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Prior Use of Antimicrobial Therapy is a Risk Factor for Culture-negative Prosthetic Joint Infection

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Abstract

Background Clinical characteristics and control of the infection of patients with culture-negative (CN) prosthetic joint infection (PJI) have not been well assessed. Prior use of antimicrobial therapy has been speculated but not proven as a risk factor for CNPJI.

Questions/purposes We therefore determined whether prior use of antimicrobial therapy, prior PJI, and postoperative wound healing complications were associated with CN PJI.

Methods We performed a retrospective case-control study of 135 patients with CN PJI treated between January 1, 1985, and December 31, 2000 matched with 135 patients with culture-positive (CP) PJIs (control patients) during the study period. The time to failure of therapy compared between cases and control patients using a Kaplan-Meier analysis.

Results The use of prior antimicrobial therapy and postoperative wound drainage after index arthroplasty were associated with increased odds of PJI being culture-negative (odds ratio, 4.7; 95% CI, 2.8–8.1 and odds ratio, 3.5; 95% CI, 1.5–8.1, respectively). The percent (± SE) cumulative incidence free of treatment failure at 2 years followup was similar for CN and CP PJI: 75% (± 4%) and 79% (± 4%), respectively.

Conclusions Prior antimicrobial therapy and postoperative wound drainage were associated with an increased risk of negative cultures among patients with PJI. Physicians should critically evaluate the need for antimicrobial therapy before establishing a microbiologic diagnosis of PJI in patients with suspected PJI.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Mayo PJI Study Group

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

This work was performed at the Mayo Clinic, Rochester, MN, USA.

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Introduction

Prosthetic joint arthroplasty is one of the most commonly performed surgical procedures in the United States with numbers reaching one million annually in the United States [6, 8]. It is estimated that this number will continue to rise to three to four million annual procedures by 2030 [7].

Prosthetic joint infection (PJI), which can occur in 1% to 2% of patients receiving prosthetic joint arthroplasty [1–4, 12], often results in limb dysfunction and is

associated with a mortality rate of 2.7% to 18% [1–4, 8–11, 13]. The cost of PJI management is estimated to be three to four times higher compared with a noninfected revision [13].

Sixty-five percent of PJIs are caused by either Staphylococcus aureus or coagulase-negative Staphylococcus species. In a substantial number of PJI-suspected patients, periprosthetic fluid and tissue cultures yield no growth in either aerobic or anaerobic media [2, 4]. In a previous report by our group, approximately 7% of all PJIs were culture-negative (CN) [3]. In this circumstance, the diagnosis of CN PJI is based on the presence of periprosthetic purulence, acute neutrophilic infiltrate of periprosthetic tissue, or the presence of a sinus tract communicating with the prosthesis.

Risk factors associated with the occurrence of culture-positive (CP) PJI have been well assessed [2]; these include elevated body mass index, elevated National Nosocomial Infection Score NNIS score [2], revision surgery, and postoperative wound healing complications. On the other hand, factors associated with CN PJI such as the use of prior antimicrobial therapy have not been the subject of case control studies. In a previous report of 60 patients with CN PJI we found 61% of patients with CN PJI had received antimicrobial therapy before their PJI diagnosis [4]. As a result of the lack of a control group, we were unable to establish an association between the use of prior antimicrobial therapy and other factors.

We therefore conducted a case-control study to (1) identify risk factors associated with the occurrence of CN PJI with the focus on the use of prior antimicrobial therapy; (2) compare the therapeutic modalities and the incidence free of treatment failure between cases and controls.

Patients and Methods

We performed a retrospective case-control study of the medical records; no patients were recalled specifically for this study. Case patients with CN PJI included 135 patients seen at the Mayo Clinic between January 1, 1985, and December 31, 2000, with CN PJI. Control patients were selected from a population of 1278 patients with CP PJI seen at our institution during the same time period. The 135 patients with CN PJI were matched by gender, diagnosis date (within 1 year), and joint site to 135 patients with CP PJI. The definition of a CN PJI (cases) is based on absence of growth of bacteria associated with the presence of periprosthetic purulence, sinus tract or the presence of neutrophilic infiltrate on periprosthetic histopathology (Table 1). If more than one matched control was provided per case, the one that was closest to the diagnosis of the CP case was chosen. All patients' records were available for review, so there were no patients excluded from the analysis. Through measuring the frequency of exposure to possible risk factors, we collected data that were used to estimate the relative risk of CN PJI related to the possible risk factors. Prior published papers helped us determine the risk factors of interest (Table 1) [2–4]. Selected patients of this group have been included in previously published reports [3, 4, 8]. Every patient was treated by an orthopaedic surgeon who made therapeutic decisions. A specialized orthopaedic infectious diseases service consultation was made available as of 1991 at our institution. All patients included had given prior authorization to allow their medical records to be used for research purposes. The study was approved by the Mayo Clinic Institutional Review Board.

