

Low relapse with oral antibiotics and two-stage exchange for late arthroplasty infections in 40 patients after 2–9 years

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Submitted 06-09-28. Accepted 06-11-07

Background and purpose Exchange surgery in late arthroplasty infection is directed against bacteria adhering to implants. Therapies based on antibiotics that are effective intracellularly have been proposed recently. We have combined both strategies to improve the cure rate.

Methods 40 consecutive patients (16 hips, 24 knees) were diagnosed with late arthroplasty infection. The organisms isolated were 35 *Staphylococcus*, 19 of which were methicillin-resistant, 4 *Enterococcus*, 6 Gram-negative bacilli, and 4 *Corynebacterium*. The infections were managed by a combined therapy consisting of two-stage exchange surgery and two oral intracellularly-effective antibiotics. The antibiotics were selected according to bacterial sensitivity and intracellular and biofilm effectiveness. Second re-implantation surgery was delayed until clinical and analytical normalization. Patients were in hospital for only 1 week after each surgery, and were followed up prospectively on an outpatient basis (2–9 years). Cure of the infection was defined as absence of clinical, serological, and radiographic signs of infection during the whole follow-up.

Results The infection was resolved in 38/40 patients (15/16 hips and 23/24 knees).

Interpretation Oral antibiotics that are effective intracellularly in combination with two-stage exchange surgery is a promising alternative for treating late arthroplasty infections. Oral antibiotics shorten hospitalization and reduce patient discomfort.

arthroplasty presents a recurrence rate ranging between 3% and 22%, even with the use of antibiotic-loaded cement in the re-implantation (Insall et al. 1983, Goldman et al. 1996, Haleem et al. 2004, Hsieh et al. 2004, Hoad-Reddick et al. 2005, Hofmann et al. 2005). In addition, patients must receive intravenous antibiotics for a long period (Insall et al. 1983), which increases costs and contributes to patient distress.

Intracellular bacteria have been identified as one of the main types of pathogenic organisms and factors that contribute to chronicity in arthroplasty infections (Proctor et al. 1995, Ellington et al. 2003, Sendi et al. 2006). Thus, in theory at least, antibiotics with intracellular activity should be effective in preventing relapses (Ellington et al. 2006, Sendi et al. 2006). Based on this hypothesis, some authors have published radically different approaches to chronic implant infection (Drancourt et al. 1993, Rissing 1997, Stein et al. 1998, Zimmerli et al. 1998, Trebse et al. 2005), but the results have not been any better than with the traditional two-stage approach—probably because they do not consider the problem of adherence of bacteria to biomaterials, i.e. biofilm formation (Gristina et al. 1991, Costerton 2005, Patel 2005), and thus the need for prompt implant removal (Brandt et al. 1997).

■ We evaluated the results of treating late arthroplasty infections with two oral intracellularly-effective antibiotics combined with two-stage exchange surgery.

Two-stage exchange surgery for a late infected

Patients and methods

Study design

This was a prospective, consecutive, therapeutic case series with no control group. All cases diagnosed consecutively as having a late arthroplasty infection between December 1996 and June 2003 (according to the criteria described below) were included in the study. No subjects declined to participate, and all of them were followed for at least 2 years.

All patients gave oral and written informed consent to participate in this study after being informed of the benefits, the risks, and other treatment alternatives. The study was approved by the institutional review boards and was carried out in accordance with the Helsinki Declaration.

Inclusion criteria

A late infection in hip or knee arthroplasty was diagnosed if both of the following criteria were fulfilled: (1) more than 3 months had passed from primary surgery (all infections were type IV according to Cierny classification system) (Cierny and DiPasquale 2002); and (2) the patient had several (3 or more) positive cultures with the same organism from intraoperative samples. 5 tissue samples taken from different macroscopically “suspicious” bone and deep soft tissues during the first surgery were sent to the microbiology laboratory and analyzed for the presence of aerobic and anaerobic bacteria according to commonly accepted protocols. New cultures were taken during the second surgery, as controls for the therapy.

Demographics (Table 1)

40 patients were included (32 female) with an average age of 72 (46–90) years when the infection was confirmed. General health and medical condition of patients were classified according to the Cierny-diPasquale (2002) classification system (Table 1).

