoffs of ≥2.0 g for vancomycin and ≥2.4 g for aminoglycoside were used based on published dosage recommendations per 40 g bag of cement.[3] A multivariate logistic regression model was used to determine risk factors for the primary outcomes, overall treatment failure, and treatment failure for infection. The logistic regression included demographic variables, baseline characteristics that differed between high and low-dose groups, information on the infecting organism, and variables below a *P*-value threshold of 0.2 in univariate analysis. Final variables included in the model for overall failure were female sex, age older than 80 years, knee, infected primary, static spacer, high-viscosity cement, diabetes mellitus, hypothyroidism, renal failure, alcohol abuse, drug abuse, tobacco use, gram-positive, gram-negative, polymicrobial, resistant organism, and culture-negative. Final variables included in the model for infectious failure were female sex, age older than 80 years, knee, infected primary, static spacer, high-viscosity cement, renal failure, liver disease, alcohol abuse, drug abuse, tobacco use, gram-positive, gram-negative, polymicrobial, resistant organism, and culture-negative. Separate regression analyses were run for total antibiotic dose and for individual vancomycin and aminoglycoside doses.

To investigate the full spectrum of total and individual antibiotic doses, sequential antibiotic dose thresholds were entered into the regression models for overall and infectious failure (eg, dose ≥1 g, dose ≥2 g, dose ≥3 g). This was done separately for the total antibiotic dose, vancomycin dose, and aminoglycoside dose. For all analyses, an alpha of 0.05 was used to determine statistical significance.

Results

In our cohort, 80% (n = 162) of patients received a high-dose spacer (>3.6 g of total antibiotic per 40 g of cement), and 20% (n = 40) received a low-dose spacer. High-dose spacers were more likely to contain tobramycin (92% versus 80%, $P = 0.026$) and to be composed of high-viscosity cement ($P < 0.001$). Regarding the infecting organism in the overall cohort, 74% (150/202) of infections were caused by gram-positive bacteria, 14% (28/202) were gram-negative bacteria, 14% (28/202) were polymicrobial, 29% (58/202) were resistant, and 17% (35/202) were culture-negative. No significant differences were observed in baseline demographics or comorbidities between high and low-dose groups (Table 2).

The overall treatment failure rate for the entire cohort was 43% (87/202), and the infectious failure rate was 31% (63/202). No significant difference was observed in the overall (40% versus 55%, $P = 0.089$) or infectious (28% versus 43%; $P = 0.085$) failure rate between high and low-dose groups when considering primary and revision infections together; however, for primary infections, high-dose antibiotic cement spacers were associated with lower odds of overall failure (OR, 0.37; 95% CI, 0.15 to 0.89; $P = 0.024$) and infectious failure (OR, 0.35; 95% CI, 0.14 to 0.86; $P = 0.020$). No differences were noted in overall or infectious failure when analyzing high-viscosity cement spacers separately; however, there was an increased overall failure rate in low-dose and low-viscosity cement spacers (OR, 0.30; 95% CI, 0.10 to 0.92; $P = 0.033$) (Table 3).

In multivariate analysis, use of a high-dose total antibiotic in spacers was not significantly associated with overall (OR, 0.71; 95% CI, 0.30 to 1.67; $P = 0.427$) or infectious (OR, 0.53; 95% CI, 0.21 to 1.32; $P = 0.172$) failure. High individual vancomycin dose (≥2.0 g of antibiotic per 40 g of cement) did not reduce the risk of overall treatment failure (OR, 0.51; 95% CI, 0.21 to 1.27; $P = 0.147$), but it was associated with a decreased risk of infectious failure (OR, 0.31; 95% CI, 0.12 to 0.81; $P = 0.016$). High individual aminoglycoside dose (≥2.4 g of antibiotic per 40 g of cement) was not associated with a reduced risk of overall (OR, 1.11; 95% CI, 0.54 to 2.29; $P = 0.785$) or infectious (OR, 1.28; 95% CI, 0.58 to 2.80; $P = 0.539$) failure. Alcohol use disorder was a predictor of infectious failure (OR, 5.61; 95% CI, 1.25 to 25.16; $P = 0.024$) (Tables 4 and 5).

