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A Retrospective Chart Review on the Role of Suppressive Therapy in the Management of Spinal Infections Involving Hardware

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Background. One percent to 8% of patients undergoing spinal instrumentation surgeries develop infections. There is no consensus on the medical and surgical management of these infections.

Methods. We conducted a retrospective chart review based on *International Classification of Diseases, Ninth Revision,* and Common Procedural Terminology codes relevant to spinal infections with hardware within Emory Healthcare over a 10-year period. Extracted data included patient demographics, clinical presentation, laboratory and microbiologic results, and surgical and medical management including choice and duration of suppressive therapy. Multivariable logistic regression was used to assess the association of length of use of suppressive antibiotics with treatment success and to identify predictors of use of suppressive antibiotics.

Results. Of 869 records, 124 met inclusion criteria. Fifty patients (40.3%) had an infection that occurred after hardware placement, mostly within 3 months postsurgery, while the remainder had vertebral osteomyelitis that required hardware placement. After initial intravenous antibiotic treatment for ≥4 weeks, 72 patients (64.5%) were given suppressive antibiotics. The overall treatment success rate was 78.2%. In spinal infections involving hardware with gram-negative rods, patients were less likely to receive suppressive antibiotics, less likely to have hardware removed, and less likely to have treatment success compared with patients with infections with *Staphylococcus* species.

Conclusions. Management of spinal infections involving hardware should be tailored to the timing of onset of infection and causative organism. Further studies are needed to determine best management practices, particularly for gram-negative rod infections where the role of further suppressive antibiotics and hardware removal may be warranted.

Keywords. hardware; spinal infections; suppressive antibiotics.

Spinal instrumentation is often needed to stabilize the spine due to trauma, degenerative disease, cancer, or infections. The rate of surgical site infection after spinal instrumentation has been reported to be 1%–8% [1–3], with several surgical and nonsurgical risk factors identified, including smoking, diabetes, longer operative times, and suboptimal timing of prophylactic antibiotics [4, 5]. Little is known on the management of spinal infections in the setting of hardware placement, and there is no consensus on the type of surgical intervention, the need for hardware removal, or the addition of oral suppressive antibiotics.

Previously, it was believed that hardware removal was essential, particularly with microorganisms known to form biofilms. However, hardware removal is often not possible, as premature removal of instrumentation compromises spinal stability and may lead to pseudoarthrosis [6]. Also, a secondary surgical intervention is sometimes difficult when patients have several comorbidities. The timing of spinal infections with hardware in place can help guide physicians on their management. Early hardware infections, usually caused by virulent organisms such as *Staphylococcus aureus* [7, 8], are treated with a combination of surgical debridement, with or without hardware removal, and a long course of parenteral antibiotics [1, 7]. Delayed infections are often caused by less virulent organisms [8, 9] and frequently require hardware removal or replacement, along with antimicrobial therapy [1]. Although it is generally agreed on that 6–8 weeks of parenteral antibiotic therapy is needed for the treatment of infected spinal instrumentation, the role of oral suppressive antibiotic therapy in the management of these infections is undetermined [1, 10].

This study aims to understand the association between use of suppressive antibiotics and treatment success in the

management of patients with spinal infections involving hardware. A secondary aim is to identify factors that predict use of oral suppressive antibiotics and guide physicians in the clinical decision-making process.

METHODS

Inclusion and Exclusion Criteria

This is a retrospective chart review based on *International Classification of Diseases, Ninth Revision* (ICD-9), and Common Procedural Terminology (CPT) codes relevant to spinal infection and hardware that were recorded at Emory University Hospitals between January 1, 2005, and December 31, 2015. Patient records were sourced from the Emory electronic Medical Record (EeMR). ICD-9 codes consistent with cases of spinal infections below the level of the fascia (osteomyelitis, diskitis, epidural abscess, etc.) and CPT codes for spinal instrumentation/hardware placement were used to identify patients. The study was approved by the Emory Institutional Review Board.

Patients were included if they received a course of intravenous antibiotics of ≥ 4 weeks and had either an infection of previously inserted hardware (group 1) or an active infection that led to hardware placement (group 2). Eligible patients must have had (1) clinical signs and symptoms consistent with spinal infection and (2) positive spine site cultures and/or at least 1 positive blood culture with growth of an organism judged to be a noncontaminant, or negative cultures in the setting of antibiotic administration before culture was taken. We excluded patients with skin and soft tissue infection at the site of surgery without involvement below the level of the fascia, patients with <6 weeks of follow-up with either an infectious disease physician or a neurosurgeon, and patients who underwent instrumentation for stabilization of the spine in the setting of a resolved spinal infection.

