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Role of Suppressive Oral Antibiotics in Orthopedic Hardware Infections for Those Not Undergoing Two-Stage Replacement Surgery

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Background. The use of suppressive antibiotics in treatment of orthopedic hardware infections (OHIs), including spinal hardware infections, prosthetic joint infections, and infections of internal fixation devices, is controversial.

Methods. Over a 4-year period at 2 academic medical centers, patients with OHI who were treated with debridement and retention of hardware components, with single-stage exchange, or without surgery were studied to determine whether use of oral antibiotics for at least 6 months after diagnosis impacts successful treatment of the infection at 1 year after diagnosis.

Results. Of 89 patients in the study, 42 (47.2%) were free of clinical infection 1 year after initial diagnosis. Suppressive antibiotics used for at least 6 months after diagnosis was not associated with being free of clinical infection (adjusted odds ratio [aOR], 5.29; 95% confidence interval [CI], .74–37.80), but being on suppressive antibiotics at least 3 months after diagnosis was associated with being free of clinical infection (OR, 3.50; 95% CI, 1.30–9.43). Causative organisms impacted the likelihood of success; patients with methicillin-resistant *Staphylococcus aureus* as well as with Gram-negative rods were both less likely to have achieved clinical success at 1 year after surgery (aOR = 0.018, 95% CI = .0017–.19 and aOR = 0.20, 95% CI = .039–.99, respectively).

Conclusions. Oral suppressive antibiotic therapy in treatment of OHI with retention of hardware for 3 months, but not 6 months, postdiagnosis increases the likelihood of treatment success. The organisms implicated in the infection directly impact the likelihood of treatment success.

Keywords. deep infections of spinal instrumentation; orthopedic hardware infections; prosthetic joint infectious; suppressive antibiotics.

Infections complicate 1% to 2% of prosthetic joints and other types of orthopedic hardware [1, 2]. One percent to eight percent of patients undergoing spinal instrumentation surgeries develop infections [3–7]. Approaches to infections of orthopedic hardware often involve surgical removal of hardware (particularly in late-onset infections) [8]. This may not be an option for some patients due to comorbidities, poor options for successful reconstruction, or patient preference.

Overall rates of cure in orthopedic hardware infections (OHIs) have varied from 14% to 100% [9–12]. In cases where not all hardware components are removed, data on treatment options and outcomes have been mixed. Debridement with implant retention and antibiotic therapy may result in durable cure in select patients with prosthetic joint infection (PJI) [8, 9, 13]. Other OHIs are also often conventionally treated with parenteral and/or oral antibiotics in an attempt to suppress the infection, especially in cases with hardware retention [8], but few data exist to guide treatment of OHIs such as spinal hardware infections or infections of internal fixation devices [14, 15]. In particular, a review of patients with infections of spinal instrumentation failed to identify medium- or high-quality evidence for the use of suppressive antibiotics in this population [15].

More data may help clarify the potential role of chronic oral suppressive antibiotic therapy in management of OHI. Some evidence suggests that chronic oral suppressive antimicrobial therapy increases the likelihood of successful outcomes [11, 14]. We undertook a retrospective study over a 4-year period to determine the role of suppressive antibiotics in successfully treating OHI.

METHODS

Eligible patients were ≥18 years with infections of prosthetic joints, spinal instrumentation, or internal fixation devices treated at 2 academic tertiary referral medical centers in 1 American city between 2009 and 2013. Patients with *International Classification of Diseases, Ninth Revision* (ICD-9) codes consistent with OHI or orthopedic hardware malfunction, or a Common

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Procedural Terminology (CPT) code indicating a repair of pre-existing orthopedic hardware were eligible (Supplementary Table 1) [8]. Of these eligible patients, we included only those treated with debridement with retention of hardware components, single-stage replacement of the hardware, or without surgical intervention. This population was selected because many of these patients are conventionally thought to require suppressive antibiotic therapy. Eligible patients must have had at least 2 positive cultures taken using aseptic technique from the same location with the same organism based on an adaptation of the Infectious Diseases Society of America (IDSA) PJI definition [8]. For spinal hardware infections, only deep infections defined as occurring below the level of the fascia were included. All patients were observed for 1 year from the time of OHI diagnosis. The Johns Hopkins University School of Medicine Institutional Review Board approved this study.

The following data were extracted: demographics, comorbid conditions, clinical features, culture and laboratory data, type of surgery, antimicrobial therapy, and treatment outcome. Two infectious diseases experts reviewed charts, and interrater reliability estimates were $\kappa = 0.85$ for the primary outcome of successful treatment. Differences in determination of the primary outcome were arbitrated by discussion between the reviewers.

Prior infection was defined as a known infection at the same site before the index infection. Comorbidities were scored based on the Charlson Comorbidity Index (CCI) [16]. Early hardware infection was defined as an infection within 3 months of hardware placement [8]. Specific antibiotic use was captured as the prescribed treatment at the time of hospital discharge or the time of first clinic visit for patients who were not hospitalized. Suppressive antibiotics were defined as oral antibiotics prescribed at any point after 4 weeks of postdiagnosis antibiotic therapy and continued for at least 6 months postdiagnosis. Appropriate antibiotic therapy was defined as an antibiotic at time of discharge that would have activity against the causative organism(s). Treatment success was a composite of (1) absence of surgery for the persistence or reappearance of inflammatory signs; (2) survival; (3) absence of second debridement at least 1 month after the first surgery; and (4) absence of prosthetic removal or amputation [17]. Patients who were lost to follow up during the study were considered lost to follow up for the main outcome. Side effects of suppressive antibiotics were collected through 1 year after diagnosis and were defined based on a notation in the chart by a provider that a patient had had a side effect to the named antibiotic.