On evaluation of sequential total and individual antibiotic dose thresholds in the regression models for overall and infectious failure, no dose threshold demonstrated statistical significance, except for vancomycin dose ≥2.0 g for infectious failure (OR, 0.31; 95% CI, 0.12 to 0.81; $P = 0.016$) (Table 6). No significant differences were found in rates of reimplantation, mortality, or readmissions for AKI or ARF between high and low-dose groups (Table 3).

Of patients who underwent reimplantation, 65% (112/171) received at least 3 months of postoperative oral antibiotics and 23% (39/171) were placed on lifelong

Table 2. Demographics and Characteristics of High and Low-Dose Groups

	High-dose (n = 162)	Low-dose (n = 40)	*P*
Female	50.6% (82/162)	55.0% (22/40)	0.619
Age (yr)	63.6 ± 10.7	63.2 ± 11.6	0.818
Knee	59.9% (97/162)	55.0% (22/40)	0.575
Infected primary	67.9% (110/162)	62.5% (25/40)	0.516
Antibiotics in spacer			
Vancomycin	99.4% (161/162)	100.0% (40/40)	0.618
Cefazolin	6.2% (10/162)	0.0% (0/40)	0.107
Tobramycin	92.0% (149/162)	80.0% (32/40)	**0.026**
Gentamicin	20.4% (33/162)	7.5% (3/40)	0.057
Static spacer	42.6% (69/162)	50.0% (20/40)	0.398
Cement			**<0.001**
High-viscosity	82.1% (133/162)	37.5% (15/40)	
Low-viscosity	16.0% (26/162)	55.0% (22/40)	
Unknown	1.9% (3/162)	7.5% (3/40)	
≥3 mo postop antibiotics	66.4% (93/140)	61.3% (19/31)	0.586
BMI	30.3 ± 8.1	29.9 ± 6.5	0.751
Diabetes mellitus	16.1% (26/162)	22.5% (9/40)	0.334
Hypothyroid	10.5% (17/162)	7.5% (3/40)	0.570
Renal failure	16.7% (27/162)	27.5% (11/40)	0.116
Liver disease	13.0% (21/162)	7.5% (3/40)	0.339
AIDS	0.6% (1/162)	0.0% (0/40)	0.618
Rheumatological disease	6.2% (10/162)	0.0% (0/40)	0.107
Alcohol abuse	4.9% (8/162)	12.5% (5/40)	0.081
Drug abuse	7.4% (12/162)	12.5% (5/40)	0.299
Psychosis	1.3% (2/162)	5.0% (2/40)	0.126
Depression	27.8% (45/162)	35.0% (14/40)	0.368
Tobacco use	9.3% (15/162)	12.5% (5/40)	0.539
ASA score	2.6 ± 0.6	2.5 ± 0.7	0.227
Host grade			0.401
A	46.9% (76/162)	37.5% (15/40)	
B	47.5% (77/162)	52.5% (21/40)	
C	5.6% (9/162)	10.0% (4/40)	
Organism			
Gram-positive	75.9% (123/162)	67.5% (27/40)	0.275
Gram-negative	14.8% (24/162)	10.0% (4/40)	0.430
Polymicrobial	14.2% (23/162)	12.5% (5/40)	0.781
Resistant organisms	27.8% (45/162)	32.5% (13/40)	0.554
Culture-negative	14.8% (24/162)	27.5% (11/40)	0.058

