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SYMPOSIUM: CURRENT ISSUES IN KNEE RECONSTRUCTION

Results after Late Polymicrobial, Gram-negative, and Methicillin-resistant Infections in Knee Arthroplasty

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Abstract

Background Previous studies of knee arthroplasty infections caused by high-virulence organisms suggest poor outcomes. Polymicrobial and Gram-negative infections are less studied.

Questions/purposes This study compared the results of treatment of knee arthroplasty infections by single versus polymicrobial isolates, Gram-positive versus Gram-negative, and methicillin-resistant versus -sensitive Staphylococci.

Methods We prospectively followed 47 patients with late knee arthroplasty infections. The mean age was 72 years (range, 20–87 years). The treatment protocol included two-stage exchange and a combination of two oral antibiotics given for 6 months. Minimum followup was 1 year (average, 4.8 ± 3 years; range, 1–12 years). Control of the infection was judged by absence of clinical, serologic, and radiologic signs of infection. The functional outcome was evaluated by Knee Society score at the last followup.

Results Infection was controlled in all 15 patients with polymicrobial and in 28 of 32 (88%) with monomicrobial infections, in eight of nine patients with Gram-negative and in 35 of 38 (92%) with Gram-positive isolates. Control was also achieved in 22 of 25 patients (88%) infected by methicillin-resistant Staphylococci and in 14 of 14 by methicillin-sensitive Staphylococci. The Knee Society scores averaged 81-63 in patients with polymicrobial infections and were higher than in monomicrobial infections (75-52). The mean KSS was 85-59 in Gram-negative infections compared to 75-55 in Gram-positive infections. The mean KSS was similar in methicillin-resistant (78-54) and methicillin-sensitive Staphylococci (73-56) infections.

Conclusions Polymicrobial and Gram-negative infections can be controlled in late knee arthroplasty infections. On the other hand, infections by methicillin-resistant Staphylococci are less likely to be controlled by the regimens we used.

Level of Evidence Level II, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

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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 Hospital Universitario La Princesa, Fundación Jiménez-Díaz, and Hospital Universitario La Paz. All three institutions are university hospitals integrated in Universidad Autónoma de Madrid, Madrid, Spain.

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Introduction

The incidence of highly resistant bacterial infection is increasing [3, 18]. Ten years ago, Garvin et al. [8] stated the prevalence of antibiotic resistance in Staphylococci had been increasing in both Staphylococcus Aureus and coagulase-negative Staphylococci. Ip et al. described no

multiple-drug resistant bacteria until 1996, but from 1997 to 2003 they detected many isolates with multiple drug resistance [13]. Fulkerson et al. have described in a recent report that, among organisms infecting joint arthroplasties, only 26% to 56% were susceptible to the usual prophylaxis [7]. Most published series of knee arthroplasty infections suggest the eradication of infection is less likely when caused by methicillin-resistant organisms [1, 10, 11, 15, 16, 21, 23, 26], however others report that these infections can be controlled [2, 28]. Few of these studies [2, 15] evaluate the functional orthopaedic outcomes of these patients.

Studies of polymicrobial and Gram-negative bacteria infection in knee arthroplasties are rare [10, 20]. Hirakawa et al. established that reimplantation was less successful in polymicrobial than in low-virulence organisms but more successful than in high-virulence ones [10].

Moran et al. described a high rate of resistance to cephalosporins among Gram-negative organisms [20]. Additional studies reporting the results of treatment of these types of infection in knee arthroplasties are needed.

Our purpose was to evaluate the success of patients treated with polymicrobial, Gram-negative and methicillin-resistant infected total knee arthroplasties. We addressed the following questions: (1) Are the rates of control of infection and the functional outcomes as assessed by the Knee Society score (KSS) after late knee arthroplasty infections with polymicrobial isolates similar to those with monomicrobial isolates? (2) Are eradication rates and functional outcomes as assessed by the KSS after late knee arthroplasty infections caused by Gram-negative bacteria similar to those after infections by Gram-positive bacteria? (3) Are the rates of control of infection and the functional outcomes as assessed by the KSS after late knee arthroplasty infections caused by methicillin-resistant Staphylococci worse than those after infections caused by methicillin-sensitive Staphylococci?