Single-variable odds ratios (ORs) for treatment success were calculated based on successful treatment. The CCI was dichotomized at 2 based on its distribution with the outcome. The referent group for location of OHI was deep infection of spinal instrumentation because this location had the largest number of patients. Multivariable logistic regression analysis was used to determine independent predictors of treatment success.

Covariates were considered for inclusion if there was an association between the covariate and the outcome at $P \leq .20$, and these were added in a stepwise fashion if the covariate led to a $\geq 10\%$ change in the point estimate. Type of antibiotic used was not included in the model because this was collinear with the organisms identified. Likewise, polymicrobial infection was collinear with the organism variables and was not included in the model. The presence of *Staphylococcus aureus* was collinear with the presence of methicillin-resistant *S aureus* (MRSA), so only MRSA was maintained in the model. Adjusted ORs (aORs) are reported, and a *P* value of <.05 was considered statistically significant. We performed prespecified subgroup analyses by the type of surgery performed (debridement or single-stage replacement). Sensitivity analyses treated patients lost to follow up as not achieving treatment success. Additional sensitivity analyses removed patients who were not treated at the time of hospital discharge or the time of first clinic visit with an antibiotic active against the cultured organism from the analysis. All analyses were performed using Stata 14.0 (StataCorp, College Station, TX).

RESULTS

A total of 4248 patients were identified with the relevant ICD-9 or CPT codes, 147 of whom had at least 2 positive bacterial cultures at the hardware site. Of these patients, 89 were treated without 2-stage replacement surgery or amputation. Of the 89 study patients, 11 patients were lost to follow up (12.4%), 36 did not achieve treatment success (40.4%), and 42 (47.2%) were free of apparent infection at the primary endpoint of 1 year. Four patients remained on oral antibiotics at study conclusion.

Debridement with retention of original hardware components was the most common kind of surgical procedure in this group (Tables 1 and 2) (N = 39, 43.8%), whereas *S aureus* was the most frequently identified bacterial species (N = 40, 44.9%). Parenteral vancomycin was the most common antibiotic given at the time of hospital discharge or first clinic visit in the absence of a hospitalization (N = 34, 38.2%), with β-lactam antibiotics a close second (N = 29, 31.5%). Spinal hardware was the most frequent site of infection (N = 47, 52.8%). Only 19 patients (21.4%) received suppressive antibiotics for at least 6 months after OHI diagnosis, whereas 31 patients (34.8%) were on suppressive antibiotics for at least 3 months after OHI diagnosis (Figure 1). Nineteen patients did not receive any suppressive antibiotic therapy (21.3%). Two patients were not treated with an antibiotic at hospital discharge or first clinic visit that would have had activity against the causative organism (2.2%).

Use of suppressive antibiotics for at least 6 months after diagnosis was not associated with treatment success (aOR, 5.29; 95% confidence interval [CI], .74–37.80). However, the use of suppressive antibiotics for at least 3 months after

Table 1. Odds of Treatment Success One Year After Diagnosis of Orthopedic Hardware Infection, With Odds Ratios and 95% Confidence Intervals

