Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jor

Original Article

Comparison of infection control rates and clinical outcomes in culture-positive and culture-negative infected total-knee arthroplasty

Young-Hoo Kim^{*}, Sourabh S. Kulkarni, Jang-Won Park, Jun-Shik Kim, Hyun-Keun Oh, Devarshi Rastogi

The Joint Replacement Center, Ewha Womans University School of Medicine, Seoul 158-710, Republic of Korea

ARTICLE INFO

Article history:

Received 29 December 2014

Accepted 24 January 2015

Available online 17 February 2015

Keywords:

Infection control rate

Culture-positive

Culture-negative

TKA

ABSTRACT

Background: To compare the outcomes of the culture positive and the culture negative infected TKA.

Methods: We determined the infection control rate in the 242 patients (140 patients with culture-positive and 102 patients with culture-negative diagnoses) with infected TKAs.

Results: The overall infection control rate was 90% in the culture positive group and 95% in the culture negative group.

Interpretation: The infection control rates and clinical outcomes of infected TKAs was not different between culture-positive and culture-negative groups.

Copyright © 2015, Professor P K Surendran Memorial Education Foundation. Publishing Services by Reed Elsevier India Pvt. Ltd. All rights reserved.

1. Introduction

Periprosthetic joint infection is one of the most challenging complications after total-knee arthroplasty (TKA) with an incidence of 1%–4% after primary TKA.^{1–4} Accurate diagnosis of periprosthetic joint infection is essential and often involves withholding antibiotic therapy in hopes of isolating an organism from a preoperative joint aspiration or intraoperative tissue cultures. Determining the causative organism then allows tailored local and systemic antibiotic therapy. Despite extensive efforts, the cultures often have a high false-negative rate despite adequate clinical, radiographic, and surgical suspicion for periprosthetic joint infection. Incidence of

negative cultures in most infection series ranged from 0% to 25%.^{5–9}

The reported control rates of treating deep infection of TKA have ranged from 20% to 68% for surgical debridement with retention of the prosthesis, 50%–87% for one-stage exchange, and 56%–100% for two-stage exchange.^{10–23} However, the clinical characteristics of culture negativity have not been well studied. In a culture-negative periprosthetic joint infection, choosing the appropriate antibiotic therapy is difficult. Therefore, it is important to understand the rates of infection control and antibiotic choices in the culture-negative periprosthetic joint infections. In many previous reports,^{1,3–8,10,16,24} the results of culture positive and culture

^{*} Corresponding author. The Joint Replacement Center, Ewha Womans University MokDong Hospital, 911-1, Mokdong, YangChun-Gu, Seoul 158-710, Republic of Korea. Tel.: +82 2 2650 5906; fax: +82 2 2650 5903.

E-mail address: younghookim@ewha.ac.kr (Y.-H. Kim).

<http://dx.doi.org/10.1016/j.jor.2015.01.020>

0972-978X/ Copyright © 2015, Professor P K Surendran Memorial Education Foundation. Publishing Services by Reed Elsevier India Pvt. Ltd. All rights reserved.

negative infected TKAs were not compared. Therefore, the current study analyzed the larger cohort of the patients with culture negative infected TKAs to determine their clinical characteristics and treatment results. Furthermore, their clinical characteristics and treatment results were compared with the patients with culture positive infected TKAs.

To confirm previous reports, we (1) compared each type of infected TKA that did not yield positive cultures at the time of treatment with those that had positive cultures to determine the control rates of infection, and (2) determined whether repeated debridement and repeated two-stage exchange TKA would improve further the control rate of infection after failed first treatment in culture-positive and culture-negative infected TKA.