Patients and Methods

We prospectively followed 47 consecutive patients diagnosed with late knee arthroplasty infection between January 1997 and January 2008. The criteria for the diagnosis of infection included the presence of a fistula. A tentative diagnosis of infection was made in the presence of unusual pain and/or progressive stiffness with elevation of the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). We performed joint aspiration only if patients had other reasons for elevated CRP and ESR (inflammatory arthritis) as well as in cases when no surgery was possible (see subsequently). Inclusion criteria also required that three or more positive cultures with the same organisms be obtained, preferably from intraoperative samples (samples taken according to the protocol described subsequently), and if more than 3 months had passed from primary surgery (all infections were Type IV according to the Cierny classification system) [3, 24]).

The patients had an average age of 72 ± 10.6 years (range, 20–87 years); 34 were women (72%) and 13 were men (28%). Patients were classified according to the Cierny-diPasquale classification system [4] (Table 1). Class "A" is defined as no local or systemic conditions rendering treatment difficult. Class B-l suggests local conditions compromise the treatment and/or results, and B-s includes patients with systemic conditions which compromise treatment. Class "C" patients cannot receive standard treatment due to concomitant medical comorbidity. No subjects declined to participate. The minimum followup after the last surgery or the end of antibiotic treatment (whatever was later) was 1 year, and average followup was 4.8 ± 3 years (range, 1–12 years) (Table 1). No patients were lost to followup.

We established an "intention-to-treat" two-stage surgical protocol, but surgery was not possible in five of the 47 patients (11%). The surgery was refused by three patients (Patients 25, 27, and 28), and contraindicated in two patients because of a severe arterial obstruction in one (Patient 34) and a concurrent cancer in another (Patient 36). These five patients were only treated with antimicrobial therapy.

In the first surgery, all implants and cement were removed in 35 of the 42 operated patients. The implants in the other seven patients (1, 9, 10, 17, 20, 24, and 33) were retained. These seven patients had elevated anesthetic and surgical risks, and six of them were implanted with a rotational hinge with cemented stems. In all 42 operated patients, we performed aggressive débridement and irrigated all tissues with 12 L of a saline solution with 120 mL 10% iodine (Betadine; Viatris Manufacturing, Mundipharma AG, Switzerland) (final concentration 1/1000). If explantation was performed a handmade static spacer of Copal (PMMA, 1 g clindamycin, 1 g gentamicin; Biomet Merck GmbH, Ried b Kerzers, CH) was applied, covering all exposed bone surfaces. Neither a spacer nor any local antibiotic treatment was used in the seven patients with only débridement.

Prior to irrigation, five tissue samples were harvested from different macroscopically suspicious sites of bone and soft tissue. Immediately after harvesting, these samples were placed in a sterile container and sent to a microbiology laboratory within 30 minutes of acquisition and within 60 minutes were processed according to commonly accepted protocols. The samples were inoculated onto the following media: Tryptic soy 5% sheep blood agar, Chocolate agar, McConkey agar, and Schaedler 5% sheep blood agar [6]. Microbiological cultures in the five patients without surgery were obtained from their fistula and/or joint aspiration.

Table 1. Age and gender of the patients, Cierny type, infected knee arthroplasties, and microbiology