Variable	Number (% of 147)	Number With Treatment Success (% of Total Variable)	Number Without Treatment Success (% of Total Variable)	Number Lost to Follow up (% of Total Variable)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Gender: Female	71 (48.3%)	39 (54.9%)	24 (33.8%)	8 (11.3%)	0.88 (.44–1.77)	NA
Race/ethnicity: White non-Hispanic (referent)	112 (76.2%)	62 (55.4%)	38 (33.9%)	12 (10.7%)	—	NA
Black non-Hispanic	26 (17.7%)	12 (46.2%)	11 (42.3%)	3 (11.5%)	0.67 (.27–1.66)	NA
Other	9 (6.2%)	5 (55.6%)	3 (33.3%)	1 (11.1%)	1.02 (.23–4.52)	NA
Age (mean, standard deviation)	56.4 (16.5)	55.7 (16.3)	57.7 (16.9)	56.0 (16.7)	0.99 (.97–1.01)	NA
Charlson Comorbidity Index ≥2	22 (15.0%)	6 (27.3%)	13 (59.1%)	3 (13.6%)	0.36 (.18–.75)	0.42 (.16–1.15)
White blood cell count ≥12 000 cells/mL	39 (26.5%)	25 (64.1%)	12 (30.8%)	2 (5.1%)	1.54 (.69–3.43)	NA
Prior infection in the same site	33 (22.5%)	14 (42.4%)	17 (51.5%)	2 (6.1%)	0.44 (.20–1.00)	0.34 (.11–1.03)
Early orthopedic hardware infection[a]	43 (29.3%)	18 (41.9%)	19 (44.2%)	6 (14.0%)	0.51 (.24–1.10)	1.06 (.35–3.17)
Hardware Site: Spinal (referent)	55 (37.4%)	28 (50.9%)	17 (30.9%)	10 (18.2%)	—	—
Shoulder	26 (17.7%)	18 (69.2%)	7 (26.9%)	1 (3.9%)	1.56 (.54–4.51)	0.49 (.10–2.50)
Tibia/Fibula/Ankle	19 (12.9%)	11 (57.9%)	7 (36.8%)	1 (5.3%)	0.95 (.31–2.93)	0.93 (.21–4.09)
Elbow/Hand	5 (3.4%)	2 (40.0%)	3 (60.0%)	0 (0.0%)	0.40 (.061–2.67)	0.69 (.06–8.32)
Knee	16 (10.9%)	8 (50.0%)	7 (43.8%)	1 (6.3%)	0.69 (.21–2.26)	0.84 (.16–4.48)
Hip	26 (17.7%)	12 (46.2%)	11 (42.3%)	3 (11.5%)	0.66 (.24–1.83)	0.65 (.15–2.81)
Organism: Coagulase-negative *Staphylococcus*	38 (25.9%)	14 (36.8%)	18 (47.4%)	6 (15.8%)	0.41 (.18–.92)	0.15 (.04–.52)
Staphylococcus aureus	63 (42.9%)	26 (41.3%)	30 (47.6%)	7 (11.1%)	0.36 (.17–.74)	0.11 (.03–.36)
Gram-negative rod	29 (19.7%)	11 (37.9%)	18 (62.1%)	0 (0.0%)	0.31 (.13–.72)	0.15 (.05–.51)
Propionibacterium acnes	32 (21.9%)	24 (25.0%)	6 (18.8%)	2 (6.3%)	3.41 (1.28–9.05)	NA
Streptococcus or *Enterococcus*	32 (21.8%)	18 (56.3%)	12 (37.5%)	2 (6.3%)	0.98 (.43–2.26)	NA
Polymicrobial[b]	51 (34.9%)	23 (45.1%)	25 (49.0%)	3 (5.9%)	0.45 (.22–.94)	NA
Surgery: None (referent)	14 (9.5%)	6 (42.9%)	4 (28.6%)	4 (28.6%)	—	—
Debridement only	33 (22.5%)	15 (45.5%)	16 (48.5%)	2 (6.1%)	0.63 (.15–2.66)	1.07 (.16–7.06)
One-stage procedure	36 (24.5%)	18 (50.0%)	13 (36.1%)	5 (13.9%)	0.92 (.22–3.94)	1.73 (.26–11.52)
Partial hardware removal	6 (4.1%)	3 (50.0%)	3 (50.0%)	0 (0.0%)	0.67 (.09–5.13)	1.76 (.14–21.57)
Full hardware removal	13 (8.8%)	8 (61.5%)	3 (23.1%)	2 (15.4%)	1.78 (.28–11.12)	7.00 (.65–75.53)
Two-stage procedure	45 (30.6%)	29 (64.4%)	13 (28.9%)	3 (6.7%)	1.49 (.36–6.18)	3.14 (.44–22.46)
Parenteral antibiotic, fluoroquinolone, or linezolid ≥42 d[c]	75 (51.0%)	40 (53.3%)	28 (37.3%)	7 (9.3%)	0.88 (.44–1.77)	NA
Any parenteral vancomycin[c]	62 (42.2%)	26 (41.9%)	28 (45.2%)	8 (12.9%)	0.42 (.20–.86)	NA
Any parenteral β-lactam[c]	48 (32.7%)	31 (64.6%)	14 (29.2%)	3 (6.3%)	1.75 (.82–3.75)	NA
Suppressive Antibiotic ≥3 mo[d]	42 (28.6%)	29 (69.1%)	11 (26.2%)	2 (4.8%)	2.45 (1.15–5.24)	3.75 (1.20–11.73)

Abbreviations: CI, confidence interval; OR, odds ratio; NA, not applicable.

[a] Early orthopedic hardware infection was defined as occurring within 3 months of the implanted hardware.

[b] More than 1 organism cultured from at least 2 samples. Patients who had (for example) an infection with both *S aureus* and *P acnes* cultured from 2 different samples were recorded as having *S aureus*, *P acnes*, and a polymicrobial infection.

[c] Antibiotic prescribed at the time of hospital discharge or first clinic appointment if not admitted to hospital.

[d] Suppressive antibiotic therapy was defined as a period of oral antibiotics that continued for at least 3 months after the original diagnosis of orthopedic hardware infection.

diagnosis was associated with treatment success (OR, 3.50; 95% CI, 1.30–9.43).

Patients with a higher CCI were less likely to achieve treatment success (OR, 0.18; 95% CI, .03–.89), although this was no longer statistically significant after adjustment for a prior infection in the same site, the infection site, and the presence of MRSA, a Gram-negative rod, or *Propionibacterium acnes*. Patients who had had a prior infection in the same site were also noted to have a lower likelihood of treatment success (OR, 0.31; 95% CI, .10–.99), although this was no longer statistically significant after adjustment for a prior infection in the same site, the infection site, and the presence of MRSA, a Gram-negative rod, or *P acnes*.