2. Materials and methods

We retrospectively reviewed data for 260 prospectively followed patients with 260 infected TKAs from January 2001 to March 2008. All operations were performed by a senior author (YHK). Of the 260 patients, 11 were lost to follow-up before 2 years, and 7 died, leaving 242 patients (242 knees) for review. The records of the 242 patients had been entered into an ongoing computerized database that was updated continuously. The study was approved by the institutional review board, and patients provided written informed consent. There were 58 men and 184 women with a mean age of 66.3 ± 8.65 years (range, 40–90 years). Their mean body mass index was 28.29 ± 4.31 kg/m² (range, 20.1–41.3 kg/m²). In all knees, the primary diagnosis was osteoarthritis. In the current series, no patient was immunocompromised due to a co-morbid disease such as rheumatoid arthritis, or long term steroid treatment, or past chemotherapy treatment, or positive HIV. The minimum duration of follow-up was 6 years (mean, 10 ± 0.92 years; range, 6–13 years) (Table 1).

As per the new definition for periprosthetic joint infection by the work group of the Musculoskeletal Infection Society (MSIS),^{25,26} diagnosis of infection was made by presence of sinus tract communicating with the prosthesis; or growth of the microorganism from at least 2 separate tissue or joint fluid specimens from the affected prosthetic joint; or when 4 of the following six criteria: elevated erythrocyte sedimentation rate (ESR, ≥ 30 mm/h) and C-reactive protein (CRP, ≥ 10 mg/L), elevated synovial white blood cell (WBC) count (≥ 2000 /UL), elevated synovial neutrophil percentage (PMN%, $\geq 65\%$), presence of purulence in the affected joint, isolation of a microorganism in one culture of tissue or fluid, more than 5 neutrophils per high-power field on histologic examination.^{27–31} Each infection was classified as early post-operative deep, late chronic, and acute hematogenous infection according to Tsukayama et al.³² Clinical host condition was classified as uncompromised, compromised, and significantly compromised based on the classification of McPherson et al.³³ In the culture positive group, 119 of 140 patients (85%) were considered to be uncompromised (systemic host A), 14 patients (10%) were considered to be compromised (systemic host B), and 7 patients (5%) were considered to be significantly compromised (systemic host C). In the culture negative group, 85 of 102 patients (83%) were

considered to be uncompromised (systemic host A), 12 patients (12%) were considered to be compromised (systemic host B), and 5 patients (5%) were considered to be significantly compromised (systemic host C).

Study patients were divided into 2 groups based on culture results from both preoperative joint aspirate and intra-operative periprosthetic tissues from the affected joint at the time of initial surgical treatment at our institution, which totaled 140 patients with positive culture results (culture-positive group), and 102 patients with negative culture results (culture-negative group). Gram-positive cocci were isolated from 84 knees, and gram-negative bacilli were cultured from 38 knees. The fungal (*Candida albicans*) and Mycobacterium (*Mycobacterium tuberculosis*) isolates came from late chronic infections (Table 2). Twenty-one of 140 patients who had negative culture initially turned culture positive later. MRSA was cultured in 10 knees, *C. albicans* in 5 knees, *Enterococcus* in three knees and *Streptococcus* in 3 knees. Patients' demographics, clinical characteristics, and treatment results were compared between the 2 study groups. The history of previous antibiotic treatment for infected TKA of the same joints and follow-up cultures of the same joints after failure of our initial surgical treatment were also documented to outline the pattern of 102 patients with negative culture results (Table 1). We used PCR analysis was performed in the culture negative TKAs in our institute. 16SrRNA gene PCR combined with sequencing (16SPCR) has proven to be useful for diagnosing various infections.³⁴ However, it does not provide any additional information to select susceptible antibiotics. Even if the positive results of PCR in the culture negative group, selection of antibiotics are still made empirically.