Patient number	Age (years)	Gender	Followup (years)	Cierny type	Infected arthroplasty	Cultured bacteria
1	87	F	1	C	Traiber Excel-HAP	Escherichia coli
2	79	F	1	C	Traiber Excel-HAP	MRSA, MSCNS
3	81	F	1	C	Exactech Optetrak	MSSA
4	78	F	1	B-s	Stryker Triathlon	MRCNS
5	73	F	1	B-s	Stryker Triathlon	MSSA
6	73	M	5	B-s	Exactech Optetrak	Enterobacter cloacae, Stenotrophomonas maltophilia, Acinetobacter sp.
7	73	F	3	B-s	Link Rotational hinge	MRSA
8	84	F	6	C	Zimmer MG-II	MSSA
9	68	F	1	C	Link Rotational hinge	MSSA
10	70	F	4	C	Link Rotational hinge	Pseudomonas aeruginosa, Enterobacter cloacae
11	80	F	5	B-s	Traiber Excel-HAP	MRCNS, Enterococcus casseliflavus
12	74	F	7	B-s	Traiber Excel-HAP	MSCNS
13	69	F	5	B-s	Zimmer MG-II	MRCNS, Streptococcus constellatus
14	77	F	5	B-s	Traiber Excel-HAP	MSCNS
15	72	M	2	B-s	Traiber Excel-HAP	Enterococcus faecalis, Enterococcus avium
16	83	F	6	B-s	Traiber Excel-HAP	MRCNS
17	77	F	5	C	Link Rotational hinge	MRCNS
18	70	M	2	C	Exactech Optetrak	MRSA, Corynebacterium, Clostridium
19	72	F	7	B-s	Link Rotational hinge	Enterococcus faecium
20	20	M	2	C	Stryker Koch tumoral modular	MSSA
21	81	F	6	B-s	Traiber Excel-HAP	Pseudomonas aeruginosa
22	69	F	5	B-s	Zimmer MG-II	MRCNS, MSCNS
23	78	F	5	B-s	Howmedica PCA primary	MRSA
24	74	F	4	C	Link Rotational hinge	MRCNS
25	81	M	6	B-l	Zimmer MG-II	MRSA
26	66	M	1	B-s	Exactech Optetrak	MSCNS, Enterobacter cloacae
27	51	F	6	B-s	Link Rotational hinge	MRCNS, Enterobacter cloacae
28	68	F	7	B-s	Traiber Excel-HAP	MSSA
29	67	F	6	B-s	Traiber Excel-HAP	MRCNS, Corynebacterium sp.
30	77	M	7	B-s	Traiber Excel-HAP	MRCNS
31	75	M	4	B-l	Traiber Excel-HAP	MRCNS, Enterococcus faecalis, Serratia marcescens,
32	70	F	5	B-s	Link Rotational hinge	MRSA
33	73	F	1	C	Link Rotational hinge	Klebsiella pneumoniae
34	75	M	2	B-l	Stryker Triathlon	MRCNS
35	73	F	7	B-s	Traiber Excel-HAP	Serratia marcescens
36	80	M	1	C	Traiber Excel-HAP	MRCNS
37	80	F	3	B-s	Exactech Optetrak	MRCNS
38	76	M	1	B-l	Stryker Triathlon	MRSA, MRCNS
39	80	F	5	B-s	Traiber Excel-HAP	MRCNS
40	86	F	5	B-s	Traiber Excel-HAP	MSCNS
41	70	M	12	B-s	Zimmer MG-II	MRCNS
42	60	M	11	B-s	Zimmer MG-II	MSCNS
43	63	F	10	B-s	Howmedica Interax	MRCNS
44	56	F	10	C	Howmedica Interax	MSCNS, MSSA

Table 1. continued

Patient number	Age (years)	Gender	Followup (years)	Cierny type	Infected arthroplasty	Cultured bacteria
45	75	F	9	B-s	Zimmer MG-II	MRCNS
46	62	F	9	C	Howmedica Interax	MSCNS
47	72	F	9	B-s	Howmedica Interax	MSCNS, Candida albicans

F = female; M = male; MSSA = methicillin-sensitive Staphylococcus aureus; MRSA = methicillin-resistant S. aureus; MSCNS = methicillin-sensitive coagulase-negative Staphylococcus; MRCNS = methicillin-resistant coagulase-negative Staphylococcus.

Multiple organisms were isolated in cultures (Table 1). Fifteen patients (32%) presented an infection with two or more isolated species (polymicrobial infections), whereas only one bacterial species grew in cultures of 32 of 47 (68%) (monomicrobial infections). Forty-one patients (87%) had an infection caused by Gram-positive bacteria (in three of them mixed with Gram-negative), and Gram-negative bacteria were cultured from nine of 47 patients (19%), four with monomicrobial and five with polymicrobial cultures (three of these latter five mixed with Gram-positive bacteria). Methicillin-resistant (MR) Staphylococci were detected in 25 of 47 patients (53%): seven of 47 were MRSA (three of them in polymicrobial infections) and 19 of 47 were MR-CNS (six of them in polymicrobial cases). Patient 38 presented simultaneously MRSA and MR-CNS. Methicillin-sensitive Staphylococci were cultured in 16 of 47 patients (34%) (Patient 44 presented simultaneously with methicillin-sensitive S. aureus and S. coagulase-negative) (Tables 1, 2).

After the first surgery, operated patients remained in the hospital for 1 week and received a short course (less than 5 days in all cases) of empiric intravenous antibiotics (cefazolin + gentamicin + clindamycin) until results of intraoperative cultures and susceptibility tests were available. After the results of cultures were available, all patients were treated with two simultaneous oral antibiotics for 6 months. Oral antibiotics were selected according to in vitro susceptibility tests of individual bacterial isolates. Among oral antibiotics effective in vitro, we selected those with accepted activity inside biofilm and supposed activity against intracellular bacteria [1, 5, 6, 14, 25–27]. Dosages were in the high range for each drug and not adjusted to individual weights (Table 3).