Patients infected with either MRSA (aOR, 0.018; 95% CI, .0017–.19) or Gram-negative rods (aOR, 0.20; 95% CI, .039–.99) were less likely to have achieved treatment success. *Staphylococcus aureus* was associated with a decreased likelihood of treatment success on unadjusted analyses (OR, 0.29; 95% CI, .11–.73), but this was not included in the final model due to its collinearity with MRSA. *Propionibacterium acnes* was

Table 2. Likelihood of Achieving Treatment Success One Year After Diagnosis of Orthopedic Hardware Infection, Among 89 Patients With Orthopedic Hardware Infections Treated With Single-Stage Revision, Debridement With Retention of Hardware, or Without Surgery

Variable	Number (% of 89)	Number With Treatment Success (% of 42)	Number Without Treatment Success (% of 36)	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)[a]
Suppressive Antibiotic ≥3 mo[b]	31 (34.8%)	21 (50.0%)	8 (22.2%)	3.50 (1.30–9.43)	—
Suppressive antibiotic ≥6 mo[b]	19 (21.4%)	11 (26.2%)	7 (19.4%)	1.47 (.50–4.30)	5.29 (.74–37.80)
Suppressive antibiotic ≥1 yr[b]	4 (4.5%)	3 (7.1%)	1 (2.8%)	2.69 (.27–27.09)	—
Gender: Female	45 (50.7%)	24 (57.1%)	15 (41.7%)	0.54 (.22–1.32)	—
Race/ethnicity: White non-Hispanic	66 (74.2%)	34 (81.0%)	25 (69.4%)	Referent	—
Black non-Hispanic	18 (20.2%)	5 (11.9%)	10 (27.8%)	0.37 (.11–1.21)	—
Other	5 (5.6%)	3 (7.1%)	1 (2.8%)	—	—
Age (as continuous variable)	56.1 (16.3)	57.4 (16.3)	55.3 (17.3)	1.19 (.86–1.64)	—
Charlson Comorbidity Index ≥2	13 (14.6%)	2 (4.8%)	8 (22.2%)	0.18 (.03–.89)	0.012 (.0001–1.09)
Diabetes	17 (19.1%)	10 (23.8%)	5 (13.9%)	1.94 (.59–6.32)	—
Prior infection in the same site	16 (18.0%)	5 (11.9%)	11 (30.6%)	0.31 (.10–.99)	0.15 (.022–1.02)
Early orthopedic hardware infection (versus late)[c]	36 (40.5%)	16 (38.1%)	15 (41.7%)	0.86 (.35–2.14)	—
Hardware Site: Spinal	47 (52.8%)	24 (57.1%)	14 (38.9%)	Referent	Referent
Shoulder	9 (10.1%)	6 (14.3%)	3 (8.3%)	1.17 (.25–5.41)	0.013 (.0004–.39)
Tibia/Fibula/Ankle	10 (11.2%)	5 (11.9%)	5 (13.9%)	—	0.22 (.027–1.90)
Elbow/Hand	4 (4.5%)	1 (2.4%)	3 (8.3%)	0.47 (.11–2.03)	0.81 (.024–27.39)
Knee	8 (9.0%)	2 (4.8%)	5 (13.9%)	0.23 (.04–1.37)	0.057 (.0034–0.96)
Hip	11 (12.4%)	4 (9.5%)	6 (16.7%)	0.39 (.09–1.62)	0.17 (.022–1.33)
Organism: Coagulase-negative *Staphylococcus*[d]	25 (28.1%)	8 (19.1%)	12 (33.3%)	0.47 (.17–1.33)	0.26 (.052–1.33)
Staphylococcus aureus	2 (2.3%)	2 (5.6%)	0 (0.0%)	0.29 (.11–0.73)	—
Methicillin-sensitive *S aureus*	40 (44.9%)	13 (31.0%)	22 (61.1%)	1.10 (.40–3.06)	—
Methicillin-resistant *S aureus*	21 (23.9%)	12 (28.6%)	9 (25.0%)	0.091 (.019–.44)	0.018 (.0017–.19)
Gram-negative rod	19 (21.6%)	3 (7.1%)	13 (36.1%)	0.29 (.10–.89)	0.20 (.039–.99)
Propionibacterium acnes	6 (6.8%)	4 (7.5%)	3 (8.3%)	5.11 (1.32–19.75)	14.09 (.78–253.08)
Streptococcus[e]	18 (20.2%)	9 (21.4%)	8 (22.2%)	1.11 (.27–4.50)	—
Enterococcus	10 (11.4%)	5 (11.9%)	4 (11.1%)	0.86 (.23–3.26)	—
Polymicrobial infection[f]	5 (5.6%)	3 (7.1%)	2 (5.6%)	0.52 (.21–1.29)	—
Surgery: None	10 (11.4%)	5 (11.9%)	5 (13.9%)	Referent	—
Debridement with retention of hardware components	19 (21.6%)	9 (21.4%)	8 (22.2%)	0.63 (.15–2.61)	—
Single-stage procedure	35 (39.8%)	15 (35.7%)	19 (52.8%)	0.92 (.22–3.94)	—
Discharged on parenteral antibiotic[g]	16 (45.7%)	4 (26.7%)	11 (57.9%)	0.77 (.29–2.03)	—
Received parenteral vancomycin[g]	14 (15.7%)	6 (14.3%)	4 (11.1%)	0.31 (.12–0.82)	—
Received a parenteral β-lactam[g]	39 (43.8%)	18 (42.9%)	19 (52.8%)	1.77 (.68–4.59)	—
Received rifampin[g]	36 (40.5%)	18 (42.9%)	13 (36.1%)	3.40 (.66–17.54)	—
Received a fluoroquinolone[g,h]	61 (68.5%)	28 (66.7%)	26 (72.2%)	0.44 (.12–1.63)	—

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Cells with a dashed line are not included in the final model.