Treatment of infection was performed as the same protocol as in the previous report.²⁴ Early deep postoperative infections were treated with debridement, replacement of the polyethylene insert of the tibial component, retention of the prosthesis, and intravenous administration of antibiotics for 6 weeks (Table 2). Parenteral antibiotic therapy was determined with consultation with an infectious disease specialist. Broad spectrum antibiotic was given empirically, and then therapy was adjusted subsequently based on the sensitivities. When the culture study showed negative results, empirical antibiotic treatment was maintained as patients with culture positive. If the infection recurred, repeated debridement and replacement of the polyethylene insert of the tibial component, retention of the prosthesis, and intravenous antibiotics for 6 weeks. If the infection recurred again, 2-stage exchange TKA was performed. First, we performed debridement, removal of all of the prosthetic components and bone cement, and placement of a vancomycin and gentamycin-impregnated (2.0 g, 800 mg per 40-g batch, respectively of bone cement) mobile cement spacer. Antibiotics were administered intravenously for 6 weeks (Table 3). After completion of antibiotic therapy, ESR, CRP levels, and total WBC count and differential in the joint aspirates were obtained, and the patient was observed for 2 more weeks. If results of these tests showed no evidence of infection, we performed TKA. Multiple cultures of specimens obtained during revision operations were performed to confirm infection eradication. If the infection recurred once again, repeated two-stage exchange arthroplasty was performed. Arthrodesis was performed if the

Table 1 – Comparison of demographics and variables between culture-positive and culture-negative patients.

Variable	Culture-positive (N = 140)	Culture-negative (N = 102)	P-value (Chi-square test)
Age (years)	65.2 ± 8.4 (range, 57–79)	67.4 ± 8.9 (range, 40–90)	0.36
Gender			0.41
Male	30	28	
Female	110	74	
Host condition			0.59
Uncompromised	98 (70%)	67 (66%)	
Compromised	42 (30%)	35 (34%)	
Implant			
Primary	140 (100%)	102 (100%)	
Type of infection			0.63
Early deep	75 (54%)	52 (51%)	
Late chronic	59 (42%)	46 (45%)	
Acute hematogenous	6 (4%)	4 (4%)	
Draining Sinus			0.16
Yes	10 (7%)	0 (0%)	
No	130 (93%)	102 (100%)	
Preoperative antibiotic treatment			0.003
Yes	97 (69%)	42 (41%)	
No	43 (31%)	60 (59%)	
IV antibiotics			0.001
Vancomycin	91 (65%)	87 (85%)	
Others	49 (35%)	15 (15%)	
Oral antibiotics			0.001
Yes	28 (20%)	61 (60%)	
No	112 (80%)	41 (40%)	
Laboratory data			
WBC (/ml)	9287 ± 3895	8081 ± 2809	0.049
ESR (mm/h)	98.1 ± 38.7	79.8 ± 29.1	0.003
CRP (mg/L)	25.1 (10.1–58.8)	15.5 (9–48.9)	0.003
Aspirates WBC (/mm ³)	46,750 (20,500–98,500)	36,501 (19,500–72,762)	0.004
Aspirate Neutrophil (%)	93 (78–96)	91 (85–93)	0.131
Follow-up (years)	9.3 (6–13)	10.6 (6–13)	0.323

infection recurred again. In very selective patients, who had mild atrophy of quadriceps and hamstring muscles with good muscle power, fusion-taken-down and TKA was performed. Late chronic infection was treated as for the recurrent early deep postoperative infection. Acute hematogenous infections were treated as for the early deep postoperative infections (Fig. 1).

On the second day after surgery, a continuous passive motion machine was used for passive range-of-motion exercise twice daily for 30 min each time. The machine settings were advanced incrementally under the supervision of a physical therapist. On the second postoperative day, patients began standing at the bedside or walking with crutches or a walker twice daily for 30 min, each time under the supervision

Table 2 – Bacterial isolates in 140 infections in positive culture results.

Pathogen	Group		
	Early deep (75)	Late chronic (59)	Acute hematogenous (6)
Gram-positive cocci (84)			
Coagulase-positive Staphylococci (n = 30)	10	16	4
Methicillin-susceptible	8	10	2
Methicillin-resistant	2	6	2
Coagulase-negative Staphylococci (n = 26)			
Methicillin-susceptible	6	10	0
Methicillin-resistant	2	4	4
Streptococcus (n = 14)	6	8	–
Enterococcus (n = 14)	8	6	–
Gram-negative bacilli (n = 38)			
Enterobacter (n = 22)	10	10	2
Acinobacter baumannii complex (n = 16)	8	8	–
Fungus (<i>Candida albicans</i>) (n = 8)	–	8	–
<i>Mycobacterium tuberculosis</i> (n = 10)	–	10	–

Table 3 – Treatment of infection with antibiotics.

