MAJOR ARTICLE

# The Management and Outcome of Spinal Implant Infections: Contemporary Retrospective Cohort Study

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***Background.*** Spinal implant infections provide unique diagnostic and therapeutic challenges.

***Methods.*** We conducted a retrospective cohort study to evaluate risk factors for treatment failure in patients with early- and late- onset spinal implant infections at the Mayo Clinic (Rochester, MN) during 1994–2002.

***Results.*** We identified 30 patients with early-onset spinal implant infection and 51 patients with late-onset spinal implant infection. Twenty-eight of 30 patients with early-onset infection were treated with debridement, implant retention, and antimicrobial therapy. The estimated 2-year cumulative probability of survival free of treatment failure for patients with early-onset infection was 71% (95% confidence interval [CI], 51%–85%). Thirty-two of 51 patients with late-onset infection were treated with implant removal. Their estimated 2-year cumulative probability of survival free of treatment failure was 84% (95% CI, 66%–93%). For patients with early-onset infections, receiving oral antimicrobial suppression therapy was associated with increased cumulative probability of survival (hazard ratio, 0.2; 95% CI, 0.1–0.7). For patients with late-onset infections, implant removal was associated with increased cumulative probability of survival (hazard ratio, 0.3; 95% CI, 0.1–0.7).

***Conclusions.*** Early-onset spinal implant infections are successfully treated with debridement, implant retention, and parenteral followed by oral suppressive antimicrobial therapy. Implant removal is associated with successful outcomes in late-onset infections.

Spinal implant infection is one of the most significant complications of spinal fusion surgery. The dramatic increase in spinal fusion surgeries being performed ensures that these infections will increasingly be encountered [1]. Their burden is tremendous in terms of patient morbidity (and rarely mortality) and health care resource use and cost. Spinal implant infections present unique diagnostic and therapeutic challenges [2–4].

The optimal goal when treating spinal implant infections is a pain-free patient with a stable spine and a cured infection. Treatment strategies to obtain this goal must consider the stability of the spine in addition to host comorbidities, pathogen-associated factors, and available medical and surgical options. Early infection typically presents with wound healing problems within weeks of implantation, and late infection may present years later, often with chronic pain, implant failure, or lack of adequate spinal fusion [3, 4]. Early-onset wound infections and late-onset implant infections differ in presentation, microbiological characteristics, and management strategies [3, 5]. During the early postoperative period prior to vertebral body fusion, spinal implants provide needed stability. In this context, adhering to the widely held principal of removing infected foreign bodies to optimize resolution of infection may have undesirable consequences. Patients with late-onset infections are more likely to have a fused, stable spine at the time of diagnosis. Therefore, patients can undergo implant removal and systemic antimicrobial therapy [2].

There is no consensus on preferred medical and surgical treatment strategies, particularly for early postoperative infections. Surgical debridement is essential, but the use of suction and/or irrigation systems, antimicrobial beads, or the vacuum-assisted closure device tends to be dependent on the provider and institution. The duration of administration of parenteral antimicrobial therapy and whether oral suppressive anti-

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**Table 1. Definitions used in a retrospective cohort study of patients with spinal implant infections at the Mayo Clinic (Rochester, MN), 1994–2002.**

| Term | Definition |
|---|---|
| Case patient | Patient ⩾18 years old with a spinal implant and symptoms or signs consistent with spinal column infection and 1 of the case conditions listed below |
| Definite case | Positive results of spine site cultures or ⩾2 sets of blood cultures |
| Probable case | Histopathology suggestive of infection, gross intraoperative purulence, the presence of a sinus tract, or a positive Gram stain result from tissue specimens |
| Possible case | Clinical and radiographic diagnosis without microbiologic or histopathologic confirmation |
| Early-onset infection | Symptoms and/or diagnosis of spinal implant infection occurred within 30 days after implant placement |
| Late-onset infection | Symptoms and/or diagnosis of spinal implant infection occurred >30 days after implant placement |
| Main parenteral antimicrobial therapy | Antimicrobial parenterally administered for at least 2 weeks and 66% of the treatment course effective against isolated pathogens |
| Oral antimicrobial suppression therapy | The use of an oral antimicrobial agent following parenteral therapy for a planned prolonged period (⩾6 months) |
| Treatment failure | Treating clinicians' decision to proceed with unanticipated surgical debridement and/or to administer a second complete course of parenteral antimicrobial therapy because of uncontrolled or recurrent spinal infection following ⩾3 weeks of appropriate therapy |

microbial therapy is used also vary. Brief follow-up periods may be particularly problematic with spinal implant infections, given the often indolent but slowly progressive nature of chronic infections. Some debate exists over whether microbial agents play a significant role in the pathogenesis of late-onset spinal implant infection [6]. Dietz [7] suggests that many cases of late-onset drainage from spinal implants may be a result of aseptic inflammation from metal corrosion and that cultures positive for low-virulence organisms from such drainage may be of no pathogenic significance.