Of the 135 patients with CN PJI, 21 (15%) occurred within 0 to 90 days of prosthesis implantation; 44 (33%) between 90 days and 2 years; and 70 (52%) 2 years after prosthesis implantation (Table 2). Degenerative joint disease was the most common reason for the implantation of a prosthetic joint in CN PJI and CP PJI patients (Table 2). Patient characteristics and clinical factors were compared between CN PJI and CP PJI patients (16% [21 of 135] who developed a CN PJI and 20% of the CP PJI patients [27 of 135] had rheumatoid arthritis). Malignancy diagnosed within 5 years before diagnosis was present in 17% (23 of 135) of CN PJI patients and 16% (22 of 135) of patients with a CP PJI (Table 2). The minimum followup was 1 day (median 1669 days; range, 1–7925 days).

In the CP PJI group, coagulase-negative Staphylococcus was recovered in 44% (59 of 135) followed by S. aureus in 19% (25 of 135) and Streptococcus sp. in 10% (14 of 135). The rest of the microorganisms (27% [37 of 135]) consisted of polymicrobial infection (12), anaerobes (eight) and aerobic Gram-negative bacilli (seven), Enterococcus sp. (six), Candida albicans (three), and Gram-positive bacilli (one). The minimum followup was 1 day (median 1610 days; range, 1–7536 days).

Patients with negative cultures were diagnosed on the basis of periprosthetic purulence only (11 [8%]), sinus tract communicating with the joint only (two [2%]), acute inflammation of periprosthetic tissue only (64 [47%]), purulence plus sinus tract (two [2%]), purulence plus acute inflammation (35 [25%]), sinus tract plus acute inflammation (nine [7%]), purulence, sinus tract plus acute inflammation (eight [6%]), and others (four [3%]). All patients were followed until development of treatment failure, death, or until the last clinical visit without evidence of treatment failure (Table 1). The minimum followup of the 270 episodes was 1 day (median, 56 months; range, 1 day to 264 months). Antimicrobial therapy within 3 months before the diagnosis of CN PJI was administered to 64% of CN PJI (87 of 135) patients

Table 1. Definitions of terms used

Term	Definitions
Culture-negative PJI	No growth of either aerobic or anaerobic cultures taken from periprosthetic tissue during surgery or by periprosthetic aspiration from patients with THA or TKA with at least one of the following: 1. Presence of periprosthetic purulence observed during surgery or at the time of aspiration 2. The presence of acute inflammation on periprosthetic tissue surgical specimens by the histopathologist 3. The presence of a cutaneous sinus tract communicating with the prosthesis
Culture-positive PJI	Isolation of the same microorganism from two or more cultures of joint aspirates or intraoperative tissue specimens or the isolation of a single microorganism with at least one of the following: 1. Presence of periprosthetic purulence observed during surgery or at the time of aspiration 2. The presence of acute inflammation on periprosthetic tissue surgical specimens by the histopathologist 3. The presence of a cutaneous sinus tract communicating with the prosthesis [5]
Treatment failure	Occurrence of a PJI resulting from the original microorganism at any time after the surgical procedure (relapse) or Occurrence of a PJI resulting from a different strain or different microorganism (reinfection) at any time after the surgical procedure or Presence of acute inflammation in the periprosthetic tissue on histopathologic examination or at any subsequent surgery on the joint or Development of a sinus tract or Death from prosthesis-related infection or Indeterminate clinical failure [5]
Main intravenous or oral antimicrobial agent	Antimicrobial agent used for 50% or more of the total duration of antimicrobial therapy course
Joint age	Time between the implantation date and the diagnosis of an infection date
Risk factors	
Prior antimicrobial therapy	Includes any use of a systemic antimicrobial within the last 3 months before the diagnosis of PJI
Malignancy	Any malignancy, excluding skin cancer other than melanoma diagnosed within 5 years before total joint arthroplasty
Steroid use	Any form of systemic steroid therapy for more than 1 week in the year before joint arthroplasty
Chronic renal insufficiency	A creatinine clearance of less than 30 mL/min [7]
Presence of postoperative wound drainage	Any drainage documented in the records after pulling the surgical drains

PJI = prosthetic joint infection.

compared with only 25% CP PJI patients (34 of 135) ($p < 0.001$). The median duration of prior antimicrobial therapy was 34.5 days (range, 1–2600 days) for CN patients and 18 days (range, 1–90 days) for CP patients. We outlined the types of prior antimicrobials used before the diagnosis of CN PJI (Table 3). The most commonly used antimicrobial was cefazolin used in 16% (22 of 135) followed by ciprofloxacin (15% [20 patients]) and cephradine (12% [16 patients]).