Bolded entries denote statistical significance at $p<0.05$

Table 3. Primary and Secondary Outcomes for High and Low-Dose Groups

	High-Dose	Low-Dose	Odds Ratio	*P*
Overall failure				
Overall	40.1% (65/162)	55.0% (22/40)	0.55 (0.27-1.10)	0.089
Primary	35.5% (39/110)	60.0% (15/25)	0.37 (0.15-0.89)	**0.024**
Revision	50.0% (26/52)	46.7% (7/15)	1.14 (0.36-3.61)	0.820
High-viscosity cement	42.1% (56/133)	46.7% (7/15)	0.83 (0.29-2.43)	0.735
Low-viscosity cement	31.0% (9/29)	60.0% (15/25)	0.30 (0.10-0.92)	**0.033**
Infectious failure				
Overall	28.4% (46/162)	42.5% (17/40)	0.54 (0.26-1.10)	0.085
Primary	24.6% (27/110)	48% (12/25)	0.35 (0.14-0.86)	**0.020**
Revision	36.5% (19/52)	33.3% (5/15)	1.15 (0.34-3.87)	0.820
High-viscosity cement	30.1% (40/133)	40.0% (6/15)	0.65 (0.22-1.93)	0.431
Low-viscosity cement	20.7% (6/29)	44.0% (11/25)	0.33 (0.10-1.10)	0.066
No reimplantation				
Overall	13.6% (22/162)	22.5% (9/40)	0.54 (0.23-1.29)	0.161
Primary	11.8% (13/110)	20.0% (5/25)	0.54 (0.17-1.67)	0.277
Revision	17.3% (9/52)	26.7% (4/15)	0.58 (0.15-2.22)	0.419
High-viscosity cement	15.0% (20/133)	33.3% (5/15)	0.35 (0.11-1.15)	0.073
Low-viscosity cement	6.9% (2/29)	16.0% (4/25)	0.39 (0.07-2.33)	0.289
Mortality				
Overall	4.9% (8/162)	5.0% (2/40)	0.99 (0.20-4.84)	0.987
Primary	3.6% (4/110)	8.0% (2/25)	0.43 (0.08-2.51)	0.339
Revision	7.7% (4/52)	0.0% (0/15)	2.88 (0.15-56.47)	0.268
High-viscosity cement	4.5% (6/133)	0.0% (0/15)	1.58 (0.09-29.43)	0.401
Low-viscosity cement	6.9% (2/29)	8.0% (2/25)	0.85 (0.11-6.53)	0.877
Readmission for AKI/ARF				
Overall	3.1% (5/162)	7.5% (3/40)	0.39 (0.09-1.72)	0.200
Primary	2.7% (3/110)	4.0% (1/25)	0.67 (0.07-6.75)	0.735
Revision	3.8% (2/52)	13.3% (2/15)	0.26 (0.03-2.03)	0.172
High-viscosity cement	3.8% (5/133)	13.3% (2/15)	0.25 (0.05-1.44)	0.098
Low-viscosity cement	0.0% (0/29)	4.0% (1/25)	—	—

AKI = acute kidney injury, ARF = acute renal failure
Bolded entries denote statistical significance at $p<0.05$

suppression. No difference was observed in the proportion of patients receiving extended postoperative oral antibiotics between high and low-dose spacer groups (Table 2). After exclusion of patients who received at least 3 months of post-reimplantation oral antibiotics without being placed on lifelong suppression (n = 93), there were no notable differences in the results. Vancomycin dose ≥2.0 g remained a significant predictor of infectious failure (OR, 0.163; 95% CI, 0.04 to 0.71; P = 0.016).

Discussion

In two-stage exchange arthroplasty for PJI, the addition of antibiotics to cement spacers is a commonly accepted practice, but clinical knowledge on the most effective type and dose of antibiotics is lacking. We found that high-dose spacers with greater than 3.6 g of total antibiotic per 40 g of cement may reduce overall and infectious failure for infected primary arthro-