[b] Suppressive antibiotic therapy was defined as a period of oral antibiotics that continued for the indicated period of time after the original diagnosis of orthopedic hardware infection.

[c] Early orthopedic hardware infection was defined as occurring within 3 months of the implanted hardware.

[d] Two patients had *Staphylococcus lugdunensis* infection.

[e] Including 2 patients with *Streptococcus anginosus* and 5 patients with Group B *Streptococcus* infections.

[f] More than 1 organism cultured from at least 2 samples. Patients who had (for example) an infection with both *S aureus* and *P acnes* cultured from 2 different samples were recorded as having *S aureus*, *P acnes*, and a polymicrobial infection. Sixteen of these patients (18.0% of all patients) had *S aureus*, and 9 of these patients (10.1% of all patients) had *Enterococcus*.

[g] Antibiotic prescribed at the time of hospital discharge or first clinic appointment if not admitted to hospital.

[h] Fluoroquinolones were given in the presence of susceptible Gram-negative rods. No fluoroquinolones were given in Gram-positive infections only.

associated with treatment success on unadjusted analyses only (OR, 5.11; 95% CI, 1.32–19.75). Other covariates did not demonstrate a statistically significant association with the outcome in the multivariable model.

We investigated the role of antibiotic choice in treatment of OHI. Patients treated with parenteral vancomycin were less likely to have achieved treatment success (OR, 0.31; 95% CI, .12–.82), although this was collinear with the presence of MRSA so it was not included in the full model. Prescription of rifampin was also not associated with the outcome (OR, 3.40; 95% CI, .66–17.54), although only a minority of patients received this therapy at any point (N = 10, 11.2%). Fluoroquinolones were
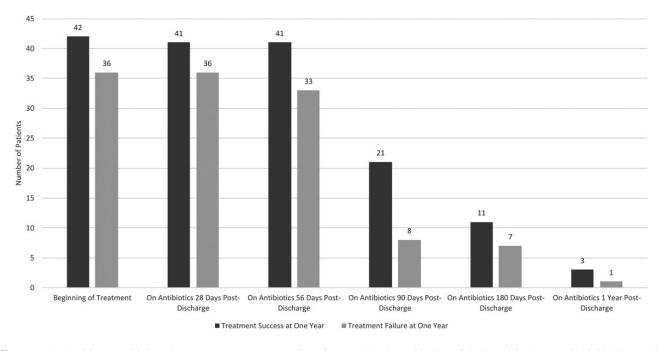
Figure 1. Length of time on antibiotics and treatment outcomes 1 year postdiagnosis, among 89 patients with orthopedic hardware infections treated with debridement with retention of components, single-stage replacement, or without surgery. Ten patients were lost to follow up.

prescribed at the time of discharge in 12 patients (13.5%), but this was not associated with the likelihood of treatment success (OR, 0.44; 95% CI, .12–1.63). No patients were treated with a combination of a fluoroquinolone and rifampin, including those with *S aureus* PJI; all fluoroquinolones were prescribed for patients with Gram-negative rod infections.

We investigated the types of suppressive antibiotics received among those who remained on suppressive antibiotics at least 6 months after diagnosis. Only 5 patients received rifampin as a part of their suppressive antibiotic course (Tables 3 and 4). The most common antibiotic used was doxycycline (N = 6, 31.6% of patients on suppressive antibiotics for at least 6 months). Only 4 patients (21.1% of patients treated with suppressive antibiotics)

had a side effect to the suppressive antibiotic regimen. Two of these 4 patients had experienced nausea as a result of rifampin therapy. No patients on suppressive antibiotic therapy acquired *Clostridium difficile* infection.

We performed subgroup analyses of patients treated with debridement alone with retention of hardware components or single-stage replacement of the hardware (Tables 5 and 6). Of 39 patients treated with debridement with retention of hardware components, the use of suppressive antibiotics for at least 6 months was not associated with treatment success (OR, 0.56; 95% CI, .11–2.79). Of 36 patients treated with single-stage replacement of the OHI, the use of suppressive antibiotics for at least 6 months was also not associated with treatment success

Table 3. Antibiotics Used for Suppressive Antibiotic Therapy, Among 19 Patients on Suppressive Antibiotics for at Least Six Months After Diagnosis of Orthopedic Hardware Infection[a]

Suppressive Antibiotic Used	Number of Patients on Antibiotic (Percent of 19)	Number With Treatment Success (Percent of Patients on Antibiotic)	Number of Patients on Antibiotic With Side Effect (Percent on Antibiotic)	Side Effects
Amoxicillin	2 (10.5%)	2 (100.0%)	1 (50.0%)	Shortness of breath
Trimethoprim-Sulfamethoxazole	3 (15.8%)	2 (66.7%)	0 (0.0%)	None
Ciprofloxacin or Levofloxacin	3 (15.8%)	2 (66.7%)	0 (0.0%)	None
Clindamycin	2 (10.5%)	1 (50.0%)	0 (0.0%)	None
Dicloxacillin	1 (5.3%)	0 (0.0%)	0 (0.0%)	None
Doxycycline	6 (31.6%)	3 (50.0%)	0 (0.0%)	None
Minocycline	2 (10.5%)	1 (100.0%)	1 (50.0%)	Diarrhea
Rifampin	5 (26.3%)	4 (80.0%)	2 (40.0%)	Nausea

[a] Including those with diagnosis of orthopedic hardware infection, among those treated with debridement with retention of hardware, a single-stage procedure, or without surgical intervention, based on treatment success at 1 year.