This study aims to describe host, pathogen, and management factors of spinal implant infections in a contemporary cohort and to assess factors that impact outcomes after an extended period of follow-up among a patient population with a variety of indications for spinal implants.

## PATIENTS, MATERIALS, AND METHODS

***Study design.*** This is a single center, retrospective cohort study that was undertaken at the Mayo Clinic (Rochester, MN) following institutional review board approval. Medical and surgical therapies were not standardized and were performed at the discretion of the treating physicians.

***Study population and case ascertainment.*** Study patients were evaluated at our institution during 1994–2002. Cases were ascertained by a search of our institutions' medical and surgical indices [8] with the codes associated with the following terms: intraspinal abscess, spinal cord abscess, epidural abscess, pyogenic spinal cord thrombosis, spine joint infection, iliopsoas abscess, psoas abscess, and disk infection. We also searched an interventional radiology database and any positive microbiologic specimens labeled as spine, back, psoas, epidural, or vertebral source. The redundancy of these search mechanisms maximized capture of all potential cases. The medical records of all potential cases were then reviewed for inclusion in the study by the principal investigator. Patients aged ⩾18 years with spinal implants and a diagnosis of spinal implant infection according to our case definition (see below) were included. Detailed information was then abstracted from the medical records by an infectious diseases physician, using a standardized data collection tool that used all aspects of the inpatient and outpatient medical records. Abstracted characteristics included clinical features, results of laboratory and imaging studies, medical and surgical therapies employed, and outcomes. To maximize capture of late treatment failure events, a follow-up survey was sent to all living patients to assess for episodes of treatment failure that had not been documented in the medical records.

***Definitions.*** The definitions used in the study are shown in table 1. Patients who developed signs or symptoms of spine site infection (fever, increasing pain, wound drainage, and wound erythema) within 30 days of implant placement were considered to have early-onset infection. All others were considered to have late-onset infection. Regarding our definition of treatment failure (table 1), cases were not considered to be treatment failures if the treating physicians used clinical dis-

cretion to extend a course of parenteral or oral antimicrobial therapy for a short period of time (≤21 days).

***Statistic analysis.*** In statistical analysis, the early- and late-onset infections were initially analyzed separately for descriptive statistics and univariate analysis. The rate of survival free of treatment failure was estimated using the Kaplan-Meier survival method [9] and reported with 95% CIs. A univariate assessment of selected risk factors was performed using a Cox proportional hazard model [10]; for some variables (e.g., diabetes mellitus and hepatic failure), limited sample size precluded statistical analysis. During the analysis of the use of oral antimicrobial suppression therapy, patients were excluded from the analysis if they developed treatment failure prior to having the opportunity to receive suppression therapy. We then combined the data from early- and late-onset infections and performed a univariate analysis of selected risk factors, using Cox proportional hazard methodology. A small sample size limited multivariate analysis. Descriptive statistics and Kaplan-Meier survival methods were analyzed using JMP, version 6.0 (SAS Institute). SAS, version 9 (SAS Institute) was used to perform analysis, using a Cox proportional hazard model.

## RESULTS

Eighty-one patients with spinal implant infection who were evaluated at our institution during the study period met our case definition and were included in the study; 30 patients had early-onset infection, and 51 patients had late-onset infection. Sixty-one of 81 patients were sent the follow-up survey; 20 patients were not able to be sent the survey because of death (18 patients) or other reasons (2 patients). Forty-six (75%) of 61 patients completed the follow-up survey. Seventeen patients with late-onset infection were diagnosed 30–365 days after implant placement. The median duration of follow-up in the early-onset and late-onset cohorts was 1039 days (range, 37–4069 days) and 1844 days (range, 28–4192 days), respectively, among patients who did not develop clinical failure. The clinical characteristics of the study cohort stratified by onset of infection are shown in table 2.