Microorganism	Antimicrobial agent	Dosage	Route
<i>Staphylococcus aureus</i> coagulate-positive or -negative Methicillin-susceptible	Nafcillin or floxacillin plus	2 g every 6 h	IV
	Rifampin for 2 weeks followed by	450 mg every 12 h	PO
	Rifampin plus	450 mg every 12 h	PO
	Ciprofloxacin or	750 mg every 12 h	PO
	Levofloxacin	750 mg every 24 h	PO
Methicillin-resistant	Vancomycin plus	1 g every 12 h	IV
	Rifampin for 2 weeks	450 mg every 12 h	PO
	Rifampin plus	450 mg every 12 h	PO
	Ciprofloxacin or	750 mg every 12 h	PO
	Levofloxacin or	750 mg every 24 h	PO
	Teicoplanin or	400 mg every 24 h	IV
	Fusidic acid	500 mg every 8 h	PO
<i>Streptococcus</i> and <i>Enterococcus</i>	Penicillin G or	5 million units every 6 h	IV
	Ampicillin or amoxicillin	2 g every 4–6 h	IV
<i>Enterobacter</i> and <i>Actinobacter</i>	Ceftazidime or cefepime plus	2 g every 8 h	IV
	Aminoglycoside for 2 weeks followed by ciprofloxacin	750 mg every 12 h	PO
Culture negative	Vancomycin plus	1 g every 12 h	IV
	Ciprofloxacin or	750 mg every 12 h	PO
	Levofloxacin or	750 mg every 24 h	PO
	Teicoplanin or	400 mg every 24 h	IV
	Fusidic acid	500 mg every 8 h	PO
<i>Candida albicans</i>	Flucorazole	400 mg OD (first day)	IV
		200 mg OD (from 2nd day)	IV
	Caspofungin	70 mg OD (first day)	IV
		50 mg OD (from 2nd day)	IV
<i>Mycobacterium tuberculosis</i>	Isoniazid	200–400 mg O.D	PO
	Ethambutol	12 mg/kg O.D	PO
	Rifampicin	450–600 mg O.D	PO
	Pyrazinamide	1.5–2.0 g OD or BiD, or TiD	PO

Fig. 1 – Diagram of the treatment pathway for an infected total-knee arthroplasty.

of a physical therapist. Patients used crutches or a walker with full weight bearing for 6 weeks and then a cane as needed thereafter. No patient received physiotherapy after discharge from the hospital.

Routine follow-up evaluation was scheduled at post-operative intervals of 3 months, 1 year, and yearly thereafter. At these intervals, we evaluated the patients and obtained radiographs. Preoperative and postoperative review data were recorded according to the system of the Knee Society.³⁵ All of the knees were evaluated by one observer who was not connected with the original surgery, and the data were entered into a computerized record. The criteria for infection control were: no pain or swelling; no wound drainage; normal serology (ESR < 20 mm/h, CRP level < 0.5 mg/dL); a synovial fluid leukocyte differential of less than 65% neutrophils (or a leukocyte count < $1.7 \times 10^3/\mu\text{L}$); and a normal radiographic finding for at least 2 years after the end of antibiotic therapy.³¹ For a knee to be considered functional, there had to be no or only slight pain upon walking (with or without the use of a cane) and no radiographic findings, such as progressive osteolysis or loosening of the prosthetic components that indicated a need for immediate or impending surgical intervention. If the initial treatment failed, we recorded the number and type of subsequent courses of treatment that were attempted. In some instances, infection eradication was achieved only after multiple courses of treatment.