Staged resection and reimplantation was the most commonly used surgical procedure in CN and CP PJI patients (Table 2). The overall distribution of surgical modalities was different between CN and CP PJI patients. Of the 34 case patients initially treated with resection arthroplasty, 44% (15 of 34) were subsequently treated with arthrodesis. Of the 30 CP PJI patients who were treated with resection arthroplasty, 53% (16 of 30) were subsequently treated with arthrodesis and 47% (14 of 30) were definitively treated with resection arthroplasty.

Descriptive statistics were used to summarize the data; medians and ranges for continuous variables and counts and percentages for categorical variables were used. The primary objective of this study was to compare clinical characteristics between patients with CN and CP PJI. The chi square or Fisher's exact test was used to assess for associations between dichotomous variables and the culture group, whereas the rank sum test was used to evaluate differences in continuous or ordinal scaled variables between the culture groups. Univariate logistic regression was used to evaluate univariate risk factors of CN PJI relative to CP PJI. The corresponding odds ratios and 95% confidence intervals are presented. To investigate independent associations, all risk factors from the univariate logistic model ($p < 0.10$) were subsequently included in a

Table 2. Demographic characteristics of culture-negative and culture-positive PJIs seen at the Mayo Clinic between 1985 and 2000

Demographic characteristics	Culture-negative (N = 135)	Culture-positive (N = 135)
Prosthesis location	N (%)	N (%)
Hip	68 (50%)	68 (50%)
Knee	67 (50%)	67 (50%)
Median age, years (range)	68.9 (17–88)	71.3 (35–93)
Gender		
Male	71 (53%)	71 (53%)
Female	64 (47%)	64 (47%)
Median joint age, days (range)	746 (4–8882)	588 (9–8195)
Underlying native joint disease		
Degenerative joint disease	72 (53%)	93 (67%)
Rheumatic disease	20 (15%)	24 (18%)
Avascular necrosis	4 (3%)	1 (0.7%)
Sepsis	6 (4%)	3 (2%)
Neoplasia	3 (2%)	0 (0%)
Congenital	6 (4%)	9 (7%)
Miscellaneous	23 (17%)	5 (3,7%)
Prior diagnosis of PJI	25 (19%)	11 (8%)
Median number of prior implants (range)	1.377 (1–8)	1.629 (1–7)
Onset of symptoms		
Pain	118 (87%)	125 (93%)
Fever	21 (16%)	29 (22%)
Local symptoms*	72 (53%)	68 (50%)
Surgical therapy		
Staged therapy†	56 (42%)	67 (49%)
Resection arthroplasty	34 (25%)	30 (22%)
Débridement and components retention	18 (13%)	15 (11%)
Amputation	5 (4%)	0 (0%)
One-stage exchange	8 (6%)	10 (7%)
No therapy	1 (0.7%)	7 (5%)
Chronic suppression	13 (10%)	6 (4%)
Duration of parenteral antimicrobial therapy in days (range)	22 (0–136 days)	28 (0–95)
Duration of prior antimicrobial therapy in days (range)	34.5 (1–2600)	18 (1–94)
Complication with antimicrobial therapy	11 (8%)	2 (2%)

* Redness swelling, warmth; †including two and more staged surgeries; PJI = prosthetic joint infection.

multivariable logistic model (Table 4). To refine the multivariable model to include only independently significant factors, stepwise selection was performed using an entrance and retention criterion ($p < 0.05$). The rate free from treatment failure was estimated by the Kaplan-Meier method and compared between CN and CP PJI groups using the log rank test. Patients who died during the followup period but did not exhibit any signs of treatment failure at any time before their death are counted as no failure with the last followup date as the date of death.