Renal, hepatic, and hematologic functions as well as ESR and CRP were checked monthly during the entire treatment by means of blood analyses (parameters controlled: creatinine, urea nitrogen, SGOT and SGPT transaminases, gamma-glutamyl-transferase, total erythrocyte count, hemoglobin, leukocyte count, platelet count, ESR, CRP).

Reimplantation surgery was delayed until clinical (wound healing, no signs of local inflammation) and serologic normalization (ESR less than 20 mm/hr and CRP less than 0.8 mg/L) were recorded. Oral antibiotics were stopped one week before reimplantation surgery. In this second stage, the spacer was removed, débridement performed, multiple samples for microbiologic culture taken for control, and a new cemented prosthesis was implanted with the antibiotic-laden cement Copal (Biomet Merck GmbH) (PMMA, 1 g gentamicin, 1 g clindamycin). Frozen histologic sections were not used in reimplantation surgery.

A knee arthrodesis was selected as the reconstruction procedure in four of the 42 operated patients (10%) (four of 47 treated patients [9%]). Patients 3 and 15 were referred to our department with an infected nonunion after several failed attempts at arthrodesis because of an infected total knee. Patient 18 was also referred with a catastrophic TKA infection, which destroyed the quadriceps and patellar tendon. Second-stage surgery was delayed for 3 years in Patient 46 because of a coagulation deficit, so her knee was finally treated with an intramedullary cemented arthrodesis nail. Infection was controlled in these four patients undergoing arthrodesis.

Reimplantation was not performed in four of the 42 operated patients, so resection arthroplasty was the final situation. Patients 2, 3, and 8 had severe dementia, which precluded any postoperative rehabilitation protocol (Patient 3 presented additionally with ipsilateral hemiplegia); Patient 44 presented with severe peripheral arterial disease with lesser toe amputations and the vascular surgeons advised against reimplantation.

After the second surgery, patients remained in the hospital for 1 week. Postoperative protocols in our hospitals include intravenous prophylactic cefazolin for 5 postoperative days in all arthroplasty revision surgery. If oral antibiotics had been administered for six months before reimplantation they were not continued; but if they had been administered for less than six months they were continued until completing the protocol of six months of oral treatment. This regimen was used in our reimplanted patients.

Patients with a retained prosthesis (those without surgery as well as those with only débridement) were treated with a similar protocol of six months of combined oral antibiotics. No patient was maintained with a chronic (unlimited in time) antibiotic protocol.

Table 2. Treatment (surgery, antibiotics) and outcome (healing of infection, orthopaedic) of patients undergoing knee arthroplasty