Table 4. Multivariate Analysis for Overall Failure

	Odds Ratio (95% CI)	*P*
Total antibiotic dose		
Female	1.405 (0.738-2.675)	0.300
Age >80 yr	1.348 (0.393-4.623)	0.635
Knee	0.945 (0.488-1.831)	0.867
Infected primary	0.750 (0.374-1.505)	0.418
Total antibiotic dose >3.6 g	0.705 (0.297-1.671)	0.427
Static spacer	1.750 (0.900-3.402)	0.099
High-viscosity cement	1.042 (0.474-2.291)	0.919
Diabetes mellitus	1.265 (0.539-2.967)	0.589
Hypothyroid	0.655 (0.216-1.990)	0.456
Renal failure	2.111 (0.939-4.748)	0.071
Alcohol abuse	3.716 (0.929-14.864)	0.063
Drug abuse	1.909 (0.599-6.091)	0.274
Tobacco use	1.593 (0.550-4.614)	0.391
Gram-positive	0.656 (0.090-4.775)	0.677
Gram-negative	1.228 (0.227-6.662)	0.811
Polymicrobial	1.810 (0.576-5.686)	0.310
Resistant organisms	2.003 (0.955-4.203)	0.066
Culture-negative	1.113 (0.140-8.873)	0.920
Individual vancomycin and aminoglycoside doses		
Female	1.419 (0.745-2.704)	0.287
Age >80 yr	1.329 (0.385-4.591)	0.653
Knee	0.958 (0.488-1.881)	0.901
Infected primary	0.753 (0.376-1.511)	0.425
Vancomycin dose ≥2.0 g	0.511 (0.206-1.266)	0.147
Aminoglycoside dose ≥2.4 g	1.107 (0.535-2.290)	0.785
Static spacer	1.771 (0.903-3.474)	0.096
High-viscosity cement	1.115 (0.511-2.432)	0.784
Diabetes mellitus	1.280 (0.541-3.029)	0.574
Hypothyroid	0.663 (0.216-2.040)	0.474
Renal failure	2.159 (0.964-4.835)	0.061
Alcohol abuse	3.614 (0.885-14.753)	0.073
Drug abuse	1.848 (0.574-5.947)	0.303
Tobacco use	1.709 (0.587-4.980)	0.326
Gram-positive	0.674 (0.092-4.940)	0.698
Gram-negative	1.246 (0.227-6.835)	0.800
Polymicrobial	1.763 (0.559-5.558)	0.333
Resistant organisms	1.990 (0.946-4.186)	0.070
Culture negative	1.143 (0.142-9.175)	0.900

Table 5. Multivariate Analysis for Infectious Failure

	Odds Ratio (95% CI)	*P*
Total antibiotic dose		
Female	1.009 (0.510-1.995)	0.979
Age >80 yr	0.391 (0.075-2.042)	0.266
Knee	1.765 (0.846-3.683)	0.130
Infected primary	0.763 (0.364-1.602)	0.475
Total antibiotic dose >3.6 g	0.527 (0.210-1.321)	0.172
Static spacer	1.653 (0.819-3.334)	0.161
High-viscosity cement	1.495 (0.628-3.559)	0.363
Renal failure	1.382 (0.598-3.192)	0.449
Liver disease	1.689 (0.590-4.835)	0.328
Alcohol abuse	5.609 (1.250-25.163)	**0.024**
Drug abuse	2.738 (0.868-8.643)	0.086
Tobacco use	1.180 (0.393-3.546)	0.768
Gram-positive	1.711 (0.220-13.328)	0.608
Gram-negative	2.393 (0.434-13.195)	0.316
Polymicrobial	1.213 (0.357-4.128)	0.757
Resistant organisms	1.874 (0.856-4.100)	0.116
Culture-negative	2.703 (0.311-23.514)	0.368
Individual vancomycin and aminoglycoside doses		
Female	1.018 (0.511-2.028)	0.958
Age >80 yr	0.376 (0.071-1.985)	0.249
Knee	1.835 (0.862-3.907)	0.115
Infected primary	0.765 (0.364-1.608)	0.480
Vancomycin dose ≥2.0 g	0.310 (0.120-0.806)	**0.016**
Aminoglycoside dose ≥2.4 g	1.278 (0.584-2.800)	0.539
Static spacer	1.695 (0.824-3.485)	0.152
High-viscosity cement	1.694 (0.703-4.080)	0.240
Renal failure	1.422 (0.613-3.298)	0.413
Liver disease	1.768 (0.614-5.094)	0.291
Alcohol abuse	5.324 (1.138-24.894)	**0.034**
Drug abuse	2.583 (0.806-8.273)	0.110
Tobacco use	1.321 (0.431-4.050)	0.627
Gram-positive	1.811 (0.228-14.379)	0.574
Gram-negative	2.446 (0.434-13.790)	0.311
Polymicrobial	1.165 (0.340-3.988)	0.808
Resistant organisms	1.860 (0.841-4.112)	0.125
Culture-negative	2.840 (0.320-25.164)	0.348

Bolded entries denote statistical significance at $p<0.05$

Table 6. **Sequential Dose Thresholds of Total Antibiotic, Vancomycin, and Aminoglycoside for Overall and Infectious Failure**