Infected arthroplasties (Table 1)

There were 24 knees and 16 hips in the study. 29 of them presented with discharging sinuses.

Bacteriology (Table 1)

Aerobic and anaerobic cultures were prepared from multiple intraoperative samples. The following

bacteria were isolated: 5 *Staphylococcus aureus* (2 of which were methicillin-resistant strains), 30 *Staphylococcus epidermidis* (17 of which were methicillin-resistant strains), 2 *Enterococcus faecium*, 1 *Enterococcus faecalis*, 1 *Enterococcus casseliflavus*, 2 *Proteus mirabilis*, 2 *Pseudomonas aeruginosa*, 1 *Serratia marcescens*, 1 *Enterobacter cloacae*, and 4 *Corynebacterium spp.* Six patients had polymicrobial infections.

Antibiotic therapy (Table 2)

After first surgery, the patients received a short course of empirical intravenous antibiotics (Cefazolin + Gentamicin + Clindamycin) until the results of cultures and susceptibility tests were available (less than 5 days in all cases). 2 oral antibiotics with biofilm and intracellular effectiveness, both taken simultaneously, were then prescribed on an outpatient basis for 6 months.

The oral antibiotics were selected according to the sensitivity of individual bacterial isolates. Dosages were in the high range for each drug, and were not adjusted to the weight of the individual. They were as follows (Tables 1 and 2): rifampin 300 mg/8 h (26 patients), ciprofloxacin 750 mg/12 h (19 patients), trimethoprim-sulfamethoxazole 400–160 mg/12 h (17 patients), ofloxacin 200 mg/8 h or levofloxacin 500 mg/12 h (8 patients), fosfomicin 1 g/8 h (6 patients), and linezolid 600 mg/12 h (2 patients).

Renal, hepatic, and hematological functions were controlled on a monthly basis during the entire treatment period by means of blood analyses. The parameters controlled were: creatinine, urea nitrogen, SGOT and SGPT transaminases, gamma-glutamyl transferase, erythrocyte count, hemoglobin, leukocyte count, and platelet count.

Surgery

The patients were operated on according to the following two-stage exchange protocol. At the first stage, the entire infected implant and cement were removed, 5 microbiological samples were taken and tested in aerobic and anaerobic media, an aggressive debridement was performed, and all tissues were irrigated with 12 liters of a saline solution with 120 mL of 10% iodine (Betadine; Viatrix Manufacturing, licence Mundipharma AG, Switzerland) at a final concentration of 1/1,000. After

Table 1. Patients (sex, age, weight, Cierny type), infected implants, and microbiology