Patient number	Surgical treatment	Time between surgeries (months)	Oral antibiotics	Healing of infection	Orthopaedic outcome
1	Débridement		Ciprofloxacin, trimethoprim-sulfamethoxazole	Yes	KSCRS 81/55
2	Resection arthroplasty (dementia)		Rifampin, clindamycin	Yes	KSCRS 45/0
3	Resection arthroplasty (ipsilateral hemiplegia, dementia)		Rifampin, ciprofloxacin	Yes	KSCRS 45/0
4	Two-stage exchange	5	Rifampin, fosfomycin	Yes	KSCRS 93/80
5	Two-stage exchange	5	Rifampin, ciprofloxacin	Yes	KSCRS 93/80
6	Two-stage exchange	6	Ciprofloxacin, trimethoprim -sulfamethoxazole	Yes	KSCRS 88/70
7	Arthrodesis (external fixator)		Rifampin, clindamycin	Yes	KSCRS 75/50
8	Resection arthroplasty (severe dementia)		Ciprofloxacin	Yes	KSCRS 45/0
9	Débridement		Rifampin, levofloxacin	Yes	KSCRS 45/0
10	Débridement		Ciprofloxacin, trimethoprim-sulfamethoxazole	Yes	KSCRS 81/55
11	Two-stage exchange	4	Rifampin, ciprofloxacin	Yes	KSCRS 93/80
12	Two-stage exchange	9	Ciprofloxacin, trimethoprim-sulfamethoxazole	Yes	KSCRS 93/80
13	Two-stage exchange	5	Linezolid	Yes	KSCRS 88/70
14	Two-stage exchange	7	Rifampin, ciprofloxacin	Yes	KSCRS 74/65
15	Arthrodesis (external fixator)		Doxycycline, amoxicillin-clavulanic acid	Yes	KSCRS 75/60
16	Two-stage exchange	19	Trimethoprim-sulfamethoxazole, fosfomycin	Yes	KSCRS 73/50
17	Débridement		Rifampin, trimethoprim-sulfamethoxazole	Yes	KSCRS 81/55
18	Arthrodesis (external fixator)		Teicoplanin + fosfomycin	Yes	KSCRS 75/60
19	Two-stage exchange	17	Linezolid, ciprofloxacin, rifampin	Yes	KSCRS 89/70
20	Débridement		Rifampin, ciprofloxacin	Yes	KSCRS 81/55
21	Two-stage exchange	6	Ciprofloxacin	Yes	KSCRS 93/60
22	Two-stage exchange	29	Ciprofloxacin, trimethoprim-sulfamethoxazole, rifampin, fosfomycin	Yes	KSCRS 93/60
23	Two-stage exchange	17	Rifampin, ciprofloxacin	Yes	KSCRS 93/50
24	Débridement		Rifampin, trimethoprim-sulfamethoxazole	Yes	KSCRS 81/55
25	(Patient refuses surgery)		Fosfomycin, clindamycin	NO (severe pain)	KSCRS 63/0
26	Two-stage exchange		Ciprofloxacin, trimethoprim-sulfamethoxazole	Yes	KSCRS 93/80
27	(Patient refuses surgery)		Ciprofloxacin, trimethoprim-sulfamethoxazole	Yes	KSCRS 88/60
28	(Patient refuses surgery)		Clindamycin, trimethoprim-sulfamethoxazole	Yes	KSCRS 88/60
29	Two-stage exchange	6	Rifampin, ciprofloxacin	Yes	KSCRS 99/80
30	Two-stage exchange	6	Rifampin, ciprofloxacin, fosfomycin, trimethoprim-sulfamethoxazole	NO	Amputation, KSCRS 0/0
31	Two-stage exchange	9	Fosfomycin, ciprofloxacin, linezolid	Yes	KSCRS 88/60
32	Two-stage exchange	24	Trimethoprim-sulfamethoxazole, doxycycline	Yes	KSCRS 88/40
33	Débridement		Trimethoprim-sulfamethoxazole, doxycycline	NO fistula	KSCRS 81/55
34	No surgery (severe peripheral arterial disease)		Clindamycin	NO (pain, swelling)	KSCRS 35/0
35	Two-stage exchange	4	Ciprofloxacin	Yes	KSCRS 73/40

Table 2. continued

Patient number	Surgical treatment	Time between surgeries (months)	Oral antibiotics	Healing of infection	Orthopaedic outcome
36	No surgery (neoplastic disease)		Rifampin, ciprofloxacin	Yes	KSCRS 83/40
37	Two-stage exchange		Rifampin, clindamycin	Yes	KSCRS 73/70
38	Two-stage exchange		Rifampin, trimethoprim-sulfamethoxazole	Yes	KSCRS 93/80
39	Two-stage exchange	6	Rifampin, ciprofloxacin	Yes	KSCRS 88/65
40	Two-stage exchange	5	Levofloxacin, rifampin	Yes	KSCRS 86/90
41	Two-stage exchange	4	Rifampin, ofloxacin	Yes	KSCRS 88/80
42	Two-stage exchange	3	Rifampin, trimethoprim-sulfamethoxazole	Yes	KSCRS 86/90
43	Two-stage exchange	3	Rifampin, ofloxacin	Yes	KSCRS 81/80
44	Resection arthroplasty (severe arterial disease)		Rifampin, ofloxacin	Yes	KSCRS 48/50
45	Two-stage exchange	6	Rifampin, ofloxacin	Yes	KSCRS 88/90
46	Arthrodesis (IM nail)	36	Trimethoprim-sulfamethoxazole, ofloxacin	Yes	KSCRS 75/60
47	Two-stage exchange	5	Rifampin, trimethoprim-sulfamethoxazole, ketoconazole	Yes	KSCRS 73/80

IM = intramedullary; KSCRS = American Knee Society clinical rating score.