	Odds Ratio (95% CI)	*P*
Overall failure		
Total ≥2.0 g	1.275 (0.127-12.832)	0.837
Total ≥3.0 g	0.644 (0.256-1.623)	0.351
Total ≥4.0 g	0.977 (0.414-2.304)	0.957
Total ≥5.0 g	0.950 (0.455-1.983)	0.890
Total ≥6.0 g	1.049 (0.406-2.709)	0.921
Total ≥7.0 g	1.173 (0.149-9.218)	0.879
Vancomycin ≥1.0 g	0.000000235 (0-∞)	0.986
Vancomycin ≥2.0 g	0.511 (0.206-1.266)	0.147
Vancomycin ≥3.0 g	1.075 (0.493-2.341)	0.856
Vancomycin ≥4.0 g	0.415 (0.066-2.608)	0.348
Aminoglycoside ≥1.0 g	0.810 (0.246-2.663)	0.729
Aminoglycoside ≥2.0 g	1.013 (0.498-2.062)	0.971
Aminoglycoside ≥3.0 g	1.216 (0.450-3.289)	0.700
Aminoglycoside ≥4.0 g	1.847 (0.293-11.633)	0.514
Infectious failure		
Total ≥2.0 g	0.729 (0.069-7.676)	0.792
Total ≥3.0 g	0.600 (0.224-1.608)	0.310
Total ≥4.0 g	0.650 (0.261-1.616)	0.353
Total ≥5.0 g	1.040 (0.471-2.298)	0.922
Total ≥6.0 g	1.113 (0.387-3.200)	0.843
Total ≥7.0 g	2.033 (0.232-17.837)	0.522
Vancomycin ≥1.0 g	0.0000000886 (0-∞)	0.985
Vancomycin ≥2.0 g	0.310 (0.120-0.806)	**0.016**
Vancomycin ≥3.0 g	1.107 (0.480-2.556)	0.811
Vancomycin ≥4.0 g	0.532 (0.080-3.518)	0.512
Aminoglycoside ≥1.0 g	0.717 (0.205-2.512)	0.603
Aminoglycoside ≥2.0 g	1.302 (0.605-2.801)	0.499
Aminoglycoside ≥3.0 g	1.282 (0.415-3.967)	0.666
Aminoglycoside ≥4.0 g	3.520 (0.507-24.411)	0.203

Bolded entries denote statistical significance at $p<0.05$

plasties, and a vancomycin dose of at least 2.0 g was independently associated with a reduced rate of infectious failure.

Current recommendations for antibiotic dosing in spacers for two-stage exchange include total antibiotic dose greater than 3.6 g, at least 2.0 g of vancomycin, and at least 2.4 g of aminoglycoside per 40 g bag of cement.[3,10-12] These suggestions are based largely off in vivo studies and expert opinion. A systematic review of antibiotic-loaded cement spacers in the treatment of PJI conducted by Iarikov et al[10] found no association between the antibiotic dose used in cement spacers and the success rates, although included studies were primarily smaller case series with heterogeneous patient populations, limited data on patient demographics and comorbidities, and variable definitions of treatment success. Another systematic review by Qiang et al[18] found no difference in reinfection rates with spacers that

contained more or less than 3.5 g of antibiotic used in the treatment of knee PJI, but this review was also limited by study heterogeneity. To our knowledge, this is the first study to evaluate the effect of antibiotic cement spacer dosing on treatment success in two-stage exchange for PJI at a single institution.

We found that high total antibiotic dose, defined as greater than 3.6 g of antibiotic per 40 g of cement, was not associated with treatment success in the overall cohort. However, among infected primary arthroplasties, high-dose spacers had reduced rates of overall and infectious failure, though the same was not seen for infected revision arthroplasties. Infections of revisions are generally more difficult to eradicate owing to the presence of more extensive instrumentation, poorer vascularization, and more resistant organisms. Because these infections are harder to treat at baseline, it may be expected that antibiotic spacer dosing would play a lesser role in treatment effect than for infected primaries.