A standardized data collection form was created and included demographics, comorbidities, immunosuppressive state, clinical presentation, inflammatory laboratory markers, microbiologic results, site and timing of spinal infection, surgical and medical management including choice and duration of intravenous and suppressive therapy, and outcome. Two independent researchers reviewed the medical records of all episodes of spinal infections involving hardware, and any conflicts were resolved by a faculty expert in infectious diseases and/or neurosurgery. If there was no consensus between the 2 independent researchers on whether the patient was eligible, an independent infectious diseases consultant was asked to review the case to determine eligibility.

Early hardware infection was defined as an infection occurring within 3 months of hardware placement, whereas late hardware infection was defined as occurring after 3 months after hardware placement. Initial antibiotic treatment was defined as any intravenous antibiotics received around the time of diagnosis for ≥4 weeks. Suppressive antibiotics refer to any oral antibiotics given after completing the initial intravenous antibiotic regimen.

The primary outcome of treatment success was a composite of (1) survival, (2) absence of additional surgical intervention for recurrent infection, (3) absence of relapse, defined as patients with recurrent signs and symptoms of spinal infection after the completion of the initial intravenous (IV) antibiotic course.

Statistical Methods

Baseline characteristics of the study population were compared by the outcome of treatment success using the chi-square/Fisher exact test for categorical variables and Student *t* test for continuous data. Crude odds ratios (ORs) were calculated to assess the association of length of suppressive antibiotic use with the outcome of treatment success. Similarly, crude ORs were calculated to identify predictors of use of suppressive antibiotics. Multivariable logistic regression was used to identify independent predictors of treatment success. Covariates were considered for inclusion in the adjusted model based on likely associations between the covariate of interest and outcome ($P \leq .20$) and whether adding the covariate to the model in a stepwise fashion led to a ≥10% change in estimate. A collinearity assessment revealed no major issues with the validity of the final selected model. In the final model, we adjusted for causative organisms, ≥3 comorbidities, and length of initial antibiotic administration. Additionally, we performed an a priori subgroup analysis of groups 1 and 2. Finally, we performed a subgroup analysis to assess whether any association exists between the causative organisms implicated in spinal infections, timing of infection, and removal of hardware. All statistical analyses were conducted using SAS 9.4 (Cary, NC, USA). A 2-sided *P* value of ≤.05 was considered statistically significant.

RESULTS

A total of 869 medical charts were reviewed. Of these, charts were excluded due to absence of surgical intervention (n = 574) or lack of appropriate follow-up (n = 161). Thus, only 124 patients met the study inclusion criteria and were included in this analysis with 50 patients (40.3%) in group 1 and 74 patients (59.7%) in group 2, with a treatment success rate of 78.2% (n = 97). Baseline characteristics of the study population are presented in Table 1. The mean age of study participants (range) was 58.3 (17–63) years, 33.1% were female, and 61.5% of the total study population had 3 or more comorbidities. Twenty-five percent of the population was diabetic, and only 7.3% was immunocompromised. The majority of spinal infections were in the lumbar region (n = 68, 54.8%). The causative organism was identified in 83.9% of all study participants, of which *Staphylococcus* was the most commonly identified species (n = 74, 71.1% of patients

Table 1. Demographic and Clinical Characteristics of Patients With Spinal Infections Involving Hardware[a]