Table 3. Oral antibiotics used, dose, frequency, and number of patients treated with each of them

Antibiotic	Dose	Period of administration (hours)	Number of patients
Rifampin	300 mg	Every 8 hours	27
Ciprofloxacin	750 mg	Every 12 hours	22
Trimethoprim-sulphamethoxazole	160–800 mg	Every 12 hours	18
Ofloxacin or levofloxacin	200 mg or 500 mg	Every 12 hours	7
Fosfomycin	1000 mg	Every 8 hours	7
Clindamycin	600 mg	Every 8 hours	6
Linezolid	600 mg	Every 12 hours	3
Doxycycline	100 mg	Every 12 hours	3
Amoxicillin + clavulanic acid	875 mg + 125 mg	Every 8 hours	1

Patients were followed clinically, radiographically, and serologically (CRP and ESR) at 4, 8, 12, 16, 20, and 24 weeks after the second surgery. Thereafter, clinical, serologic, and radiologic controls have been performed every 6 months. Control of infection was defined as an absence of clinical, serologic, and radiologic signs of infection during the entire followup. For this purpose, clinical signs suspicious of infection were considered: chronic severe pain, persistent regional inflammatory signs, wound drainage, wound dehiscence, and/or fistula. Serologic signs suspicious of infection were ESR over 20 mm/hr and/or CRP over 0.8 mg/L. Radiologic signs suggestive of infection were: definite loosening, progressive migration of the implant, progressive radiolucent lines, and/or progressive osteolysis. At each followup visit, we obtained a KSS [12].

For qualitative variables (infection control versus no infection control), Chi square (uncorrected, Mantel-Haenszel and Yates) and Fisher exact tests were used. For quantitative variables (comparison of KSS), Bartlett test was used to check the normality of the data, and then ANOVA or Kruskal-Wallis tests were used for comparison of the series when adequate ($p = 0.05$). All statistical analyses were performed using Epi Info 3.5.1 software (CDC. Atlanta, GA, USA).

Results

Control of infection was as predictable for polymicrobial as for monomicrobial infections ($p = 0.202$). Infection was eradicated in 15 of 15 patients with polymicrobial cultures,

whereas it was controlled in only 28 of 32 patients (88%) with monomicrobial cultures. In the same way, KSS scores were similar between the groups and averaged 81 ± 16 to 63 ± 20 in patients with polymicrobial cultures, compared to an average of only 75 ± 20 to 52 ± 29 in those with monomicrobial ones ($p = 0.3282$ (significance of comparison of first figure of KSS) to $p = 0.1565$ (significance of comparison of second figure of KSS).

Infection control was similar for Gram-negative and for Gram-positive bacteria ($p = 0.586$). Infection was controlled in eight of nine patients (89%) with Gram-negative isolates and in 35 of 38 (92%) with only Gram-positive isolates. KSS scores offered also no differences: 85 ± 6 to 59 ± 10 in the nine patients with Gram-negative bacteria versus 75 ± 21 to 55 ± 29 in the 38 patients with only Gram-positive bacteria ($p = 0.3060$ for comparison of first figure and $p = 0.7024$ for comparison of second figure).

There were no differences in eradication of infection between methicillin-resistant and methicillin-sensitive Staphylococci ($p = 0.588$). Infection was controlled in 22 of 25 patients (88%) infected by methicillin-resistant Staphylococci and in 14 of 14 patients infected by methicillin-sensitive Staphylococci. KSS scores were also similar between these subgroups: KSS reached 78 ± 22 to 54 ± 27 in patients infected with methicillin-resistant Staphylococci, whereas it averaged 73 ± 19 to 56 ± 32 in those infected with methicillin-sensitive Staphylococci ($p = 0.3450$ for the comparison of first value and $p = 0.6022$ for the comparison of second value of KSS).

One monomicrobial infection by a methicillin-resistant coagulase-negative Staphylococcus was not eradicated after multiple surgeries (including two consecutive two-stage exchanges) and the patient elected to have an amputation.

Discussion

In this study we assessed our ability to treat and control polymicrobial, Gram negative and methicillin resistant infections in patients with total knee arthroplasties. We aimed to assess our treatment protocol which includes two-stage surgical management and an extended organism-specific treatment with oral antibiotics. In addition, we wished to address unresolved controversies in the literature [1, 2, 9, 10, 15–17, 21, 23, 26–28]. We were successful in treating the majority of these complex infections but experienced greater difficulty and subsequently poorer results in patients with monomicrobial, methicillin-resistant Staphylococcal infections.

The major limitation of this study is the relatively small number of cases. Late knee arthroplasty infection is, fortunately, a low-frequency complication reported to occur in only 1% to 2% of patients with total knee replacements [17, 18, 22]. Estimating an incidence of 2%, more than 2300 total knees must be operated to reach 47 infected cases, as in the series presented here. Furthermore, the subgroups with specific bacterial infections (polymicrobial, Gram-negatives, methicillin-resistant) are too small to ensure adequate statistical power. As a result, we must accept that this is a pilot study and therefore present only raw data, simple percentages, and the value of "p" for statistical significance, but we have not elaborated further statistical analysis.