Patient	Sex	Age (years)	Weight (kg)	Cierny type ^a	Implant infected ^b	Organism(s) cultured ^c
1	M	55	70	B-s	Charnley cemented THA with Slooff / Ling impacted allograft (second exchange)	SE
2	M	70	82	B-s	Howmedica Interax cemented TKA	MRSE
3	F	65	54	B-s	Charnley cemented THA	SE, <i>Proteus mirabilis</i> , <i>Corynebacterium difteriae</i>
4	M	63	90	B-s	Cemented TKA	SE
5	F	46	65	A	Charnley cemented THA	SE
6	F	78	63	B-s	Cemented all-PE cup with Slooff impacted allograft, De Puy Solution stem (second exchange)	SA, SE, <i>Corynebacterium difteriae</i> [not the same format as with patient 3]
7	F	63	78	B-s	Howmedica Interax cemented TKA	SE
8	F	56	66	C	Howmedica Interax-PS cemented TKA	MRSE, SA
9	F	75	81	B-s	Zimmer Miller-Galante II uncemented TKA	MRSE
10	F	62	78	C	Howmedica Interax cemented TKA	MRSE
11	F	72	79	B-s	Howmedica Interax cemented TKA	SE
12	F	62	73	B-s	Charnley cemented THA	SE
13	F	73	96	B-s	Traiber Excel HAP TKA	<i>Serratia marcescens</i>
14	M	77	68	B-s	Traiber Excel HAP TKA	MRSE
15	F	89	57	C	Cemented THA	MRSE
16	M	65	72	A	JRI HAP-Furlong THA	MRSE
17	F	71	81	B-s	JRI HAP-Furlong BHA	MRSE
18	F	80	61	B-s	JRI HAP-Furlong BHA	MRSE
19	F	74	83	B-s	Traiber Excel HAP TKA	SE
20	F	72	91	B-s	Link Rotational-hinge TKA (first exchange)	<i>Enterococcus faecium</i>
21	F	72	53	C	Traiber Autoblocking cemented BHA	MRSA + <i>Corynebacterium</i> spp.
22	F	67	77	B-s	Traiber Excel HAP TKA	SE + <i>Corynebacterium</i> spp.
23	F	73	63	B-s	JRI HAP-Furlong BHA	SE
24	F	84	61	C	Cemented TKA	SA
25	F	83	58	B-s	Traiber Excel HAP TKA	MRSE
26	M	73	79	B-s	Unknown hybrid TKA	<i>Enterobacter cloacae</i>
27	F	81	63	B-s	Traiber Excel HAP TKA	<i>Pseudomonas aeruginosa</i>
28	F	70	79	B-s	Link Rotational-hinge TKA	MRSA
29	F	90	74	C	Thompson cemented hip hemiarthroplasty	<i>Proteus mirabilis</i> , <i>Pseudomonas aeruginosa</i> , <i>Enterococcus faecium</i>
30	F	77	88	B-s	Traiber Excel HAP TKA	MRSE
31	F	86	75	B-s	Traiber Excel HAP TKA	SE
32	F	69	91	B-s	Unknown cemented TKA	MRSE
33	M	56	95	B-s	Wagner uncemented long-stem THA (second exchange)	MRSE
34	F	69	55	B-s	Uncemented Miller-Galante I TKA	SE
35	M	82	75	B-s	Wagner uncemented long-stem THA (first exchange)	<i>Enterococcus faecalis</i>
36	F	69	92	B-s	Traiber Autoblocking cemented BHA	MRSE
37	F	78	61	B-s	Uncemented Howmedica PCA Primary TKA	MRSE
38	F	80	83	B-s	Traiber Excel HAP TKA	MRSE
39	F	80	85	B-s	Traiber Excel HAP TKA	<i>Enterococcus casseliflavus</i>
40	F	82	62	B-s	Johnson S-ROM uncemented THA	MRSE

^a Cierny physiological classification of health and condition of patients affecting treatment and prognosis (Cierny and DiPasquale 2002): A-patients: healthy, with no healing deficiencies; B-patients: compromised by one or more local (B-I) and/or systemic parameters (B-s); C-patients: not considered candidates for aggressive surgical intervention.

^b BHA: bipolar hip arthroplasty; THA total hip arthroplast; TKA total knee arthroplasty

^c MRSA: methicillin-resistant *Staphylococcus aureus*; MRSE: methicillin-resistant *Staphylococcus epidermidis*; SA *Staphylococcus aureus*; SE *Staphylococcus epidermidis*

Table 2. Patients, antibiotics, period from resection to re-implantation surgery, re-implanted prostheses, follow-up, and final score