Table 3. Antimicrobials used before PJI diagnosis

Antimicrobial used	Culture-negative (cases) (N = 89)	Culture-positive (control subjects) (N = 34)
Beta-lactam	26	7
Quinolone	10	3
Vancomycin	2	0
Combination therapy*	35	14
Other†	16	10

Some patients received monotherapy and combination therapy at different point of time so the sum is higher than the number of patients who received antimicrobial therapy; *beta-lactam + quinolones, beta-lactam + vancomycin, quinolone + vancomycin, beta lactam + quinolone + vancomycin; †rifamycin, tetracycline, aminoglycoside, nitroimidazole, or penicillins; PJI = prosthetic joint infection.

Results

Patients with CN PJI were more likely to have received prior antimicrobial therapy in the preceding 3 months before their diagnosis when compared with CP PJI control patients (matched odds ratio: 4.11; 95% confidence interval: 2.3–7.25). Furthermore, patients with CN PJI were more likely to have postoperative wound drainage when compared with those with CP PJI (matched odds ratio: 3.46; 95% confidence interval: 1.49–8.05) (Table 5).

One hundred thirty-four patients with CN PJI and 129 patients with CP PJI were treated with parenteral or oral antimicrobial therapy after the diagnosis. Six patients in the CP PJI group did not get the opportunity to receive antimicrobial therapy because of early surgical treatment failure. The most common parenteral antimicrobials used in patients with CN PJI were cefazolin (69% [88 of 128]) and vancomycin (13% [17 of 128]). Some patients received combination parenteral antimicrobial therapy. Thirty percent of patients with CN PJI (41 of 135) received oral antimicrobial therapy as well. Thirty-seven percent of those (15 of 41) received chronic oral antimicrobial suppression. Within the group of patients who received oral antimicrobial therapy, the median duration was 29 days (range, 2–2589 days) for patients with CN PJI and 33.5 days (range, 1–2242 days) for patients with CP PJI. Eleven patients with CN PJI (8%) and two (2%) with CP PJI developed an adverse reaction to systemic antimicrobial therapy, including nephrotoxicity, hepatotoxicity, and gastrointestinal toxicity. After their initial therapy, 70% of patients

Table 4. Univariate analysis of risk factors for culture-negative prosthetic joint infection and their matched controls seen at the Mayo Clinic Rochester between 1985 and 2000

Risk factor	Culture-negative (N = 135)	Culture-positive (N = 135)	Matched odds ratio (95% confidence interval)	p value*
Preoperative factors				
Prior use of antimicrobial therapy	86 (64%)	32 (24%)	5.21 (3.09–8.80)	< 0.001
Last dose within 1 week of diagnosis	18 (13%)	6 (4%)	1.4 (0.5–4.2)	0.5
Last dose within greater than 1 week of diagnosis	22 (16%)	6 (4%)	1.7 (0.6–5)	0.29
Rheumatoid arthritis	21 (16%)	27 (20%)	0.74 (0.39–1.38)	0.34
Systemic steroids	15 (11%)	9 (7%)	1.75 (0.74–4.15)	0.20
Methotrexate	5 (4%)	2 (2%)	2.56 (0.49–13.41)	0.45†
Diabetes mellitus	16 (12%)	20 (15%)	0.77 (0.38–1.57)	0.47
Systemic malignancy	23 (17%)	22 (16%)	1.05 (0.56–2.00)	0.87
Chronic renal disease	7 (5%)	3 (2%)	2.41 (0.61–9.50)	0.20
Liver cirrhosis	4 (3%)	0	5.39 (0.67–∞)	0.12†
Local risk factors				
Vascular insufficiency	10 (7%)	2 (1.5%)	5.32 (1.14–24.75)	0.018
Prior PJI	11 (8%)	25 (19%)	2.71 (1.27–5.77)	0.008
Postoperative risk factors				
Postoperative site infection	4 (3%)	4 (3%)	1.00 (0.24–4.08)	1.0†
Presence of postoperative wound drainage	30 (22%)	9 (7%)	4.00 (1.82–8.80)	< 0.001
Postoperative urinary tract infection	4 (3%)	4 (3%)	1.00 (0.24–4.08)	1.0†
Number of implants prior to PJI, number (%)				0.14
1	79 (59%)	84 (67%)		
2	32 (24%)	29 (23%)		
3	17 (13%)	9 (7%)		
4	5 (4%)	3 (2%)		
7	1 (1%)	0 (0%)		
8	0 (0%)	1 (1%)		

* Unless otherwise noted, p values were calculated using the chi square test for dichotomous variables and the Wilcoxon rank sum test for continuous variables; †p value was calculated using a Fisher's exact test; PJI = prosthetic joint infection.