Medical and surgical treatment information for patients with early-onset infection is shown in table 3. Two patients experienced treatment failure prior to completing a course of parenteral antimicrobial therapy and, therefore, did not have the opportunity to receive oral antimicrobial suppression therapy, and 1 patient had implants removed and, therefore, was not a candidate for suppression therapy. Twenty-three (85%) of 27 candidate patients who had the opportunity to receive oral antimicrobial suppression therapy did so. Nine patients (39%) received $\beta$-lactam antimicrobial therapy, 5 patients (22%) received minocycline therapy, and 3 patients each (13%) received trimethoprim-sulfamethoxazole therapy, a fluoroquinolone, or combination antimicrobial therapy. No patient receiving suppressive antimicrobial therapy had an adverse event related to therapy documented.

Of the 23 patients with early-onset infection treated with suppressive antimicrobial therapy, 22 were treated with the surgical strategy of debridement, implant retention, and parenteral antimicrobial therapy followed by suppressive antimicrobial therapy (1 patient was managed with antimicrobial therapy alone and was treated with oral suppressive antimicrobial therapy). Five of the 22 patients treated with debridement, implant retention, and parenteral antimicrobial therapy followed by suppressive antimicrobial therapy experienced treatment failure. All 5 patients were still receiving suppressive antimicrobial therapy at the time of treatment failure. Seventeen of 22 patients did not experience treatment failure, 7 of whom continued to receive suppression therapy at the time of the last follow-up visit. Suppression therapy was stopped for the remaining 10 patients after a median duration of 468 days (interquartile range [IQR], 169–687 days). Treatment failure was not documented after discontinuation of suppressive antimicrobial therapy for any patient after a median duration of follow-up of 872 days (IQR, 305–1654 days). Of the patients treated with debridement, implant retention, and parenteral antimicrobial therapy but not oral suppressive antimicrobial therapy, 5 of 6 experienced treatment failure (as noted above, 2 patients experienced treatment failure prior to having the opportunity to receive oral antimicrobial suppression therapy).

Table 3 shows details of antimicrobial therapy type, route, and duration for patients with late-onset infection. Thirty-two (63%) of 51 patients with late-onset infection were treated with surgical debridement and implant removal, 13 patients (25%) were treated with surgical debridement with implant retention, and 6 patients (12%) were treated nonsurgically, with antimicrobial therapy alone. Treatment failed in 7 patients (22%) treated with surgical debridement and implant removal, 7 patients (54%) treated with surgical debridement with implant retention, and 4 patients (67%) treated with antimicrobial therapy alone. Ten (31%) of the 32 patients from whom implants were removed subsequently underwent replacement of implants either in a single stage (6 patients had a new implant placed within 3 weeks of removal of the infected implant) or 2-stage (4 patients had a new implant placed >3 weeks after removal of the infected implant) manner. Four of the 6 patients who had single-stage reimplantation were treated with oral antimicrobial suppression therapy, 1 of whom experienced treatment failure. No other patient who had an implant removed and subsequent new implants placed experienced treatment failure. Of the 13 patients treated with surgical debridement and retention, 8 were treated with suppressive antimicrobial therapy. Four of 8 patients treated with suppression therapy and 3 of 5 patients not treated with suppression therapy experienced treatment failure.