Patient	Antibiotics ^a	Interime period ^b	Prosthesis re-implanted	FU ^c	Score ^d
1	Rifampin + T-S	...	(Girdlestone)	9	HHS 77
2	Rifampin + T-S	2	Howmedica cemented Interax-PS	8	KSCRS 88/80
3	Rifampin + ofloxacin	...	(Girdlestone)	8	HHS 65
4	Rifampin + T-S	4	Howmedica cemented Interax-PS	8	KSCRS 86/90
5	Rifampin + ofloxacin	24	Howmedica Exeter cemented THA with Slooff / Ling impacted allograft	8	HHS 86
6	Rifampin + T-S	...	(Girdlestone)	7	HHS 66
7	Rifampin + ofloxacin	4	Howmedica cemented Interax-PS	7	KSCRS 81/80
8	Rifampin + ofloxacin	...	(Resection arthroplasty)	7	KSCRS 48/50
9	Rifampin + ofloxacin	7	Howmedica cemented Interax-PS	6	KSCRS 88/90
10	T-S + ofloxacin	36	Knee arthrodesis (Link cemented i.m. nail)	6	KSCRS 75/60
11	Rifampin + T-S	4	Howmedica cemented Interax-PS	6	KSCRS 73/80
12	Rifampin + ofloxacin	16	De Puy uncemented Solution THA	5	HHS 84
13	Ciprofloxacin + T-S	5	Exactech PS Optetrak with stems	4	KSCRS 59/45
14	Rifampin + T-S	9	Exactech PS Optetrak with stems	4	KSCRS 43/80
15	Rifampin + ciprofloxacin	...	(Girdlestone)	4	HHS 58
16	Rifampin + ciprofloxacin	12	Exactech Accumatch modular THA	4	HHS 98
17	Rifampin + fosfomicin	24	Link cemented long-stem Lubinus	4	HHS 96
18	Rifampin + ciprofloxacin	...	(Girdlestone)	4	HHS 58
19	Ciprofloxacin + T-S	9	Exactech PS Optetrak with stems	4	KSCRS 93/80
20	Ciprofloxacin + linezolid	12	Link Rotational-hinge TKA	4	KSCRS 73/40
21	Fosfomicin + T-S	...	(Girdlestone)	4	HHS 56
22	Rifampin + ciprofloxacin	6	Exactech PS Optetrak with stems	3	KSCRS 93/80
23	Fosfomicin + T-S	17	Link cemented long-stem Lubinus	3	HHS 96
24	Rifampin + ciprofloxacin	...	(Resection arthroplasty)	3	KSCRS 45/0
25	Fosfomicin + T-S	12	Exactech PS Optetrak with stems	3	KSCRS 76/50
26	Ciprofloxacin + T-S	10	Link Hinged TKA	3	KSCRS 93/70
27	Ciprofloxacin + T-S	6	Exactech PS Optetrak with stems	3	KSCRS 93/70
28	Fosfomicin + T-S	13	Link Rotational-Hinge TKA	3	KSCRS 88/65
29	Fosfomicin + T-S	...	(Girdlestone)	3	HHS 58
30	Rifampin + ciprofloxacin	12	Exactech PS Optetrak with stems	2	KSCRS 75/30
31	Rifampin + levofloxacin	10	Exactech PS Optetrak with stems	2	KSCRS 88/60
32	Ciprofloxacin + linezolid	5	Exactech PS Optetrak with stems	2	KSCRS 88/70
33	Rifampin + ciprofloxacin	14	Link cemented long-stem Lubinus	2	HHS 94
34	Ciprofloxacin + T-S	10	Exactech PS Optetrak with stems	2	KSCRS 79/65
35	Rifampin + ciprofloxacin	...	(Girdlestone)	2	HHS 71
36	Rifampin + ciprofloxacin	9	Link cemented long-stem Lubinus	2	HHS 98
37	Rifampin + ciprofloxacin	9	Link Rotational-Hinge TKA	2	KSCRS 74/60
38	Rifampin + ciprofloxacin	5	Exactech PS Optetrak with stems	2	KSCRS 88/65
39	Rifampin + ciprofloxacin	7	Exactech PS Optetrak with stems	2	KSCRS 88/65
40	Rifampin + T-S	5	Link cemented long-stem Lubinus	2	HHS 98

^a T-S: trimethoprim-sulphamethoxazole.

^b Period from first to second surgery (months),

^c Follow-up after last surgery (years),

^d Clinical score at end of follow-up:

HHS: Harris hip score,

KSCRS: Knee Society clinical rating system.

first surgery, a spacer was not used in hips, and knees were treated with a hand-made static spacer of Copal (PMMA – clindamycin 1g – gentamicin 1g; Biomet Merck GmbH, Ried b Kerzers, Switzerland) covering all exposed bone surfaces.

After the first surgery, the patients remained in

hospital for 1 week. They received intravenous antibiotics until the results of cultures (less than 5 days in all cases) and then simultaneous treatment with 2 oral antibiotics was begun as described.

Between the first and second surgeries, the patients were followed on an outpatient basis.

Re-implantation surgery was delayed until clinical normalization (wound healing) and serological normalization (ESR < 20 and CRP < 0.8) had been reached, so the interval between surgeries averaged 10 (2–24) months (Table 2). The spacer was removed, multiple cultures were obtained from tissues, a debridement was performed, and a new cemented prosthesis (except for patients 12 and 16, in whom an uncemented implant was used) (Table 2) was implanted with the antibiotic-laden cement Copal (PMMA-gentamicin-clindamycin). Frozen histological sections were not used in re-implantation surgery.