Table 5. Multivariate analysis for culture-negative prosthetic joint infection and their matched controls seen at the Mayo Clinic Rochester between 1985 and 2000

Variable	Model 1*
Postoperative drainage	3.46 (1.49, 8.05) [0.004]
Vascular insufficiency	3.21 (0.65, 15.83) [0.152]
Antibiotic therapy received within the last 3 months prior to diagnose date	4.11 (2.33, 7.25) [< 0.001]
Prior PJI	1.45 (0.63, 3.34) [0.390]

* Model constructed using all factors detected from the univariate analysis as $p < 0.10$; PJI = prosthetic joint infection.

with CN PJI (94 of 135) and 73% of with CP PJI (98 of 135) did not develop subsequent PJI. The mean time without failure was 2912 days for patients with CN PJI and 2623 days for those with CP PJI. The estimated 5-year cumulative incidence (SD) of being free of failure after treatment was 67% (SD) for a CN PJI patient and 60% (SD) for CP PJI patients (Table 6) ($p = 0.24$).

Discussion

Risk factors associated with CN PJI have not been assessed. We previously found 7% of all PJIs were CN [3]. CN PJI can be problematic in its management given the uncertainty that surrounds the diagnosis as well as the optimal choice of antimicrobial and surgical therapy. It is therefore important to evaluate risk factors for negative cultures in PJI to understand how to prevent its occurrence. We therefore conducted a case-control study to (1) identify risk factors associated with the occurrence of CN PJI with the focus on the use of prior antimicrobial therapy; and (2) compare the therapeutic medical and surgical modalities used and the incidence free of treatment failure between cases and controls.

Table 6. Incidence free of treatment failure at 2 and 5 years among 135 culture-negative (CN) and 135 culture-positive (CP) in CN and CP PJI and by type of surgical therapy treated at the Mayo Clinic between 1985 and 2000 (Kaplan-Meier analysis)

Patients subgroups	Percent free of treatment failure (SD)		
	2 years	5 years	p value*
Overall population			
CN PJI (135)	75% (4)	66% (5)	0.24
CP PJI (135)	79% (4)	61% (5)	
Two-stage exchange			
CN PJI (56)	87% (5)	79% (6)	0.09
CP PJI (67)	88% (4)	74% (6)	
Débridement and retention			
CN PJI (18)	78% (11)	78% (11)	0.23
CP PJI (15)	86% (10)	51% (14)	
Permanent resection arthroplasty			
CN PJI (34)	49% (12)	43% (12)	0.67
CP PJI (30)	54% (10)	30% (10)	

* Comparisons made using the log rank test between CN PJI and CP PJI; PJI = prosthetic joint infection.

There are at least three limitations of this case-control study. First, there would be a possibility of a differential recall bias on prior use of antimicrobial therapy between cases and control patients. While we thoroughly reviewed the records for prior antimicrobial use (anesthesia records, medication list) it is possible that some patients would have received antibiotics without notation in the records; thus we may have underestimated the number of patients on antibiotics specifically in CP PJI patients. This differential bias may have lead to an overestimation of the association between CN PJI and prior use of antimicrobials. Second, important or unknown risk factors could have been omitted from the analysis because they either were not commonly encountered or because they were not analyzed. Third, multivariable analysis of nonrandomized trials is always limited by the fact that confounding variables are not always known or measured. This can lead to residual confounding when one has incompletely controlled for all confounding variables. We made a priori literature search and analyzed all previously reported potential risk factors or those we believed important.

Our data suggest several factors are associated with increased odds of CN PJI when compared with CP PJI. Antimicrobial therapy in the 3 months before the diagnosis of PJI was associated with a 4.7 increased odds of being CN. Given the wide range of antimicrobial therapy type used before the diagnosis of PJI, we were unable to establish a specific antimicrobial-free time period that would optimize the chances of having a positive culture. We believe this is attributable in part to the different pharmacologic properties of antimicrobials used. A prior study by Trampuz et al. looked at the effect of prior antimicrobial therapy use on the sensitivity of culture results in assessing the use of sonication cultures [11]. In their report, any use of antibiotic in the preceding 2 weeks before diagnosis was associated with a lower sensitivity of positive cultures [11]. In our practice in elective cases, we usually allow a 2-week antimicrobial-free period before surgical intervention. A second risk factor associated with CN PJI was the presence of prolonged wound drainage after index arthroplasty. We believe this factor is a residual confounder because many clinicians would tend to prescribe antimicrobial therapy to patients with draining wounds. We believed the same would apply to patients with peripheral vascular insufficiency or patients with prior PJI, because many of these patients have chronic wound ulcers and are receiving prolonged courses of systemic antimicrobial therapy (Table 5).