**Table 2. Characteristics of patients with spinal implant infections at the Mayo Clinic (Rochester, MN), 1994–2002.**

| Characteristic | Patients with early-onset infection ($n$ = 30) | Patients with late-onset infection ($n$ = 51) |
|---|---|---|
| Age, years (IQR) | 56 (45–71) | 56 (43–64) |
| Male sex | 17 (57) | 29 (57) |
| Case definition | | |
| Definite | 29 (97) | 43 (84) |
| Probable | 0 | 5 (10) |
| Possible | 1 (3) | 3 (6) |
| Duration of follow-up, median days[a] (IQR) | 1039 (353–1383) | 1844 (979–2701) |
| Risk factors | | |
| Diabetes mellitus | 2 (7) | 1 (2) |
| Systemic malignancy | 8 (27) | 6 (12) |
| Hepatic failure | 0 | 1 (2) |
| Immunosuppressive medication use | 5 (17) | 8 (16) |
| End-stage renal disease[b] | 1 (3) | 1 (2) |
| Prior spinal radiation therapy | 8 (27) | 4 (8) |
| Median body mass index[c] (IQR) | 29.5 (24.8–35.6) | 25.7 (22.0–30.6) |
| Infection location[d] | | |
| Cervical | 4 (13) | 8 (16) |
| Thoracic | 9 (30) | 25 (49) |
| Lumbosacral | 17 (57) | 18 (35) |
| Prior history of spine infection | | |
| No. of patients | 1 (3) | 22 (43) |
| Time since prior infection, median days (IQR) | 40 | 439 (129–1451) |
| Time from implant to symptoms, median days (IQR) | 8 (5–14) | 747 (351–1441) |
| Time from implant to diagnosis, median days (IQR) | 14 (9–22) | 778 (277–1649) |
| Microbiological characteristics | | |
| *Staphylococcus aureus* | 10 (33) | 11 (22) |
| Coagulase-negative staphylococci | 3 (10) | 9 (18) |
| Gram-negative bacilli | 4 (13) | 1 (2) |
| Streptococci | 3 (10) | 3 (6) |
| *Propionibacterium acnes* | 1 (3) | 6 (12) |
| Polymicrobial infection[e] | 7 (23) | 12 (24) |
| Culture negative[f] | 1 (3) | 8 (16) |
| Other[g] | 1 (3) | 1 (2) |
| Condition at diagnosis | | |
| Back pain present | 22 (73) | 33 (67) |
| Temperature, median °C (IQR) | 38.3 (37.7–39) | 37.9 (37.4–38.7) |
| Wound drainage | 27 (90) | 16 (31) |
| Neurologic deficits | 4 (13) | 8 (16) |
| Sinus tract present | 0 | 13 (25) |
| ESR, median mm/h (IQR) | 58 (51–81) | 45 (20–72) |
| CRP level, median mg/dL (IQR) | 7.1 (3.0–13.7) | 3.9 (0.6–6.8) |
| WBC count, median $\times 10^9$ cells/mL (IQR) | 9.7 (6.9–13.4) | 9.7 (6.8–11.4) |
| Positive blood culture results | 9 (43) | 6 (21) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range.

[a] Among patients who did not develop treatment failure.

[b] Creatinine level ⩾2.0 mg/dL.

[c] Calculated as the weight in kilograms divided by the square of height in meters.

[d] Categorized by most superior segment involved.

[e] Early infections: gram-negative bacilli (6 patients), *S. aureus* (3), coagulase-negative staphylococci (3), *Peptostreptococcus* species (2), streptococci (2), *P. acnes* (1), *Corynebacterium* species (1); late infections: streptococci (8), *S. aureus* (4), coagulase-negative staphylococci (4), *P. acnes* (3), *Candida* species (3), *Corynebacterium* species (2), *Lactobacillus* species (1).

[f] Seven of the 9 patients with culture-negative infection received prior antimicrobial therapy within 2 weeks of culture samples being obtained.

[g] Early-onset infection, *Corynebacterium* species; late-onset infection, anaerobic gram-positive streptococci (not further speciated).

**Table 3. Treatment information for patients with spinal implant infections at the Mayo Clinic (Rochester, MN), 1994–2002.**

| Treatment strategy | Patients with early-onset infection ($n$ = 30) | Patients with late-onset infection ($n$ = 51) |
|---|---|---|
| Surgical management strategy | | |
| Debridement and retention | 28 (93) | 13 (25) |
| Implant removal | 1 (3) | 32 (63) |
| No surgery[a] | 1 (3) | 6 (12) |
| Main parenteral antimicrobial therapy | | |
| $\beta$-Lactam[b] | 12 (40) | 21 (41) |
| Vancomycin | 8 (27) | 15 (29) |
| Combination therapy[c] | 6 (20) | 8 (16) |
| Fluoroquinolone | 1 (3) | 0 |
| Carbapenem | 0 | 1 (2) |
| Other[d] | 3 (10) | 6 (12) |
| Suppressive antimicrobial therapy strategy attempted | 23 (77) | 16 (31) |
| Suppressive antimicrobial used | | |
| $\beta$-Lactam | 9 (39) | 3 (19) |
| Minocycline | 5 (22) | 4 (25) |
| TMP-SMX | 3 (13) | 0 |
| Fluoroquinolone | 3 (13) | 1 (6) |
| Clindamycin | 0 | 1 (6) |
| Combination therapy[c] | 3 (13) | 7 (44) |
| Duration of antimicrobial therapy, median days (IQR) | | |
| Parenteral | 41 (27–43) | 42 (36–44) |
| Oral[e] | 30 (26–33) | 39 (20–50) |
| Suppressive | 303 (147–672) | 410 (61–667) |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Antimicrobial therapy alone.