In the overall cohort, a vancomycin dose of at least 2.0 g per 40 g of cement was associated with a reduced risk of infectious failure. Notably, vancomycin dose was not associated with a decreased risk of overall failure, likely because of the more encompassing MSIS definition of failure used in this study, which included patients who were not reimplanted, underwent unplanned revision surgery for any reason, or died.[17]

Our results suggest vancomycin dose may be a more important factor in infection clearance than overall antibiotic dose. This finding has several possible explanations. First of all, vancomycin has excellent gram-positive coverage,[19] and nearly three quarters of infections in this study were caused by gram-positive bacteria. Although aminoglycosides display broad-spectrum activity, including against *Staphylococcus*, their primary utility is against gram-negative organisms.[20] Furthermore, there are reports of high resistance to aminoglycosides among staphylococci isolated in PJI, ranging from 41% to 74%.[21,22]

In addition, tobramycin has better elution characteristics than vancomycin,[23] and as a result, its effects could be less dependent on the dosage in the spacer. Studies have also shown that higher antibiotic doses in cement do not necessarily lead to greater elution, and other factors, such as complex antibiotic-cement and antibiotic-antibiotic interactions, likely contribute.[24] Indeed, in vivo research shows that the addition of vancomycin and tobramycin to bone cement enhances the elution of both antibiotics compared with either alone[11]; therefore, aminoglycosides likely still play an important role in the composition of antibiotic spacers.

Another important factor in the composition of spacers is the viscosity of the cement used. High-viscosity cement has demonstrated enhanced elution characteristics compared with low-viscosity cement,[13] but prior systematic reviews evaluating antibiotic dosing in cement spacers have failed to account for this variable.[10,18] We found an increased risk of overall failure in low-dose and low-viscosity cement spacers. Given its inferior elution characteristics, antibiotic dose may be a more important factor in low-viscosity cement compared with high-viscosity cement; however, additional investigation is warranted.

Using higher doses of antibiotics in spacers can compromise the mechanical properties of the spacer and increase the risk of nephrotoxicity.[14,25,26] We did not find any difference in readmissions for AKI or ARF between high and low-dose antibiotic groups. However, we did not evaluate the actual incidence of AKI after spacer placement, but this has been well documented elsewhere. Dagneaux et al[14] found a twofold increase in risk of AKI if greater than 3.6 g of either vancomycin or aminoglycoside was used per batch of cement, emphasizing the importance of using the lowest effective dose of the antibiotic in cement spacers. We found that a vancomycin dose of at least 2.0 per 40 g of cement decreased the risk of infectious failure while higher threshold values did not, suggesting that using more than 2.0 g of vancomycin may confer additional risk without providing a clear clinical benefit.

Our study is subject to several limitations. First, it is retrospective in nature, and the clinical information collected is dependent on accurate and complete documentation. Furthermore, there is a degree of selection bias. For example, it is possible that older patients or those with worse baseline renal function received lower antibiotic doses in their spacers. It is also possible that patients with worse infections received higher doses or different combinations of antibiotics in their spacers. No baseline differences were noted in patient demographics, comorbidities, or the presence of resistant or polymicrobial infections between high and low-dose groups, and we controlled for these factors in multivariate analysis; still, the opportunity for selection bias remains. Notably, the high-dose group had markedly more patients who received high-viscosity cement, which has better elution characteristics than low-viscosity cement[13]; however, cement viscosity had no effect on overall or infectious failure in multivariate analysis. In addition, extended oral antibiotics were commonly used after reimplantation in our cohort, which can reduce reinfection rates.[27] Possibly, this practice could delay diagnosis of failure beyond our minimum 1-year follow-up

period, but our results were not meaningfully altered after exclusion of such patients. Furthermore, many of the surgical techniques, decisions on implant use, and specific antibiotic spacer type and dose were based on surgeon discretion because there is no standard of care established. Finally, it is difficult to compare the overall treatment failure rate of our study with prior studies because we used a recent definition of treatment failure that is more inclusive. The higher failure rate in our study relative to other reports is likely a result of the broader definition used and the inclusion of infected revision arthroplasties, which comprised one-third of our overall cohort.

Conclusion

During two-stage exchange for PJI, high-dose spacers with greater than 3.6 g of total antibiotic per 40 g of cement may reduce rates of overall and infectious failure for infected primary arthroplasties. Furthermore, using at least 2.0 g of vancomycin could independently decrease the risk of infectious failure. Additional prospective research is warranted to confirm the effects of antibiotic spacer dosing on treatment success in two-stage exchange.

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