One of the study's authors evaluated the final radiographs. We defined radiographic loosening as a complete radiolucent line of ≥ 2 mm in width at the bone-cement or the prosthesis–cement interface or shift in position of a component or components on serial radiographic examination.³⁶

2.1. Statistical analysis

We performed a sample size calculation based on detecting difference in the postoperative Knee Society Knee scores of 5 points between the 2 study groups, assuming a type-2 error (2-sided) of 5% with a statistical power of 80% (type-2 error = 0.20). With these assumptions, approximately 91 cases were needed in each group. Chi-square, descriptive, and Student's t-test analyses were used to compare demographics and comorbidities between the patients with culture-negative and culture-positive. The differences among the four types of infection in culture-positive and culture-negative groups for discrete variables (including age, period of follow-up, CRP, ESR, leukocyte count, and leukocyte differential) were

compared using Fisher's exact probability two-tailed t-test. Logistic regression was used to assess the rate of failure associated with the different types of infection in both groups. One-way analysis of variance was used to confirm differences among the different types of infection with respect to the final clinical score. The level of significance was set at $P < 0.05$. All analyses were performed with use of SPSS software (version 18; SPSS, Chicago, Illinois).

3. Results

Overall rates of infection control, successful first treatment, and functional knee were not statistically different between the culture-positive and culture-negative groups ($P < 0.05$). Moreover, overall rates of infection control, successful first treatment and functional knee were not statically different between the gram-positive and gram-negative groups ($P < 0.05$). Overall infection control rate was 100% in both groups at means of 9.3 years and 10.6 years follow-up, respectively. If the patients with arthrodesis or amputation were defined as a failure of infection control, infection control rate was 90% in the culture-positive group and 95% in the culture-negative group. A functional knee was obtained in 90% in the culture-positive group and 95% in the culture-negative group. In the culture-positive group, the initial course of treatment was successful for 41 of 75 knees (55%) with early deep postoperative infection, 47 of 59 knees (80%) with late chronic infection, and 2 of 6 knees with acute hematogenous infection. In the culture-negative group, the initial course of treatment was successful for 31 of 52 knees (60%) with early deep postoperative infection, 38 of 46 knees (83%) with late chronic infection (Table 2), and 1 of 4 knees with acute hematogenous infection.

Infection control and maintenance of functional TKA after first treatment were further improved by repeated débridement and repeated 2-stage exchange TKA (Table 4). The mean Knee Society knee and function scores in the culture-positive group were 87 and 77 points, respectively, and they were 89 and 75 points, respectively, in the culture-negative group. In the culture-positive group, 7 knees (5%) were revised for aseptic loosening of femoral and/or tibial components, and 2 knees were required above-knee amputation for persistent infection after 2 revisions. These 2 patients who underwent above-knee amputation were immunocompromised by prolonged antibiotic therapy and

Table 4 – Summary of overall results for each group.

Results	Culture-positive (N = 140)			Culture-negative (N = 102)		
	Early deep infection (75 knees)	Late chronic infection (59 knees)	Acute hematogenous infection (6 knees)	Early deep infection (52 knees)	Late chronic infection (46 knees)	Acute hematogenous infection (4 knees)
Successful first treatment	41 knees (55%)	47 knees (80%)	2 knees (33%)	31 knees (60%)	38 knees (83%)	1 knee (25%)
Infection eradicated	75 knees (100%)	59 knees (100%)	6 knees (100%)	52 knees (100%)	46 knees (100%)	4 knees (100%)
Functional knee	70 knees (93%)	56 knees (95%)	5 knees (83%)	48 knees (92%)	44 knees (96%)	4 knees (100%)

superimposed MRSA with *C. albicans* infection. In the culture-negative group, 8 knees (8%) were revised for aseptic loosening of the femoral and/or tibial components. Survivorship of TKA at 9.3 years as the end point of revision, or arthrodesis, or amputation was 94% (95% confidence interval, 0.91–0.97) in the culture-positive group, and it was 92% (95% confidence interval, 0.89–0.98) in the culture-negative group.

4. Discussion

Although identification of a causative microorganisms from operative tissue samples or joint aspiration is the standard for diagnosis of periprosthetic joint infection, negative cultures are frequent in treatment of periprosthetic joint infections. In the present study, incidence of negative culture result was 42% (102 of 242 knees), which was substantially higher compared to other published series in the literature.^{6,7,37,38} We suggest that this finding may be explained by higher incidence of previous intravenous and oral antibiotic treatment, which was consistent with the previous reports.^{6,39} This suggests that a higher incidence of previous antibiotic treatment has led to the lower ESR and CRP values seen in the culture-negative group ($p = 0.03$).