The most common surgical therapy for patients with CN and CP PJI was a staged exchange, a procedure that is typically associated with a high success rate. The distribution of various surgical modalities is similar to the experience of others [9, 12, 13]. There were more patients with CP than CN who were treated with two-stage exchange. We believe this is the result of the fact that surgeons favor two-stage exchanges in CP PJI patients, because sometimes the diagnosis of CN PJI is not recognized until after a one-stage revision, a procedure often preformed for aseptic loosening. After surgical therapy, most patients received systemic antimicrobial therapy. The mean duration of medical therapy was 6 days shorter for patients with CN PJI than with CP PJI. We believe this is likely related to the uncertainty that surrounds the diagnosis of CN PJI when compared with CP PJI. The demographics and outcome of CN and CP PJI patients were similar; therefore, we believe the presumed microbiology of patients with CN PJI is similar to that of patients with CP PJI. The best form of therapy of CN PJI can only be assessed in a prospective randomized clinical trial. While making decisions on the antimicrobial therapy in patients with CN PJI, a number of factors such as type and prior use of antimicrobials, surgical procedure modality as well as the type of antimicrobials used in the cement spacer will need to be factored in. In our practice, we try to design a regimen that would mimic the spectrum of antimicrobial therapy that was used before the diagnosis of CN PJI while covering the most common culprits.

In conclusion, prior antimicrobial therapy and postoperative wound drainage were associated with an increased risk of negative cultures among patients with PJIJI. Physicians should always consider the risk of a negative culture if they prescribe an antimicrobial therapy for a presumed infection, especially in settings where it is unlikely to be effective.

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References

1. Ahlberg A, Carlsson AS, Lindberg L. Hematogenous infection in total joint replacement. *Clin Orthop Relat Res*. 1978;137: 69–75.
2. Berbari EF, Hanssen AD, Duffy MC, Steckelberg JM, Ilstrup DM, Harmsen WS, Osmon DR. Risk factors for prosthetic joint infection: case-control study. *Clin Infect Dis.* 1998;27:1247–1254.
3. Berbari EF, Marculescu C, Sia I, Lahr BD, Hanssen AD, Steckelberg JM, Gullerud R, Osmon DR. Culture-negative prosthetic joint infection. *Clin Infect Dis*. 2007;45:1113–1119.
4. Berbari EF, Osmon DR, Duffy MC, Harmssen RN, Mandrekar JN, Hanssen AD, Steckelberg JM. Outcome of prosthetic joint infection in patients with rheumatoid arthritis: the impact of medical and surgical therapy in 200 episodes. *Clin Infect Dis*. 2006;42:216–223.
5. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
6. Kurtz S, Lau E, Halpern M, Ong K. Trend shows growing orthopedic surgery case load. Will surgeons be able to keep up? *Mater Manag Health Care*. 2006;15:61–62.
7. Lavernia CJ, Sierra RJ, Hernandez RA. The cost of teaching total knee arthroplasty surgery to orthopaedic surgery residents. *Clin Orthop Relat Res.* 2000;380:99–107.
8. Marculescu CE, Berbari EF, Hanssen AD, Steckelberg JM, Harmsen SW, Mandrekar JN, Osmon DR. Outcome of prosthetic joint infections treated with debridement and retention of components. *Clin Infect Dis*. 2006;42:471–478.
9. Powers KA, Terpenning MS, Voice RA, Kauffman CA. Prosthetic joint infections in the elderly. *Am J Med*. 1990;88:9N–13N.
10. Sia IG, Berbari EF, Karchmer AW. Prosthetic joint infections. *Infect Dis Clin North Am*. 2005;19:885–914.
11. Trampuz A, Piper KE, Jacobson MJ, Hanssen AD, Unni KK, Osmon DR, Mandrekar JN, Cockerill FR, Steckelberg JM, Greenleaf JF, Patel R. Sonication of removed hip and knee prostheses for diagnosis of infection. *N Engl J Med*. 2007;357:654–663.
12. Zimmerli W, Ochsner PE. Management of infection associated with prosthetic joint infection. *Infection*. 2003;31:99–108.
13. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med*. 2004;351:1645–1654.