Characteristic	Total (n = 124)	Treatment Success[b] (n = 97)	Treatment Failure (n = 27)	P Value[c]
Demographics				
Age, mean (SD), y	58.3 (13.0)	58.4 (12.6)	58.1 (14.7)	.94
Female	41 (33.1)	35 (36.1)	6 (22.2)	.18
White	87 (75.7)	68 (75.6)	19 (76.0)	.96
Comorbidities				
0	3 (2.5)	3 (3.2)	0 (0.0)	.48
1	18 (14.8)	13 (13.7)	5 (18.5)	.54
2	26 (21.3)	21 (22.1)	5 (18.5)	.81
≥3	75 (61.5)	58 (61.1)	17 (63.0)	.77
Immunosuppressed	9 (7.3)	5 (5.2)	4 (14.8)	.10
Diabetes mellitus	31 (25.0)	30 (30.9)	1 (3.70)	.01
Lab characteristics				
WBC, mean (SD)	14.7 (5.5)	14.8 (5.6)	14.3 (5.3)	.72
ESR, mean (SD)	80.4 (31.8)	80.5 (31.0)	80.0 (35.0)	.94
CRP, mean (SD)	116.5 (99.3)	109.3 (74.1)	143.0 (109.3)	.13
Organism				
Causative organism identified	104 (83.9)	78 (80.4)	26 (96.3)	.07
MSSA	30 (24.2)	25 (25.8)	5 (18.5)	.71
MRSA	30 (24.2)	22 (22.7)	8 (29.6)	.46
Coagulase-negative *Staphylococcus*	14 (11.3)	9 (9.3)	5 (18.5)	.18
Propionibacterium acnes	6 (4.8)	4 (4.1)	2 (7.4)	.61
Strep or *Entero*	22 (17.7)	13 (13.4)	9 (33.3)	.02
Gram-negative rods	18 (14.5)	9 (9.3)	9 (33.3)	.01
Polymicrobial	18 (14.5)	9 (9.3)	9 (33.3)	.01
Site and timing of spinal infection				
Cervical	29 (23.4)	23 (23.7)	6 (22.2)	.87
Thoracic	35 (28.2)	23 (23.7)	12 (44.4%)	.03
Lumbar	68 (54.8)	54 (55.7)	14 (51.9)	.72
Sacral	23 (18.0)	19 (18.8)	4 (14.8)	.99
Infection of hardware	50 (40.3)	33 (34.0)	17 (63.0)	.01
Early hardware infection	37 (74.0)	23 (69.7)	14 (82.4)	.50
Hardware removal	15 (30.0)	10 (30.3)	5 (29.4)	.95
Initial antibiotics administered[d]				
Beta-lactam	70 (56.5)	56 (57.7)	14 (51.9)	.59
Vancomycin or daptomycin	76 (61.3)	57 (58.8)	19 (70.4)	.27
Fluoroquinolones	21 (16.9)	15 (15.5)	6 (22.2)	.40
Aminoglycoside	3 (2.4)	3 (3.1)	0 (0.0)	.47
Rifampin[e]	47 (37.9)	37 (38.1)	10 (37.0)	.92
Length of initial Abx treatment, mean (SD), wk	7.4 (3.2)	6.9 (1.9)	9.4 (5.5)	.01
Suppressive antibiotics (n = 80)				
Bactrim	29 (23.4)	20 (20.2)	9 (33.3)	.35
Beta-lactam	29 (23.4)	23 (23.2)	6 (22.2)	.50
Fluoroquinolones	11 (8.9)	8 (8.1)	3 (11.1)	.99
Clindamycin	2 (1.6)	1 (1.0)	1 (3.7)	.45
Rifampin	16 (12.9)	15 (15.5)	1 (3.7)	.19
Follow-up, mean (SD), mo	12.0 (12.7)	12.0 (13.5)	11.9 (9.4)	.96

Abbreviations: Abx, antibiotics; CRP, C-reactive protein; *Entero, Enterococcus*; ESR, erythrocyte sedimentation rate; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; *Strep, Streptococcus*; WBC, white blood cell count.

[a]Data are given as No. (%) unless otherwise specified.

[b]Treatment success was a composite of (1) survival, (2) absence of additional surgical intervention for recurrent infection, (3) absence of relapse, defined as patients with recurrent signs and symptoms of spinal infection after the completion of the initial IV antibiotic course.

[c]Chi-square or Fisher exact test for categorical variables; Student *t* test for continuous variables.

[d]Initial antibiotics mostly parenteral.

[e]Fourteen individuals received rifampin both initially and as suppressive antibiotics.

with positive culture). Methicillin-sensitive *Staphylococcus aureus* (MSSA) was identified in 30 patients, methicillin-resistant *Staphylococcus aureus* (MRSA) in 30 patients, and coagulase-negative *Staphylococcus* (CoNS) in 14 patients. The rest had either gram-negative rods (GNRs; 18 patients) or polymicrobial infections (18 patients). Vancomycin and daptomycin were the parenteral antibiotics most commonly prescribed (n = 76, 61.3%), followed closely by beta-lactam antibiotics (n = 70, 56.5%). Rifampin was added to the initial antibiotic regimen in 47 patients (37.9%). The average length of initial antibiotic treatment (SD) was 7.4 (3.2) weeks. Patients in the treatment failure group received longer courses of intravenous antibiotics (mean [SD], 9.4 [5.5] weeks) as compared with the treatment success group (6.9 weeks; $P = .01$). In total, 64.5% of the study population received suppressive antibiotics; however, duration and type of suppressive antibiotics received varied greatly, with 27 receiving up to 6 months (24.8%), 18 receiving between 6 and 12 months (16.5%), and 27 receiving >12 months of suppressive oral antibiotics (24.8%). Trimethoprim/sulfamethoxazole (n = 29, 23.4%) and beta-lactam antibiotics (n = 29, 23.4%) were most often prescribed as suppressive oral antimicrobial treatment. Rifampin was used as suppressive oral antibiotics in 12.9% of cases (n = 16), and it was used as monotherapy in only 1 case. The mean follow-up time was 12.0 months (range [SD], 1.5–96 [12.7] months).