Malekzadeh et al³⁹ reported the largest series of culture-negative periprosthetic joint infection, which includes 135 cases (10.6% incidence) within 16 years. They found no differences in treatment failure between the culture-negative and culture-positive cases. Huang et al³⁷ also found no differences in treatment failure between culture-negative and culture-positive cases. On the contrary, Choi et al³⁸ reported that the culture-negative group showed significantly higher treatment success rates compared to the culture-positive group. They suggested that high usage of vancomycin and additional surgical treatment (reimplantation or arthrodesis) in culture-negative patients might have contributed to more favorable outcomes in their study. The findings of the current study showed no significant differences in the treatment failure between culture-negative and culture-positive groups. We believe that initial surgical treatment and subsequent aggressive additional treatments (repeated débridement, repeated two-stage exchange arthroplasty, arthrodesis or amputation), led to improved eradication of infection in both culture-negative and culture-positive groups.

In various series ranging in size from 5 to 116 infections, the overall infection control rate associated with the use of irrigation and débridement for the treatment of early deep postoperative infection ranged from 0 to 100%.^{10,18,19,24,40} Mont et al¹⁸ reported that a protocol of multiple débridement was successful for the treatment of 10 of 10 early deep postoperative infections (defined as those that occurred less than 4 weeks after index arthroplasty). In our study, the success rate of initial treatment in early postoperative infection was 55% in the culture-positive group and 60% in the culture-negative group, which is similar to the 50% reported for other series.²⁰ The infection control rate was improved to 100% in both culture-positive and culture-negative groups after repeated débridement, repeated 2-stage revision, arthrodesis, or amputation. The infection control rate of initial treatment in the late chronic infection in our series was 80% in the

culture-positive group and 83% in the culture-negative group. These figures are similar to the 83% reported for other series.²⁰ After repeated débridement and repeated 2-stage revision, the infection control rate was improved to 100% in both groups. The infection control rate of the first course of treatment (retention of the prosthesis, débridement, and intravenous antibiotics for 6 weeks) for acute hematogenous infection was lower (33% versus 25%) than the rates reported by others.^{18,20} We do not know why this was the case.

Segawa et al²⁰ reported that 5 of 10 patients with early deep postoperative infection, and 24 of 29 with late chronic postoperative infection were able to walk with no or only slight pain (some with the assistance of a cane). None of their patients had radiographic findings (such as evidence of implant migration or progressive osteolysis) that would have indicated a need for immediate or impending surgical intervention. In the current series, 7 knees (5%) in the culture-positive group and 8 knees (8%) in the culture-negative group were revised for aseptic loosening of femoral and/or tibial components. 2 patients in the culture-positive group required above-knee amputation for persistent infection after 2 revisions. These two patients had persistent MRSA superimposed with *C. albicans* infection.

There are a few limitations in our study. First, although all patients in this study were prospectively followed, the design of the study was to test retrospectively our classification-based treatment algorithm for infected TKA. Second, owing to limited patient numbers, we were unable to analyze data for patients stratified according to infecting organism. It is possible that the infection control after infected TKA was influenced by the virulence of the infecting organism. Third, 11 of 260 patients (4%) were lost to follow-up, and 7 (3%) died. Nevertheless, the percentage of patients who died or were lost to follow up was small and likely did not influence the findings of our study, unless the majority of these lost and died cases had become reinfected.

The results of present study demonstrate that no significant differences exist in the infection control rate and clinical outcomes between culture-positive and culture-negative groups. The data suggest that treatment according to the types of infection in both culture-positive and culture-negative groups after TKA controlled infection and maintained functional TKA with a firm level of fixation for most patients. Repeated débridement and repeated 2-stage exchange TKA further improved infection control rates after the initial treatment and increased the likelihood of maintaining a functional TKA.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Della Valle CJ, Zuckerman JD, Di Cesare PE. Periprosthetic sepsis. *Clin Orthop Relat Res*. 2004 Mar;420:26–31.