[b] Cefazolin (18 patients), ceftriaxone (5), cefepime (4), nafcillin (3), and other (3).

[c] More than 1 class of antimicrobial agent meets definition for main antimicrobial therapy.

[d] None of these patients' parenteral treatments met our definition to be included in the main parenteral antimicrobial therapy category (patients either did not receive parenteral therapy, received therapy for <2 weeks, or had sequential monotherapy with different classes of antimicrobials that individually did not meet criteria).

[e] When oral therapy was used as primary therapy (instead of parenteral therapy) or for a brief time period following parenteral therapy (i.e., 2–4 weeks).

The estimated rate of 2-year survival free of treatment failure was 71% (95% CI, 51%–85%) for all patients with early-onset infection. Patients treated with surgical debridement, implant retention, and parenteral antimicrobial therapy followed by oral antimicrobial suppression therapy demonstrated a rate of 2-year survival free of treatment failure of 80% (95% CI, 57%–92%). Patients treated with surgical debridement and implant retention who did not receive oral antimicrobial suppression therapy had an expected rate of 2-year survival free of treatment failure of 33% (95% CI, 8%–73%). It is noteworthy that treatment failure was diagnosed >1 year after implant placement in 3 of 10 patients who experienced treatment failure. One patient with early-onset infection died while in the hospital. Of the patients who experienced treatment failure, 6 of 10 patients then had their implants removed in an attempt to eradicate the infection.

The estimated rate of 2-year survival free of treatment failure was 66% (95% CI, 52%–78%) for all patients with late-onset infection. For patients treated with implant removal, the 2-year survival rate was 84% (95% CI, 66%–93%), but the estimated survival rate was much lower for patients who did not have their implants removed (36%; 95% CI, 17%–61%). Five of 18 patients who experienced treatment failure did so >1 year after diagnosis of spinal implant infection. One patient died of a multisystem organ failure and persistent bacteremia.

A univariate analysis of risk factors for treatment failure in patients with early- and late-onset spinal implant infections is shown in table 4. Receipt of antimicrobial suppression therapy was associated with a reduction in treatment failure in early-onset infection (figure 1). This effect was not seen in cases of late-onset infection or in the combined analysis. In late-onset infection, implant removal was associated with a reduction in

treatment failure (figure 2). Only 3 patients and 1 patient had diabetes mellitus and hepatic failure, respectively. However, all patients with those conditions developed treatment failure.

## DISCUSSION

This retrospective cohort study details the clinical and management differences between early- and late-onset spinal implant infections. The importance of prolonged duration of follow-up to accurately assess outcomes of treatment strategies is emphasized, because 8 (28.6%) of 28 patients who experienced treatment failure did so >1 year after diagnosis. In addition, we have shown for the first time, to our knowledge, that the use of oral antimicrobial suppression therapy is associated with an improved rate of failure-free survival and limited adverse events in patients with early-onset spinal implant infection.

Previously published reports detailing the management of early-onset spinal implant infection largely advocate debridement, implant retention, and systemic antimicrobial therapy [4, 5, 11–15]. Success with this therapeutic approach varies widely from <50% [4] to 100% [11]. Our findings support this surgical management approach. There is less agreement with regard to the benefits of subsequent oral antimicrobial suppression therapy in the published literature, although this practice is commonly used. It is not clear how many patients described in prior published articles received oral antimicrobial suppression therapy or how that may have affected reported outcomes, although for the majority of patients, oral antimicrobial suppression therapy was not reported to be used. The duration of follow-up in these previously published articles varies, but it is notable that some series reported a relatively brief duration of follow-up of <1 year [12, 14]. Thus, the rate of late treatment failure may be underestimated. At our institution, in select circumstances (based on host factors, such as pronounced age or comorbid diseases), oral antimicrobial suppression therapy is continued indefinitely. If treatment failure should manifest late (after spinal fusion has occurred and oral antimicrobial suppression therapy has been discontinued), the patient could then have the implants removed. At our institution, we typically assess for spinal fusion, using routine radiographic images and the opinion of the surgeon.