Results from our logistic regression model are displayed in Table 2. We examined the associations between different causative organisms and treatment success and considered these as potential covariates for inclusion in the final model. Having *Streptococcus* or *Enterococcus* species (odds ratio [OR], 0.31; 95% CI, 0.11–0.83), GNRs (OR, 0.20; 95% CI, 0.07–0.59), or a polymicrobial infection (OR, 0.20; 95% CI, 0.07–0.59) was inversely associated with treatment success. We also observed that longer courses of initial antimicrobial therapy (OR, 0.81; 95% CI, 0.70–0.93) and thoracic spinal infections (OR, 0.39; 95% CI, 0.16–0.95) were inversely associated with treatment success. Finally, patients in group 2 were more likely to have treatment success (OR, 3.30; 95% CI, 1.36–8.00), whereas patients in group 1 were less likely to have treatment success (OR, 0.30; 95% CI, 0.12–0.74), with no statistically significant difference observed between patients who had hardware removal and those who had their hardware kept in place (OR, 1.04; 95% CI, 0.29–3.75).

To better characterize how clinicians approach spinal infections of hardware, we also conducted analyses to identify predictors of suppressive antibiotic use in our study population (Table 3). Laboratory markers of inflammation, including white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), were not significantly associated with use of suppressive antibiotics. Infection with any *Staphylococcus* species (MSSA, MRSA, or CoNS) was a predictor of suppressive antibiotic use (OR, 2.11; 95% CI, 1.00–4.46).

There was an inverse relationship between the use of oral suppressive antibiotics and the following microorganisms: *P. acnes*, *Streptococcus* or *Enterococcus*, GNRs, and polymicrobial infections; however, these results were not statistically significant. In addition, although not statistically significant, patients in group 2 were less likely to receive suppressive oral antibiotics (OR, 0.49; 95% CI, 0.22–1.07), as compared with patients in group 1 (OR, 2.05; 95% CI, 0.94–4.49). There was no significant association between early infection of hardware and use of suppressive oral antibiotics (OR, 0.43; 95% CI, 0.08–2.27) or those who had removal of their hardware (OR, 0.95; 95% CI, 0.24–3.76). Finally, the choice and length of initial antimicrobial therapy did not help predict use of oral suppressive therapy.

We also did a subgroup analysis to investigate length of suppressive antibiotic use by timing of infection relative to hardware placement in study patients (Table 4). We found that suppressive antibiotic use for >12 months was significantly associated with group 2.

Additionally, we conducted a subgroup analysis of patients by timing of hardware infection (early vs late) in group 1 (n = 50) to identify causative organisms (Table 5). Of note, we found that infections caused by *Streptococcus* and *Enterococcus* species were significantly associated with early infections ($P = .05$). Furthermore, we found that early infection was inversely associated with hardware removal in those who had infections of hardware (OR, 0.24; 95% CI, 0.06–0.91). Finally, in a descriptive analysis, we found that 96.7% of included study participants had surgical debridement, with no significant difference between groups 1 and 2 ($P = .30$).

We also completed a subgroup analysis of hardware removal and retention in patients from group 1 (Table 6). We found that having MSSA, MRSA, or CoNS infections was associated with hardware removal, whereas having a GNR infection was inversely associated with hardware removal, although this was not statistically significant due to the small sample size. Finally, we found no association between the use of oral suppressive antibiotics and hardware removal or retention (OR, 0.95; 95% CI, 0.24–3.76).

DISCUSSION

There is currently no consensus on the optimal medical and surgical management of spinal infections involving hardware. To our knowledge, this is the largest retrospective observational study to date that aims to describe baseline characteristics of patients with spinal infections involving hardware, to assess the association of suppressive antibiotic therapy with treatment success, and to identify factors that predict use of suppressive antibiotics in patients with spinal infections involving hardware.

We identified several important factors that help characterize patients with spinal infections involving hardware. The most commonly identified species was *Staphylococcus aureus,*

Table 2. Odds of Treatment Success Among Included Study Patients (n = 124)