It has not been proven that polymicrobial infections present worse prognosis that monomicrobial ones. One report [10] suggests polymicrobial infections are more difficult to treat than monomicrobial low-virulence infections (successful reimplantation in 71% of cases versus 80% successful reimplantation, respectively) but easier than MRSA infections (67% successful reimplantation). In our series, the infection was eradicated in all 15 of our patients with polymicrobial cultures, which compares favorably (with no statistical significance, $p = 0.202$) with controls in only 28 of 32 patients (88%) with monomicrobial cultures. It is true that in our series, infection was controlled in 14 of 14 patients infected by methicillin-sensitive Staphylococci in accordance with a referred paper [10]. The functional scores at the end of followup were also better after polymicrobial infections.

It is not clear that infections caused by Gram-negative bacteria are more difficult to treat than those caused by Gram-positives. This topic has received almost no consideration in the orthopaedic literature. One paper communicates a high rate of resistance to cephalosporins and recommends use of carbapenems [20]. Expanding the literature search to include hip infections, Gram-negative infection is considered a factor for failure in direct exchange of total hips [14]. Nine knees of the 47 studied in our series presented Gram-negative bacteria in their cultures; eight of these nine were controlled (89%), which is quite similar (statistically there are no differences, $p = 0.586$) to the eradication rate of 35 of 38 (92%) in patients with only Gram-positive bacteria in their isolates. Moreover, functional outcome at end of followup was better in Gram-negative patients than in patients with only Gram-positive bacteria.

Infections by methicillin-resistant Staphylococci present the worst figures for control of infection and functional outcomes. In fact, they are considered by most authors as the worst microbiological situation [21]. A hazard ratio of 9.2 has been communicated for treatment failure [23] as well as a higher failure rate after débridement and oral treatment [1], which may reach an odds ratio of 17.6 [26]. One-stage exchange obtains control in only 61% of patients [16]. One study of a mixed series of acute and late

infections reported even lower eradication rates; successful total knee after débridement or exchange occurred in only 18% (versus 89% in methicillin-sensitive) [15]. In a multicenter series with no comparison with sensitive strains, the infection was controlled in 76% of patients after two-stage [19]. Another report found eradication was obtained after two-stage in 67% of cases (versus 80% in methicillin-sensitive) [10]. Other authors, on the other hand, suggest no statistical differences between low and high bacterial virulence or resistance with one- or two-stage exchange [2, 28]. Our results were worse for methicillin-resistant infections, but statistical differences were not found ($p = 0.58$); infection was controlled in 22 of 25 patients (88%) with methicillin-resistant Staphylococci and in 14 of 14 patients with methicillin-sensitive Staphylococci. Furthermore, the functional outcomes were similar.

In conclusion, we found polymicrobial and Gram-negative bacteria isolates were not poor prognostic factors in the treatment of late knee arthroplasty infections. On the other hand, we found infections by methicillin-resistant Staphylococci, S. aureus as well as coagulase-negative Staphylococci had a lower chance of eradication of infection.