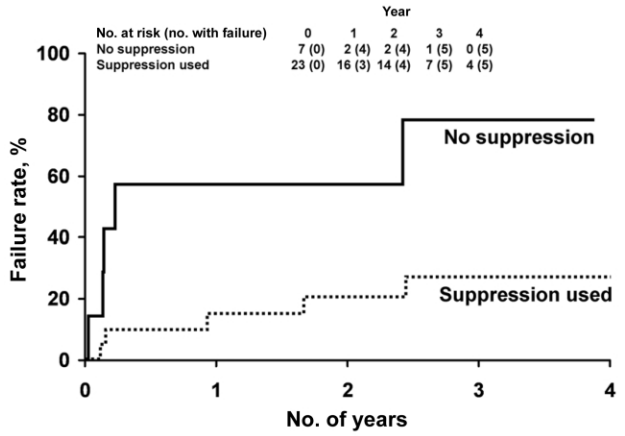


**Figure 1.** Kaplan-Meier failure plot of patients with early-onset infection by the use of oral antimicrobial suppression therapy.

We note a number of important differences between our results and those of previous studies. First, in our study, treatment failure sometimes occurred late, even 2 years after diagnosis. Second, none of the patients received adjunctive therapy with suction and/or irrigation systems or antibiotic beads.

**Table 4. Univariate analysis of risk factors for treatment failure among patients with early- and late-onset spinal implant infections.**

| | Patients with early-onset infection ($n$ = 30) | | Patients with late-onset infection ($n$ = 51) | | Combined ($n$ = 81) | |
|---|---|---|---|---|---|---|
| Variable | HR (95% CI) | $P$ | HR (95% CI) | $P$ | HR (95% CI) | $P$ |
| Case definition | NA[a] | NA[a] | 3.1 (0.4–23.2) | .274 | 0.5 (0.2–1.8) | .323 |
| Immunocompromise | 2.8 (0.7–10.9) | .136 | 1.2 (0.3–4.0) | .821 | 1.7 (0.7–4.1) | .275 |
| Systemic malignancy | 7.7 (2.1–28.1) | .002 | 3.1 (1.0–9.4) | .050 | 4.3 (2.0–9.4) | .0003 |
| Body mass index | 1.0 (0.9–1.1) | .557 | 1.0 (0.9–1.1) | .223 | 1.0 (0.9–1.1) | .197 |
| Prior radiation therapy | 7.7 (2.1–28.1) | .002 | 3.3 (0.9–11.6) | .061 | 4.5 (2.0–10.0) | .0003 |
| Albumin level at diagnosis, g/dL | 1.8 (0.3–11.3) | .553 | 1.1 (0.4–2.7) | .895 | 1.2 (0.6–2.4) | .660 |
| Lymphocyte count at diagnosis, $\times 10^9$ cells/L | 1.0 (0.3–3.4) | .975 | 0.6 (0.3–1.3) | .191 | 0.7 (0.4–1.3) | .277 |
| *Staphylococcus aureus* | 1.2 (0.3–4.4) | .760 | 1.5 (0.5–4.2) | .445 | 1.3 (0.6–3.0) | .464 |
| Duration of parenteral antimicrobial therapy | 0.97 (0.93–1.01) | .111 | 1.0 (0.99–1.04) | .267 | 1.0 (0.99–1.0) | .77 |
| Oral antimicrobial suppression used | 0.2 (0.1–0.7) | .01 | 1.1 (0.4–2.9) | .858 | 0.6 (0.3–1.4) | .265 |
| Implant removal | NA[a] | NA[a] | 0.3 (0.1–0.7) | .01 | 0.4 (0.2–0.9) | .032 |