After the second surgery, the patients remained in hospital for 1 week. Intravenous prophylactic cefazolin was used for 5 postoperative days, as in any aseptic arthroplasty exchange.

Follow-up

The patients were controlled clinically, radiologically, and serologically at 2, 4, 8, 12, 16, 20, and 24 weeks after the second surgery. Thereafter, clinical, serological and radiological controls were performed every 6 months.

Criteria for cure of infection

Cure of infection was defined as an absence of clinical, serological, and radiological signs of infection during the whole follow-up. For this purpose, clinical signs giving suspicion of infection were considered: chronic severe pain, persistent regional inflammatory signs, wound drainage, wound dehiscence, and fistula. Serological signs giving suspicion of infection were: ESR > 20 and/or CRP > 0.8. Radiographic signs giving suspicion of infection were: definite loosening, progressive migration of the implant, progressive radiolucent lines, and/or progressive osteolysis.

Results

After an average follow-up of 4 (2–9) years, the infection had healed in 38/40 patients.

Hip arthroplasties (Tables 1 and 2)

15/16 infections healed. Patient number 21 needed a Wagner diaphyseal osteotomy to extract a well-fixed cemented stem during resection surgery. She

suffered a transverse fracture of femur which was stabilized with a Dall-Miles plate and consolidated after 6 months, and clinical and serological signs of infection disappeared at 4 months post-surgery. Suppuration reappeared after 18 months, so the plate and cables were removed. Clinical and serological signs of infection vanished again after 3 months. Suppuration reappeared again after a further 12 months, and a chronic suppressive antibiotic treatment was given.

8 patients were re-implanted with a total hip arthroplasty; at the end of follow-up, their infection continued to be healed and their Harris hip score averaged 94 (84–98).

Patient number 1 rejected re-implantation because he was satisfied with the Girdlestone. He did not suffer pain, used a 3-cm sole-elevator, and had returned to his previous work. Patients 18 and 35 rejected re-implantation because they did not accept the risk of recurrence and had no pain. Re-implantation was rejected in patients 3 (rheumatoid arthritis), 6, 15 (Alzheimer), 21 (hemiplegia), and 29 (Alzheimer) because of poor general health, anesthetic risks, and absence of pain. The Harris hip score of Girdlestone patients averaged 64 (56–77) (Table 2).

Knee arthroplasties (Tables 1 and 2)

23/24 infections healed. After second surgery, patient 14 had persistent pain and signs of inflammation. Serological markers were positive 3 months after re-implantation. He was treated with a second 2-stage exchange, which also failed. 21 patients were re-implanted with a cemented total knee and 20 of them fulfilled the criteria of resolved infection: their Knee Society clinical rating system scores averaged 83 (59–93) (objective score) and 67 (30–90) (functional score) (Table 2).

Patients 20, 25, 30, 34, 37, and 39 needed intermediate surgery for a second debridement, irrigation, and change of spacer because of postoperative drainage (patient 34), persistent signs of inflammation (patient 25), and/or persistent elevated CRP/ESR (patients 20, 25, 30, 34, 37, and 39), so re-implantation surgery was actually their third surgery, but after re-implantation their infection did not reappear. Antibiotics were changed in patient 25 because a mutant *Staphylococcus epidermidis* (resistant to the antibiotics originally used) was

cultured from the second debridement. Patient 27 required a third surgery for debridement and irrigation because of persistent clear aseptic drainage at 6 weeks after re-implantation, but her wound closed uneventfully after this third surgery and her serological markers normalized, so the infection was considered healed.

Patient 10 was treated with a knee arthrodesis (intramedullary cemented nail) because she maintained the spacer for more than 1 year because of a very severe coagulation deficit.

Re-implantation surgery was rejected in patient 8 (Buerger's disease, popliteal artery obstruction > 90%, lesser toes amputated) and patient 24 (advanced Alzheimer's, confined to a wheelchair for the previous 2 years).