Table 4. Odds Ratios for Likelihood of Treatment Success, in a Subgroup Analysis of 55 Patients With Infections of Spinal Hardware[a]

Variable	Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)
Suppressive antibiotic for three months	0.98 (.29–3.26)	1.38 (.25–7.72)
Prior infection	0.31 (.083–1.14)	0.26 (.04–1.88)
Leukocytosis (WBC ≥12)	5.63 (1.08–29.42)	10.12 (.68–151.29)
Coagulase-negative Staphylococcus	0.39 (.08–2.01)	0.04 (.002–.88)
Staphylococcus aureus	0.18 (.049–.68)	0.03 (.003–.36)
Gram-negative rod	0.39 (.10–1.46)	0.06 (.005–.72)

Abbreviation: WBC, white blood cells.

[a] Ten patients who were lost to follow up were not included in the analysis.

(OR, 6.00; 95% CI, .62–57.68). Among the patients treated with single-stage procedures, coagulase-negative *Staphylococcus* infections and having a prior infection in the same site were each associated with a decreased likelihood of treatment success (OR = 0.17, 95% CI = .033–.89 and OR = 0.17, 95% CI = .033–.89, respectively), whereas patients with *P acnes* infections were more likely to achieve treatment success (OR, 10.67; 95% CI, 1.12–101.34).

In secondary analyses treating patients lost to follow up as not achieving treatment success, the primary outcome did not change significantly (Supplementary Table 2). Likewise, in secondary analyses excluding 2 patients not treated with an antibiotic at the time of hospital discharge or first clinic visit with activity against the causative organism, the primary outcome did not change significantly (Supplementary Table 3).

DISCUSSION

In our study, the use of suppressive antibiotics at least 6 months post-OHI diagnosis was not associated with treatment success, although suppressive antibiotics at least 3 months post-OHI diagnosis was associated with treatment success. This supports IDSA PJI guidance suggesting that continuing antibiotics in PJI with retention of hardware for 3 to 6 months should be standard. These findings also provide clarity in management after 6 months postdiagnosis, as guideline committee members disagreed whether indefinite chronic oral antimicrobial suppression should be recommended during that time period [8]. These findings may contradict another study suggesting that continuing oral suppressive antibiotic therapy in PJI was successful but the risk of treatment failure increased in the 4 months after antimicrobial discontinuation [11]. Our data suggest that treating patients for longer than 6 months with oral suppressive antibiotics may not be as important as treating patients with OHI and retention of hardware components for at least 3 to 6 months with highly effective antibiotic therapy, although our findings are limited by study size.

We also found that patients with *S aureus* (in particular, MRSA) were less likely to have treatment success, as discussed in IDSA PJI guidelines [8]. Unlike data suggested in these guidelines, our data also suggest that patients with Gram-negative rods may also be considered higher risk for treatment failure [8]. Further investigations could determine whether certain treatment options are preferable for patients with OHI due to Gram-negative rods.

Patients with *P acnes* infections were more likely to be successfully treated on unadjusted analyses only. *Propionibacterium acnes* have been increasingly recognized as a cause of OHIs, particularly shoulder PJIs [18]. Our study suggests that although *P acnes* is an important causative organism of OHI, it can be successfully treated without a 2-stage surgical strategy.

Unlike prior studies, early-onset infection of OHI was not associated with treatment success [8, 14, 19]. Patients who had had a prior OHI in the same site were less likely to achieve treatment success. Patients who have recurrent infections may be particularly difficult to treat [8, 20], and future research should focus on optimizing outcomes in this subpopulation.

Our study included patients with deep infections of spinal instrumentation. Data on the use of suppressive antimicrobial therapy in these patient populations have been limited. Although one study did show that most early-onset deep infections of spinal surgeries with instrumentation were treated with debridement, implant retention, and parenteral antibiotics followed by oral suppressive antibiotics [14], a recent review failed to identify medium- or high-quality evidence for suppressive antibiotics in infections of retained spinal instrumentation [15]. We did not find that this group was at a higher likelihood of treatment failure than other groups.

Patients in our study rarely received either rifampin or fluoroquinolones as part of their therapy, and none received both rifampin and a fluoroquinolone, unlike the recommended guidelines for treatment of *Staphylococcus* PJIs that were published towards the end of the study period [8, 21, 22]. In our study, these agents were not associated with treatment success. Rifampin was associated with nausea in this study, so providers may have avoided rifampin to avoid side effects. In addition, many of our patients had high CCI scores [16]. It is possible that providers were avoiding rifampin to avoid interactions with other medications patients may have taken for their comorbidities.

In this study, fluoroquinolones were primarily used to treat susceptible Gram-negative rods, but not *S aureus* PJIs as recommended in guidelines [8]. There may have been concerns among clinicians in these hospitals for increased fluoroquinolone resistance among Gram-positive bacteria including *S aureus*. In an era in which fluoroquinolone toxicity and contribution to antibiotic resistance are increasingly recognized [23], our data show how patients might be managed without fluoroquinolones.