2. Duff GP, Lachiewicz PE, Kelley SS. Aspiration of the knee joint before revision arthroplasty. *Clin Orthop Relat Res.* 1996 Oct;331:132–139.
3. Peersman G, Laskin R, Davis J, Peterson M. Infection in total knee replacement: a retrospective review of 6489 total knee replacements. *Clin Orthop Relat Res.* 2001 Nov;392:15–23.
4. Phillips JE, Crane TP, Noy M, Elliott TS, Grimer RJ. The incidence of deep periprosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey. *J Bone Joint Surg Br.* 2006 Jul;88:943–948.
5. Choi HR, von Knoch F, Zurakowski D, Nelson SB, Malchau H. Can implant retention be recommended for treatment of infected TKA? *Clin Orthop Relat Res.* 2011 Apr;469:961–969.
6. Berbari EF, Marculescu C, Sia I, et al. Culture negative prosthetic joint infection. *Clin Infect Dis.* 2007 Nov;45:1113–1119.
7. Marculescu CE, Berbari EF, Hanssen AD, et al. Outcome of prosthetic joint infections treated with debridement and retention of components. *Clin Infect Dis.* 2006 Feb;42:471–478.
8. Masri BA, Panagiotopoulos KP, Greidanus NV, Garbuz DS, Duncan CP. Cementless two-stage exchange arthroplasty for infection after total hip arthroplasty. *J Arthroplasty.* 2007 Jan;22:72–78.
9. Ure KJ, Amstutz HC, Nasser S, Schmalzried TP. Direct-exchange arthroplasty for the treatment of infection after total hip replacement. An average ten-year follow-up. *J Bone Joint Surg Am.* 1998 Jul;80:961–968.
10. Borden LS, Gearen PF. Infected total knee arthroplasty. A protocol for management. *J Arthroplasty.* 1987 Jan;2:27–36.
11. Brandt CM, Duffy MC, Berbari EF, Hanssen AD, Steckelberg JM, Osmon DR. Staphylococcus aureus prosthetic joint infection treated with prosthesis removal and delayed reimplantation arthroplasty. *Mayo Clin Proc.* 1999 Jun;74:553–558.
12. Burger RR, Basch T, Hopson CN. Implant salvage in infected total knee arthroplasty. *Clin Orthop Relat Res.* 1991 Dec;273:105–112.
13. Deirmengian C, Greenbaum J, Stern J, et al. Open debridement of acute gram-positive infection after total knee arthroplasty. *Clin Orthop Relat Res.* 2003 Nov;416:129–134.
14. Hirakawa K, Stulberg BN, Wilde AH, Bauer TW, Secic M. Results of 2-stage reimplantation for infected total knee arthroplasty. *J Arthroplasty.* 1998 Jan;13:22–28.
15. Jacobs MA, Hungerford DS, Krackow KA, Lennox DW. Revision of septic total knee arthroplasty. *Clin Orthop Relat Res.* 1989 Jan;238:159–166.
16. Johnson DP, Bannister GC. The outcome of infected arthroplasty of the knee. *J Bone Joint Surg Br.* 1986 Mar;68:289–291.
17. McLaren AC, Spooner CE. Salvage of infected total knee components. *Clin Orthop Relat Res.* 1996 Oct;331:146–150.
18. Mont MA, Waldman B, Banerjee C, Pacheco IH, Hungerford DS. Multiple irrigation, debridement, and retention of components in infected total knee arthroplasty. *J Arthroplasty.* 1997 Jun;12:426–433.
19. Schoifet SD, Morrey BF. Treatment of infection after total knee arthroplasty by debridement with retention of the components. *J Bone Joint Surg Am.* 1990 Oct;72:1383–1390.
20. Segawa H, Tsukayama DT, Kyle RF, Becker DA, Gustilo RB. Infection after total knee arthroplasty. A retrospective study of the treatment of eighty-one infections. *J Bone Joint Surg Am.* 1999 Oct;81:1434–1445.
21. Tsukayama DT, Goldberg VM, Kyle R. Diagnosis, and management of infection after total knee arthroplasty. *J Bone Joint Surg Am.* 2003;85-A(suppl 1):75–80.