	No. (%)			OR (95% CI)	
Variable	Total	Treatment Success (n = 97)[a]	No Treatment Success (n = 27)	Unadjusted	Adjusted[b]
Suppressive antibiotic use[c]					
None	37 (33.9)	34 (39.1)	3 (13.6)	Referent	Referent
0–6 mo	27 (24.8)	22 (25.3)	5 (22.7)	0.39 (0.08–1.79)	0.23 (0.04–1.22)
6–12 mo	18 (16.5)	14 (16.1)	4 (18.2)	0.31 (0.06–1.56)	0.16 (0.03–1.01)
> 12 mo	27 (24.8)	17 (19.5)	10 (45.5)	0.15 (0.04–0.62)	0.11 (0.02–0.56)
Demographic/clinical characteristics					
Age, y	58.3 (13.0)	58.4 (12.6)	58.1 (14.7)	1.00 (0.97–1.03)	—
Immunosuppressed	9 (7.3)	5 (5.2)	4 (14.8)	0.31 (0.08–1.26)	—
Diabetes	31 (25.0)	30 (30.9)	1 (3.70)	11.64 (1.51–89.82)	—
≥3 comorbidities	75 (61.5)	58 (61.1)	17 (63.0)	0.87 (0.36–2.11)	1.02 (0.33–3.16)
Causative organism					
MSSA	30 (24.2)	25 (25.8)	5 (18.5)	1.40 (0.45–4.33)	—
MRSA	30 (24.2)	22 (22.7)	8 (29.6)	0.77 (0.28–2.10)	—
Coagulase-negative *Staphylococcus*	14 (11.3)	9 (9.3)	5 (18.5)	0.45 (0.14–1.48)	—
Propionibacterium acnes	6 (4.8)	4 (4.1)	2 (7.4)	0.54 (0.09–3.11)	—
Strep or *Entero*	22 (17.7)	13 (13.4)	9 (33.3)	0.31 (0.11–0.83)	0.35 (0.09–1.37)
Gram-negative rods	18 (14.5)	9 (9.3)	9 (33.3)	0.20 (0.07–0.59)	0.55 (0.08–3.89)
Polymicrobial	18 (14.5)	9 (9.3)	9 (33.3)	0.20 (0.07–0.59)	0.45 (0.07–3.06)
Infection of hardware[d]	50 (40.3)	33 (34.0)	17 (63.0)	0.30 (0.12–0.74)	—
Early infection	37 (74.0)	23 (69.7)	14 (82.4)	0.49 (0.12–2.10)	—
Hardware removal	15 (30.0)	10 (30.3)	5 (29.4)	1.04 (0.29–3.75)	—
Initial antibiotics administered[e]					
Beta-lactam	70 (56.5)	56 (57.7)	14 (51.9)	1.27 (0.54–2.98)	—
Vancomycin or daptomycin	76 (61.3)	57 (58.8)	19 (70.4)	0.60 (0.24–1.51)	—
Fluoroquinolones	21 (16.9)	15 (15.5)	6 (22.2)	0.64 (0.22–1.85)	—
Aminoglycoside	3 (2.4)	3 (3.1)	0 (0.0)	—	—
Rifampin	47 (37.9)	37 (38.1)	10 (37.0)	1.05 (0.43–2.53)	—
Length of initial Abx treatment, wk	7.4 (3.2)	6.9 (1.9)	9.4 (5.5)	0.81 (0.70–0.93)	0.85 (0.69–1.05)
Suppressive antibiotics (n = 80)					
Bactrim	29 (23.4)	20 (20.2)	9 (33.3)	0.52 (0.20–1.33)	—
Beta-lactam	29 (23.4)	23 (23.2)	6 (22.2)	1.09 (0.39–3.02)	—
FQ	11 (8.9)	8 (8.1)	3 (11.1)	0.88 (0.18–2.92)	—
Clindamycin	2 (1.6)	1 (1.0)	1 (3.7)	0.27 (0.02–4.48)	—
Rifampin	16 (12.9)	15 (15.5)	1 (3.7)	4.76 (0.60–37.76)	—
Site of spinal infection					
Cervical	29 (23.4)	23 (23.7)	6 (22.2)	1.09 (0.39–3.02)	—
Thoracic	35 (28.2)	23 (23.7)	12 (44.4)	0.39 (0.16–0.95)	—
Lumbar	68 (54.8)	54 (55.7)	14 (51.9)	1.17 (0.50–2.74)	—
Sacral	23 (18.0)	19 (18.8)	4 (14.8)	1.22 (0.37–3.99)	—

Abbreviations: Abx, antibiotics; CI, confidence interval; *Entero, Enterococcus*; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; OR, odds ratio; *Strep, Streptococcus*.

[a]Treatment success was a composite of (1) survival, (2) absence of additional surgical intervention for recurrent infection, (3) absence of relapse, defined as patients with recurrent signs and symptoms of spinal infection after the completion of the initial IV antibiotic course.

[b]Odds ratios adjusted for causative organisms including strep/entero, polymicrobial, gram-negative rods, ≥3 comorbidities, and length of initial antibiotic administration.