References

1. Barberán J, Aguilar L, Carroquino G, Giménez MJ, Sánchez B, Martínez D, Prieto J. Conservative treatment of Staphylococcal prosthetic joint infections in elderly patients. *Am J Med*. 2006;119:993.e7–10.
2. Bauer T, Piriou P, Lhotellier L, Leclerc P, Mamoudy P, Lortat-Jacob A. Results of reimplantation for infected total knee arthroplasty: 107 cases. *Rev Chir Orthop Reparatrice Appar Mot*. 2006;92:692–700.
3. Chambers HF. The changing epidemiology of Staphylococcus aureus? *Emerg Infect Dis.* 2001;7:178–182.
4. Cierny G III, DiPasquale D. Periprosthetic total joint infections: staging, treatment, and outcomes. *Clin Orthop Relat Res*. 2002; 403:23–28.
5. Cordero-Ampuero J, Esteban J, García-Cimbrelo E. Oral antibiotics are effective for highly resistant hip arthroplasty infections. *Clin Orthop Relat Res*. 2009;467:2335–2342.
6. Cordero-Ampuero J, Esteban J, García-Cimbrelo E, Munuera L, Escobar R. Low relapse with oral antibiotics plus two-stage exchange for late arthroplasty infections in 40 patients alter 2-to-9 years. *Acta Orthop*. 2007;78:511–519.
7. Fulkerson E, Valle CJ, Wise B, Walsh M, Preston C, Di Cesare PE. Antibiotic susceptibility of bacteria infecting total joint arthroplasty sites. *J Bone Joint Surg Am.* 2006;88:1231–1237.
8. Garvin KL, Hinrichs SH, Urban JA. Emerging antibiotic-resistant bacteria. Their treatment in total joint arthroplasty. *Clin Orthop Relat Res.* 1999;369:110–123.
9. Hanssen AD, Rand JA. Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. *Instr Course Lect.* 1999;48:111–122.
10. Hirakawa K, Stulberg BN, Wilde AH, Bauer TW, Secic M. Results of 2-stage reimplantation for infected total knee arthroplasty. *J Arthroplasty.* 1998;13:22–28.
11. Hope PG, Kristinsson KG, Norman P, Elson RA. Deep infection of cemented total hip arthroplasties caused by coagulase-negative Staphylococci. *J Bone Joint Surg Br.* 1989;71:851–855.
12. Insall JN, Dorr LD, Scott RD, Scott WN. Rationale of the Knee Society Clinical Rating System. *Clin Orthop Relat Res.* 1989; 248:13–14.
13. Ip D, Yam SK, Chen CK. Implications of the changing pattern of bacterial infections following total joint replacements. *J Orthop Surg (Hong Kong)*. 2005;13:125–130.
14. Jackson WO, Schmalzried TP. Limited role of direct exchange arthroplasty in the treatment of infected total hip replacements. *Clin Orthop Relat Res.* 2000;381:101–105.
15. Kilgus DJ, Howe DJ, Strang A. Results of periprosthetic hip and knee infections caused by resistant bacteria. *Clin Orthop Relat Res.* 2002;404:116–124.
16. Kordelle J, Frommelt L, Klüber D, Seemann K. Results of one-stage endoprosthesis revision in periprosthetic infection caused by methicillin-resistant Staphylococcus aureus. *Z Orthop Ihre Grenzgeb.* 2000;138:240–244.
17. Leone JM, Hanssen AD. Management of infection at the site of a total knee arthroplasty. *Instr Course Lect.* 2006;55:449–461.
18. Meehan J, Jamali AA, Nguyen H. Prophylactic antibiotics in hip and knee arthroplasty. *J Bone Joint Surg Am.* 2009;91:2480–2490.
19. Mittal Y, Fehring TK, Hanssen A, Marculescu C, Odum SM, Osmon D. Two-stage reimplantation for periprosthetic knee infection involving resistant organisms. *J Bone Joint Surg Am.* 2007;89:1227–1231.
20. Moran E, Masters S, Berendt AR, McLardy-Smith P, Byren I, Atkins BL. Guiding empirical antibiotic therapy in orthopaedics: the microbiology of prosthetic joint infection managed by débridement, irrigation and prosthesis retention. *J Infect*. 2007; 55:1–7.
21. Parvizi J, Azzam K, Ghanem E, Austin MS, Rothman RH. Periprosthetic infection due to resistant Staphylococci: serious problems on the horizon. *Clin Orthop Relat Res*. 2009;467:1732–1739.
22. Robertsson O, Knutson K, Lewold S, Lidgren L. The Swedish Knee Arthroplasty Register 1975–1997. An update with special emphasis on 41223 knees operated on in 1988–1997. *Acta Orthop.* 2001;72:503–513.
23. Salgado CD, Dash S, Cantey JR, Marculescu CE. Higher risk of failure of methicillin-resistant Staphylococcus aureus prosthetic joint infections. *Clin Orthop Relat Res*. 2007;461:48–53.
24. 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;81:1434–1445.
25. Sendi P, Rohrbach M, Graber P, Frei R, Ochsner PE, Zimmerli W. Staphylococcus aureus small colony variants in prosthetic joint infection. *Clin Infect Dis*. 2006;43:961–967.
26. Soriano A, García S, Bori G, Almela M, Gallart X, Maculé F, Sierra J, Martínez JA, Suso S, Mensa J. Treatment of acute post-surgical infection of joint arthroplasty. *Clin Microbiol Infect*. 2006;12:930–933.
27. Trebse R, Pisot V, Trampuz A. Treatment of infected retained implants. *J Bone Joint Surg Br.* 2005;87:249–256.
28. Volin SJ, Hinrichs SH, Garvin KL. Two-stage reimplantation of total joint infections: a comparison of resistant and non-resistant organisms. *Clin Orthop Relat Res*. 2004;427:94–100.