**NOTE.** HR, hazard ratio; NA, not available.

[a] Limited events precluded analysis

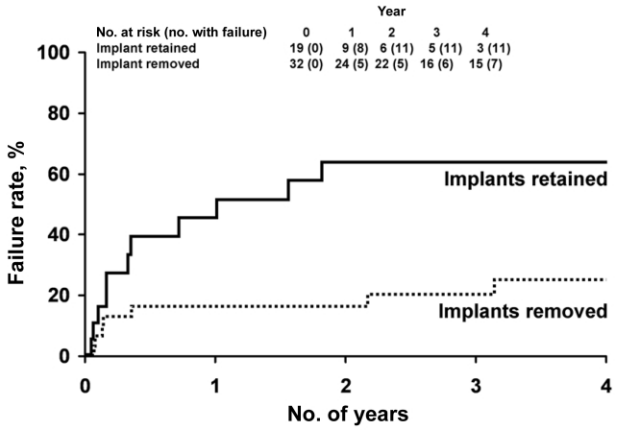


**Figure 2.** Kaplan-Meier failure plot of late-onset infection by implant removal.

Finally, our definition of treatment failure was more inclusive than those typically used. In our cohort, patients were considered to have experienced failure of their initial management strategy if they were treated with unexpected surgical debridement after receiving >3 weeks of presumed effective therapy. In previously published reports, these patients may not have been considered to have experienced treatment failure at that point, but instead may have undergone multiple surgeries for months to years to eventually achieve a result considered successful. In our opinion, our definition of treatment failure more accurately assesses the initial management strategy employed but almost certainly results in higher treatment failure rates being reported.

This cohort emphasizes differences between early- and late-onset infections. The microbiological characteristics of early-onset infection is representative of virulent pathogens that would be expected to cause surgical site infection (such as *Staphylococcus aureus,* $\beta$-hemolytic streptococci, and aerobic gram-negative bacilli). Late-onset infections were more typically culture negative or were caused by avirulent pathogens that were likely inoculated perioperatively (such as coagulase-negative staphylococci and *Propionibacterium acnes*). As expected, management strategies differed by infection onset. Finally, many patients with late-onset infection had a prior history of spine infection. This is likely because of referral patients who had previous early spine implant infections diagnosed at other institutions, experienced treatment failure late, and then were treated at our institution.

Our data support the consensus opinion in the literature that late-onset spinal implant infections are best managed with debridement and implant removal [3, 16–18]. Late-onset infections are caused primarily by organisms known to produce biofilm, such as *S. aureus,* coagulase-negative staphylococci, and *P. acnes.* The presence of biofilm in a chronic infection makes eradication difficult without foreign body removal, similar to other bone and joint infections involving prosthesis [19]. Because only 1 patient received rifampin-based therapy, we are unable to comment on the role of rifampin therapy in this context.

Discussion in the published literature continues with regard to whether late-onset spinal implant pain with inflammation is an infectious or immunologically mediated process. Some series report that >80% of "infections" are culture negative [16], but others report that there is >90% culture positivity when extended culture incubation times are employed [18]. In our cohort, 16% of patients with late-onset spinal implant infection had negative culture results. This, in concert with the microbiological characteristics of late-onset infection, suggests that inoculation of low-virulence organisms at the time of surgical manipulation is the most likely cause of late-onset spinal implant infection. As more sensitive means of detecting microorganisms are developed via novel culture techniques and molecular methods, however, the question may shift further from whether microorganisms are present to what degree of their presence is indicative of a clinically significant infection.

This study has a number of strengths. Rigorous case ascertainment methodology ensured maximum capture of cases. This cohort represents one of the largest cohorts of patients with spine implant infections published. Strict definitions of spinal implant infection and treatment failure allow accurate assessment of the treatment strategy used. The duration of follow-up is prolonged, the importance of which is evident in the number of late treatment failures we observed. Finally, the cohort is relatively contemporary, maximizing relevance to clinicians. The major limitations to our study are inherent to its retrospective nature. The Mayo Clinic is a quaternary referral center, and the potential for referral bias exists. Accordingly, our patient population may involve more complicated cases of spinal implant infection than other centers may typically observe. Patient treatment strategies were not randomly chosen, and thus, an uncontrolled selection bias could have occurred. This is unavoidable in the current study design but of potential significance in generalizing outcomes. Our inclusive definition of treatment failure makes simple comparisons between our cohort and other reports difficult. It is possible that patients may have not recalled episodes of treatment failure when contacted years after it had occurred.

In conclusion, spinal implant infections promise to increasingly pose challenges to clinicians. Management strategies should be tailored to the onset of infection (early vs. late), predisposing host comorbidities, and microbial etiology and susceptibility. We advocate the use of oral antimicrobial suppression therapy until spine fusion has occurred in patients with early-onset infection who have received adequate debridement and parenteral antimicrobial therapy. For late-onset

infections, implant removal remains the crux of effective therapy.

## Acknowledgments

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