[c]Suppressive antibiotic use was defined as any oral antibiotics given after completing the initial intravenous antibiotic regimen; unknown length of use of suppressive antibiotics (n = 15), treatment success (n = 10), no treatment success (n = 5).

[d]Defined as infections occurring within 3 months of hardware placement.

[e]Initial antibiotics mostly parenteral.

isolated in 48.4% of patients, which is in alignment with the current literature [7, 10–12]. Twenty-five percent of patients had diabetes mellitus, which is a predictor of surgical site infection in spinal surgery [13]. As can be expected in the setting of an active infection, baseline laboratory markers including WBC count, ESR, and CRP were elevated, although both ESR and CRP values are more useful than WBC count in the diagnosis of spinal infections [14].

From our data, hardware was more likely to be removed in late postoperative infections as compared with early infections. In the early postoperative period, the lack of spinal fusion and stability can lead to several complications. In a

Table 3. Predictors of Suppressive Antibiotic Use in the Treatment of Spinal Infections Involving Hardware

Variable	Total	Suppressive Antibiotics[a] (n = 80)	No Suppressive Antibiotics (n = 44)	OR (95% CI)
		No. (%)		
Clinical characteristics				
≥3 comorbidities	75 (61.5)	48 (60.8)	27 (62.8)	0.94 (0.44–2.01)
Organism				
MSSA	30 (24.2)	24 (30.0)	6 (13.6)	3.31 (1.19–9.20)
MRSA	30 (24.2)	21 (26.3)	9 (20.5)	1.93 (0.77–4.87)
Coagulase-negative *Staphylococcus*	14 (11.3)	8 (10.0)	6 (13.6)	0.70 (0.23–2.18)
All staph (*S. aureus*, coNS)	71 (57.3)	51 (63.8)	20 (45.5)	2.11 (1.00–4.46)
Propionibacterium acnes	6 (4.8)	3 (3.8)	3 (6.8)	0.53 (0.10–2.76)
Strep or *Entero*	22 (17.7)	12 (15.0)	10 (22.7)	0.60 (0.24–1.53)
Gram-negative rods	18 (14.5)	11 (13.8)	7 (15.9)	0.84 (0.30–2.36)
Polymicrobial	18 (14.5)	10 (12.5)	8 (18.2)	0.64 (0.23–1.77)
Site and timing of spinal infection				
Cervical	29 (23.4)	19 (23.8)	10 (22.7)	1.06 (0.44–2.53)
Thoracic	35 (28.2)	21 (26.3)	14 (31.8)	0.76 (0.34–1.71)
Lumbar	68 (54.8)	45 (56.3)	23 (52.3)	1.17 (0.56–2.46)
Sacral	21 (16.9)	14 (17.5)	7 (15.9)	1.12 (0.42–3.03)
Infection followed by hardware placement	74 (59.7)	43 (53.8)	31 (70.5)	0.49 (0.22–1.07)
Infection of hardware	50 (40.3)	37 (46.3)	13 (29.6)	2.05 (0.94–4.49)
Early infection[b]	37 (74.0)	26 (70.3)	11 (84.6)	0.43 (0.08–2.27)
Hardware removal	15 (30.0)	11 (29.7)	4 (30.8)	0.95 (0.24–3.76)
Initial antibiotics administered[c]				
Beta-lactam	70 (56.4)	44 (55.0)	26 (59.1)	0.85 (0.40–1.78)
Vancomycin or daptomycin	76 (61.3)	48 (60.0)	28 (63.6)	0.86 (0.40–1.83)
Fluoroquinolones	21 (16.9)	10 (12.5)	11 (25.0)	0.43 (0.17–1.11)
Aminoglycoside	3 (2.4)	1 (1.3)	2 (4.6)	—
Rifampin	47 (37.9)	35 (43.8)	12 (27.3)	2.07 (0.93–4.60)
Length of initial Abx treatment, wk	7.4 (3.2)	7.2 (2.8)	7.9 (3.7)	0.93 (0.83–1.04)

Abbreviations: Abx, antibiotics; coNS, coagulase-negative *Staphylococcus*; *Entero, Enterococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; OR, odds ratio; *Strep, Streptococcus*.

[a]Suppressive antibiotic use was defined as any oral antibiotics given after completing the initial intravenous antibiotic regimen; unknown length of suppressive antibiotic use (n = 15), treatment success (n = 10), no treatment success (n = 5).

[b]Defined as infections occurring within 3 months of hardware placement.

[c]Initial antibiotics mostly parenteral.