Table 5. Subgroup Analyses of 39 Patients Treated With Debridement With Retention of Hardware and 36 Patients Treated With Single-stage Replacement, for Likelihood of Achieving Treatment Success One Year After the Diagnosis of Orthopedic Hardware Infection

Variable	Odds Ratios (95% Confidence Intervals) Among 39 Patients Treated With Debridement and Retention of Hardware[a]	Odds Ratios (95% Confidence Intervals) Among 36 Patients Treated With Single-Stage Revision[a]
Suppressive antibiotic ≥3 mo[b]	2.80 (.71–11.10)	5.50 (.94–32.21)
Suppressive antibiotic ≥6 mo[b]	0.56 (.11–2.79)	6.00 (.62–57.68)
Gender: Male	0.90 (.25–3.27)	0.22 (.048–1.02)
Race/ethnicity: White non-Hispanic	Referent	Referent
Black non-Hispanic	0.23 (.023–2.34)	0.37 (.069–1.98)
Age (as continuous variable)	0.10 (.63–1.59)	1.37 (.78–2.41)
Charlson Comorbidity Index ≥2	—	0.20 (.012–2.15)
Diabetes	2.05 (.41–10.24)	—
Prior infection in the same site	0.47 (.075–2.94)	0.17 (.033–.89)
Early orthopedic hardware infection[c]	1.13 (.31–4.10)	0.46 (.095–2.21)
Hardware site: Spinal (referent)	Referent	Referent
Shoulder	1.00 (.051–19.36)	2.08 (.19–22.67)
Tibia/Fibula/Ankle	1.00 (.18–5.68)	—
Elbow/Hand	0.50 (.036–6.86)	—
Knee	0.67 (.084–5.31)	—
Hip	1.50 (.19–11.93)	0.14 (.011–1.68)
Organism: Coagulase-negative *Staphylococcus*	1.07 (.22–5.13)	0.17 (.033–.89)
Staphylococcus aureus	0.47 (.13–1.74)	0.24 (.052–1.16)
Methicillin-sensitive *S aureus*	4.23 (.91–19.99)	0.30 (.045–1.98)
Methicillin-resistant *S aureus*	—	0.44 (.063–3.16)
Gram-negative rod	0.49 (.11–2.09)	0.20 (.032–1.27)
Propionibacterium acnes	2.25 (.19–27.22)	10.67 (1.12–101.34)
Streptococcus	0.31 (.030–3.34)	1.60 (.13–19.84)
Enterococcus	1.06 (.13–8.47)	0.73 (.089–6.04)
Polymicrobial infection[d]	0.45 (.12–1.70)	0.56 (.13–2.41)
Discharged on parenteral antibiotic	0.69 (.15–3.14)	0.98 (.23–4.25)
Received parenteral vancomycin[e]	0.17 (.039–0.71)	0.62 (.13–2.82)
Received a parenteral β-lactam[e]	3.39 (.72–16.07)	1.43 (.32–6.49)
Received rifampin[e]	1.06 (.061–18.30)	2.40 (.22–26.12)
Received fluoroquinolone[e]	0.62 (.14–2.70)	No patients included

[a] Cells with a dashed line did not contain enough patients to calculate an odds ratio.

[b] Suppressive antibiotic therapy was defined as a period of oral antibiotics that continued for the indicated period of time after the original diagnosis of orthopedic hardware infection.

[c] Early orthopedic hardware infection was defined as occurring within 3 months of the implanted hardware.

[d] More than 1 organism cultured from at least 2 samples. Patients who had (for example) an infection with both *S aureus* and *P acnes* cultured from 2 different samples were recorded as having *S aureus*, *P acnes*, and a polymicrobial infection. Sixteen of these patients (18.0% of all patients) had *S aureus*, and 9 of these patients (10.1% of all patients) had *Enterococcus*.

[e] Antibiotic prescribed at the time of hospital discharge or first clinic appointment if not admitted to hospital.

Our study did not address whether all OHIs should be suppressed, particularly those caused by organisms such as *P acnes*, which were not associated with treatment failure. In addition, MRSA and Gram-negative rods were associated with treatment failure. It is unclear whether infections caused by these organisms need earlier treatment or a more aggressive surgical intervention, such as a 2-stage intervention. It is possible that suppressive antibiotics only lead to temporary clinical success. Alternatively, perhaps current oral suppressive antibiotics do not adequately treat infections caused by these organisms. Future studies should compare suppressive antibiotic regimens.

There was also heterogeneity among the study patients. In particular, intramedullary and periosteal osteomyelitis may not respond in the same way to surgical and antibiotic interventions. Although we controlled for the location of the infection, anatomic and physiologic differences between infection sites may have further contributed to heterogeneity.

The study was relatively small, and it was limited to 2 tertiary-care academic medical centers in one city that serve as referral centers for orthopedic surgery; therefore, this study may not be representative of other experiences. We chose to follow all patients for the same period of time (1 year) to limit lead-time

Table 6. Odds of Treatment Success One Year After Diagnosis of Orthopedic Hardware Infection, With Odds Ratios and 95% Confidence Intervals[a]