22. Wilde AH, Ruth JT. Two-stage reimplantation in infected total knee arthroplasty. *Clin Orthop Relat Res.* 1988 Nov;236:23–35.
23. Windsor RE, Insall JN, Urs WK, Miller DV, Brause BD. Two-stage reimplantation for the salvage of total knee arthroplasty complicated by infection. Further follow-up and refinement of indications. *J Bone Joint Surg Am.* 1990 Feb;72:272–278.
24. Kim Y-H, Choi Y-W, Kim J-S. Treatment based on the type of infected TKA improves infection control. *Clin Orthop Relat Res.* 2011 Apr;469:977–984.
25. Workgroup. New definition for periprosthetic joint infection. *J Arthroplasty.* 2011 Dec;26:1136–1138.
26. Parvizi J, Zmistowski B, Berbari EF, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. *Clin Orthop Relat Res.* 2011 Nov;469:2992–2994.
27. Della Valle CJ, Sporer SM, Jacobs JJ, Berger RA, Rosenberg AG, Paprosky WG. Preoperative testing for sepsis before revision total knee arthroplasty. *J Arthroplasty.* 2007 Sep;22(6 suppl 2):90–93.
28. Schinsky MF, Della Valle CJ, Sporer SM, Paprosky WG. Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty. *J Bone Joint Surg Am.* 2008 Sep;90:1869–1875.
29. Ghanem E, Parvizi J, Burnett RS, et al. Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. *J Bone Joint Surg Am.* 2008 Aug;90:1637–1643.
30. Parvizi J, Ghanem E, Menashe S, Barrack RL, Bauer TW. Periprosthetic infection: What are the diagnostic challenges? *J Bone Joint Surg Am.* 2006 Dec;88(suppl 4):138–147.
31. Trampuz A, Hanssen AD, Osmon DR, Mandrekar J, Steckelberg JM, Patel R. Synovial fluid leukocyte count and differential for the diagnosis of prosthetic knee infection. *Am J Med.* 2004 Oct;117:556–562.
32. Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. *J Bone Joint Surg Am.* 1996 Apr;78:512–523.
33. McPherson EJ, Woodson C, Holtom P, Roidis N, Shufelt C, Patzakis M. Periprosthetic total hip infection: outcomes using a staging system. *Clin Orthop Relat Res.* 2002 Oct;403:8–15.
34. Marin M, Garcia-Lechuz JM, Alonso P, et al. Role of universal 16SrRNA gene PCR and sequencing in diagnosis of prosthetic joint infection. *J Clin Microbiol.* 2012 Mar;50:583–589.
35. Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the Knee Society clinical rating system. *Clin Orthop Relat Res.* 1989 Nov;248:13–14.
36. Insall JN, Thompson FM, Brause BD. Two-stage reimplantation for the salvage of infected total knee arthroplasty. *J Bone Joint Surg Am.* 1983 Oct;65:1087–1098.
37. Huang R, Hu CC, Adeli B, Mortazavi J, Parvizi J. Culture-negative periprosthetic joint infection does not preclude infection control. *Clin Orthop Relat Res.* 2012 Oct;470:2717–2723.
38. Choi HR, Kwon YM, Freiberg AA, Nelson SB, Malchau H. Periprosthetic joint infection with negative culture results: clinical characteristics and treatment outcome. *J Arthroplasty.* 2013 Jun;28:899–903.
39. Malekzadeh D, Osmon DR, Lahr BD, Hanssen AD, Berbari EF. Prior use of antimicrobial therapy is a risk factor for culture-negative prosthetic joint infection. *Clin Orthop Relat Res.* 2010 Aug;468:2039–2045.
40. Teeny SM, Dorr L, Murata G, Conaty P. Treatment of infected total knee arthroplasty. Irrigation and debridement versus two-stage reimplantation. *J Arthroplasty.* 1990 Mar;5:35–39.