Table 4. Subgroup Analysis of Study Patients by Timing of Infection Relative to Hardware Placement (Group 1 vs Group 2)[a]

	OR (95% CI)			
	Infection of Hardware (n = 50)		Infection Then Hardware (n = 74)	
Variable	Unadjusted	Adjusted[b]	Unadjusted	Adjusted
Suppressive antibiotic use[c]				
None	Referent	Referent	Referent	Referent
0–6 mo	0.38 (0.05–2.77)	0.17 (0.02–1.91)	0.62 (0.04–10.54)	0.43 (0.02–9.83)
6–12 mo	0.88 (0.10–7.95)	0.55 (0.03–9.29)	0.14 (0.01–1.71)	0.08 (0.01–1.42)
>12 mo	0.42 (0.07–2.65)	0.30 (0.03–3.10)	0.07 (0.01–0.70)	0.06 (0.01–0.84)
Suppressive antibiotic use				
≥3 mo	0.57 (0.16–1.98)	0.19 (0.03–1.30)	0.24 (0.06–1.02)	0.14 (0.02–0.89)
≥6 mo	1.20 (0.37–3.86)	1.03 (0.23–4.56)	0.19 (0.05–0.75)	0.10 (0.01–0.61)
≥12 mo	0.80 (0.23–2.76)	0.78 (0.17–3.56)	0.18 (0.04–0.82)	0.16 (0.03–0.95)

Abbreviation: OR, odds ratio.

[a]Group 1: patients who had an infection of previously inserted hardware; Group 2: patients who had an active infection that led to hardware placement.

[b]Odds ratios adjusted for causative organisms including *Streptococcus/Enterococcus*, polymicrobial, gram-negative rods, ≥3 comorbidities, and length of initial antibiotic administration.

[c]Suppressive antibiotic use was defined as any oral antibiotics given after completing the initial intravenous antibiotic regimen; unknown length of suppressive antibiotic use (n = 15), treatment success (n = 10), no treatment success (n = 5).

Table 5. Subgroup Analysis of Early vs Late Infection of Hardware (n = 50)

	No. (%)		
	Early Infection[a] (n = 37)	Late Infection (n = 13)	P Value[b]
Causative organism			
MSSA	9 (24.3)	5 (38.5)	.47
MRSA	11 (29.7)	4 (30.8)	.99
Coagulase-negative *Staphylococcus*	6 (16.2)	2 (15.4)	.99
Propionibacterium acnes	1 (2.7)	1 (8.3)	.43
Strep or *Entero*	10 (27.0)	0 (0.0)	.05
Gram-negative rods	8 (21.6)	2 (16.7)	.99
Polymicrobial	13 (35.1)	1 (8.3)	.14

Abbreviations: *Entero, Enterococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; *Strep, Streptococcus*.
[a]Defined as infections occurring within 3 months of hardware placement.
[b]Chi-square or Fisher exact test for categorical variables.

retrospective cohort review, Kowalski et al. showed an improvement in infection-free survival when instrumentation was removed in late infections [15]. However, there is no clear evidence for the management of early postoperative spinal hardware infections.

There are currently no guidelines for length of parenteral antibiotics treatment of spinal infections involving hardware. In our study, we found that the average length of initial intravenous antibiotics was 7.4 (3.2) weeks. This is in alignment with current knowledge that parenteral antibiotics are prescribed for 6–8 weeks [1]. This is also similar to current Infectious Diseases Society of America (IDSA) guidelines for native vertebral osteomyelitis, in which parenteral antibiotics are recommended for 6 weeks [16]. Patients in the treatment failure group received longer courses of intravenous antibiotics as expected. Data on the use of oral suppressive antibiotics in patients with spinal infections involving hardware have been limited. In our study, 64.5% of patients received suppressive antibiotics, with the most commonly prescribed being trimethoprim/sulfamethoxazole and beta-lactam antibiotics (dicloxacillin, amoxicillin, penicillin, cephalexin, amoxicillin-clavulanic acid), whereas

rifampin was only used in 12.9% of cases despite *Staphylococcus* being the most common causative organism. This may be due to the fact that most patients in our study had 3 or more comorbidities, therefore may have had several medications with potential interaction with rifampin. Other possibilities might be related to the lack of susceptibility and lack of tolerability of the drug.