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Suppressive antibiotic ≥3 mo[b]	2.45 (1.15–5.24)	3.92 (1.46–10.50)
Prior infection	0.44 (.20–1.00)	0.43 (.36–1.14)
Charlson Comorbidity Index ≥2	0.43 (.22–.84)	0.62 (.26–1.44)
Early orthopedic hardware infection[c]	0.51 (.24–1.10)	0.95 (.36–2.50)
Presence of coagulase-negative Staphylococcus	0.39 (.18–.85)	0.17 (.06–.50)
Presence of Staphylococcus aureus	0.41 (.21–.80)	0.18 (.07–.48)
Presence of Gram-negative rod	0.45 (.20–1.03)	0.29 (.10–.83)
Surgery: None (referent)	—	—
Debridement only	1.11 (.31–3.92)	1.62 (.32–8.20)
One-stage procedure	1.33 (.38–4.63)	1.96 (.41–9.43)
Partial removal of hardware	1.33 (.20–9.08)	2.53 (.26–24.44)
Full hardware removal	12.13 (.46–9.94)	4.62 (.66–32.51)
Two-stage procedure	2.42 (.71–8.20)	4.06 (.74–22.41)
Hardware Site: Spinal	—	—
Shoulder	2.17 (.81–5.82)	0.79 (.19–3.29)
Tibia/Fibula/Ankle	1.33 (.46–3.80)	1.62 (.43–6.04)
Elbow/Hand	0.64 (.10–4.15)	1.34 (.15–12.26)
Knee	0.96 (.32–2.94)	1.25 (.29–5.28)
Hip	0.83 (.32–2.11)	0.80 (.23–2.79)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] In this sensitivity analysis, patients who were lost to follow up were treated as treatment failures.

[b] Suppressive antibiotic therapy was defined as a period of oral antibiotics that continued for at least 3 months after the original diagnosis of orthopedic hardware infection.

[c] Early orthopedic hardware infection was defined as occurring within 3 months of the implanted hardware.

Table 7. Odds of Treatment Success One Year After Diagnosis of Orthopedic Hardware Infection, With Odds Ratios and 95% Confidence Intervals[a]

Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Suppressive antibiotic ≥3 mo[b]	2.20 (.98–4.94)	3.80 (1.20–12.03)
Prior infection	0.44 (.20–1.01)	0.36 (.12–1.09)
Charlson Comorbidity Index ≥2	0.37 (.18–.76)	0.43 (.16–1.17)
Early orthopedic hardware infection[c]	0.48 (.22–1.04)	1.02 (.34–3.13)
Presence of coagulase-negative Staphylococcus	0.41 (.18–.92)	0.16 (.05–.57)
Presence of Staphylococcus aureus	0.36 (.18–.76)	0.12 (.04–.40)
Presence of Gram-negative rod	0.27 (.11–.66)	0.14 (.04–.48)
Surgery: None (referent)	—	—
Debridement only	0.47 (.10–2.22)	0.89 (.12–6.34)
One-stage procedure	10.65 (.14–3.12)	1.19 (.16–8.88)
Partial removal of hardware	0.50 (.06–4.15)	1.46 (.11–19.47)
Full hardware removal	1.17 (.17–8.09)	5.11 (.41–63.02)
Two-stage procedure	1.12 (.24–5.16)	2.44 (.32–18.90)
Hardware site: Spinal	—	—
Shoulder	1.52 (.52–4.44)	0.52 (.10–2.60)
Tibia/Fibula/Ankle	0.93 (.30–2.89)	0.92 (.21–4.09)
Elbow/Hand	0.20 (.02–2.06)	0.52 (.03–8.16)
Knee	0.68 (.21–2.22)	0.83 (.16–4.42)
Hip	0.65 (.23–1.80)	0.66 (.15–2.82)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Four patients who were not given initially appropriate antibiotics were excluded from the analysis. All other antibiotics given were appropriate.

[b] Suppressive antibiotic therapy was defined as a period of oral antibiotics that continued for at least 3 months after the original diagnosis of orthopedic hardware infection.

[c] Early orthopedic hardware infection was defined as occurring within 3 months of the implanted hardware.

bias, so we likely missed some very late OHI relapses. However, in at least 1 prior study of PJI, over half of relapses happened in the first year [11]. Although we excluded patients who were lost to follow up, we performed a sensitivity analysis in which patients lost to follow up were categorized as treatment failures, and our findings did not change. This study did not address certain side effects of long-term antibiotic therapy (eg, antibiotic resistance). We used a modification of IDSA culture criteria for PJI to only include patients with 2 positive cultures taken sterilely with the same organism [8]. This may have excluded many patients with OHIs from the study, particularly those who did not have multiple positive cultures; however, we believed that it was important to ensure that we were only capturing patients with OHI. Study patients with OHI may not have been treated according to PJI guidelines published by the IDSA, because these guidelines were published at the end of the study period [8]. In addition, in the 2 institutions studied here, the practice is typically to reserve single-stage surgeries for spinal instrumentation infections or when a PJI is not suspected. It was not a common practice in the 2 hospitals studied to perform single-stage replacement of PJI in the presence of known infection.

We were also underpowered to study many of the outcomes. This may point to the difficulty in studying OHI: of over 4000 patients over the course of 4 years at 2 large academic medical centers with an ICD-9 or CPT code indicating a possible OHI, only 89 met study inclusion criteria. Orthopedic hardware infections are fortunately infrequent, but their treatment is complicated. Larger studies, possibly using multicenter registries, would help address basic but important questions, such as which antibiotic regimens might be most effective and best tolerated.

CONCLUSIONS

Our study supports the importance of oral suppressive antibiotic therapy in the management of OHI between 3 and 6 months after OHI diagnosis, but continuing suppressive treatment for longer than 6 months may not be as beneficial. More data are needed to determine the optimal approaches and duration of treatment in patients with OHI for whom complete removal of hardware or a 2-stage procedure is impossible.

Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases* online (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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