We found that the use of oral suppressive antibiotics for more than 12 months after initial intravenous antibiotic administration was inversely associated with treatment success, likely due to more complicated infections or infections that relapsed despite prior antimicrobial therapy. This contrasts with findings published by Keller et al. suggesting that use of suppressive antibiotics in orthopedic hardware infections for at least 3 months was associated with treatment success, whereas use for >6 months was not statistically significantly associated with treatment success [10]. In their study, orthopedic hardware included, but was not limited to, spinal hardware. This also contrasts with the study done by Kowalski et al., which showed that the use of oral antimicrobial suppression therapy is associated with longer failure-free survival in patients with early spinal

Table 6. Subgroup Analysis of Hardware Removal vs Hardware Retention in Patients who Had Infections of Previously Inserted Hardware (n = 50)

	No. (%)		
	Hardware Removal[a]	Hardware Retention[b]	OR (95% CI)
Organism			
MSSA	4 (26.7)	10 (28.6)	0.91 (0.23–3.54)
MRSA	7 (46.7)	8 (22.9)	2.96 (0.82–10.68)
Coagulase-negative *Staphylococcus*	3 (20.0)	5 (14.3)	1.50 (0.31–7.28)
Propionibacterium acnes	1 (6.7)	1 (2.9)	2.43 (0.14–41.60)
Strep or *Entero*	1 (6.7)	9 (25.7)	0.21 (0.02–1.80)
Gram-negative rods	2 (13.3)	8 (22.9)	0.52 (0.10–2.80)
Polymicrobial	2 (13.3)	12 (34.3)	0.29 (0.06–1.53)
Suppressive antibiotics (n = 80)	11 (73.3)	26 (74.3)	0.95 (0.24–3.76)

Abbreviations: *Entero, Enterococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; OR, odds ratio; *Strep, Streptococcus*.
[a]Hardware removal: n = 15.
[b]Hardware retention: n = 35.

hardware infections [15]. Oral suppressive antibiotics were used indefinitely at their institution.

Furthermore, we found that patients with *Staphylococcus* species infections were more likely to receive suppressive antibiotics and more likely to have their hardware removed. In fact, infection with *Staphylococcus* species (MSSA, MRSA, CoNS) was the only predictor in our study of suppressive antibiotic use. No other factors, such as age, number of comorbidities, or site of spinal infection, seemed to predict a clinician's decision to use suppressive antibiotics in our population. The IDSA guidelines for treatment of MRSA infections recommend treating early-onset spinal hardware infections or spinal infections with hardware placement with intravenous antibiotics and rifampin followed by oral suppressive therapy (unclear duration, but at least until spinal fusion has occurred), whereas for late-onset hardware infections, hardware removal is recommended [17]. Our results found that hardware retention was not more frequently associated with the use of oral suppressive antibiotics.

On the other hand, we found that patients who have infection with *Streptococcus* or *Enterococcus*, polymicrobial infection, or GNRs were less likely to have treatment success. Patients who had gram-negative rod infections were less likely both to receive suppressive antibiotics and to have hardware removed, factors that may contribute to the less favorable outcomes observed in this population. This is consistent with the data published by Keller et al., where patients with orthopedic hardware infections with GNRs were at higher risk of treatment failure [10]. Given that GNRs are also capable of biofilm formation [18], providers may need to consider suppressive therapy as part of the management of GNR spinal hardware infections and hardware removal when possible. Further studies are needed to determine the preferred management for patients with spinal hardware infections due to GNRs.

The strengths of this study include the size of the study population in comparison with other existing literature, robust data collection including demographics, clinical presentation, laboratory markers, microbiologic results, and choice and length of antibiotic therapy, and the 10-year period over which data were collected.

There are multiple notable limitations of this study, including its retrospective design. Given that the study was limited to tertiary care centers of Emory University, it is possible that only the most severe cases were included in our retrospective study, leading to referral bias. Thus, the findings from this study may not be generalizable. Additionally, while inclusion criteria for the analysis included follow-up for at least 6 weeks, variable length of follow-up among our patient population may have contributed to lead-time bias. Also, there was a large number of patients who were excluded from the study due to lack of appropriate follow-up, which can lead to selection bias. Furthermore, there is a lack of standardization of the definition of treatment

success and failure in the literature. While our definition of treatment failure was based on initial management strategy and was more inclusive than those typically used, it may also result in higher treatment failure rates being reported. Finally, although this is the largest retrospective chart review to date, the study's small sample size may have limited the ability to detect small but statistically significant differences between comparative groups. Larger multisite studies are necessary to devise appropriate recommendations regarding the optimal surgical and medical management of spinal infections involving hardware.

CONCLUSIONS

This study contributes to the limited literature regarding optimal management of spinal infections with hardware. Surgical and medical management of spinal infections involving hardware should be tailored to the timing of onset of infection and causative organism. GNR infections are associated with biofilm formation [18], and this study, as well as current literature, shows higher failure rates in treating these infections [10]. Therefore, when managing GNR spinal infections, more aggressive management may be needed, such as hardware removal when possible or oral suppressive antibiotic therapy. Further studies are needed to determine best management practices, particularly for GNR infections where the role of further suppressive antibiotics and hardware removal may be warranted.

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