Discussion

Treatment of late arthroplasty infections still remains a challenge despite the availability of a broad spectrum of antimicrobial agents and surgical techniques. Several mechanisms of bacterial resistance have been proposed (Cordero and Garcia-Cimbrelo 2000). Firstly, antibiotics do not reach implants because they are not vascularized. Secondly, many biomaterials reduce the efficiency of the immune system (Rae 1975, Petty 1978a, b). Thirdly, bacteria adhere to implant surfaces, produce exopolysaccharides and glycocalyx, and develop biofilms in which the microorganisms exist in a dormant state and diversify phenotypically or express resistance genes, which protects them from phagocytosis and antibiotics (Gristina et al. 1991, Costerton 2005, Patel 2005). Fourthly, under adverse conditions some bacteria transform into variants that can enter cells and survive inside them, thus protecting them from antibodies and antibiotics (Proctor et al. 1995, Ellington et al. 2003, Ellington et al. 2006, Sendi et al. 2006). Although it is speculative in some respects, probably all of the conditions mentioned above could exist in implant infection and must be taken into account when designing a therapeutic approach.

Two-stage exchange (Lieberman et al. 1994, Hofmann et al. 2005) is directed against 3 of the above causes of bacterial persistence: implants are removed, thus avoiding the first, the second and the

third mechanisms (Costerton 2005, Hofmann et al. 2005, Patel 2005). Even so, 3–22% of patients continue to suffer infection after two-stage protocols even with the use of antibiotic-loaded cement for re-implantation (Insall et al. 1983, Lieberman et al. 1994, Goldman et al. 1996, Haleem et al. 2004, Hsieh et al. 2004, Hoad-Reddick et al. 2005, Hofmann et al. 2005). The possibility that intracellular bacteria may not have been treated appropriately (the fourth mechanism of resistance) may be the cause. Apart from this, in conventional treatment patients must receive intravenous antibiotics for 3 to 6 weeks (Insall et al. 1983, Lieberman et al. 1994, Hofmann et al. 2005), which increases costs and patient distress and in most cases requires that the patient be hospitalized for this long period. Some proposed variations in protocols have tried to avoid these disadvantages (Hoad-Reddick et al. 2005) but the final results have been worse.

Since the 1990s, antibiotics that are effective against intracellular bacteria have emerged as a therapeutic alternative. The lack of intracellular activity of penicillins and aminoglycosides and also the high efficiencies of rifampin and fluoroquinolones have been well established (Yancey et al. 1991, Maurin and Raoult 1994, Proctor et al. 1995, Cordero and García-Cimbrelo 2000, Ellington et al. 2003, Ellington et al. 2006). Based on the hypothesis involving intracellular bacteria, some authors have published radically different approaches to chronic implant infection (Drancourt et al. 1993, Rissing 1997, Stein et al. 1998, Zimmerli et al. 1998, Trebse et al. 2005), but their results have been no better than with traditional two-stage treatment: 74% cure rate in THA (88% in exchanged and 62% if no surgery) and 69% in TKA (Drancourt et al. 1993). These approaches do not consider the problem of bacterial adherence to biomaterials, and also biofilm development and maturation (Gristina et al. 1991, Costerton 2005, Patel 2005), and thus the need for prompt implant removal. This is a probable explanation for their low cure rate (Brandt et al. 1997).

We have combined therapeutic strategies that take biofilm (two-stage surgery) and intracellular bacteria (intracellularly-effective antibiotics) into account, in order to improve cure rate and reduce the rate of relapse. There is a secondary advantage with this approach: the antibiotics used are as

effective taken orally as they are when given by the intravenous route, so patients can be treated between surgeries with oral antibiotics on an outpatient basis, thus avoiding prolonged hospital treatment, reducing costs, and minimizing discomfort. Nowadays, oral antibiotics have excellent bioavailability and reach bone and systemic levels that are similar to those obtained with parenteral therapy (Mader et al. 2002).

The time from original surgery, the elevated proportion of discharging sinuses, the Cierny type, and the results of bacteriology (Table 1) all highlight the difficulty of treatment in the present series. The proportion of methicillin-sensitive to methicillin-resistant *Staphylococcus* significantly affects the final result: the cure rate for methicillin-sensitive strains reached 80–89%, while it was only 18–48% for methicillin-resistant strains (Hope et al. 1989, Masterson et al. 1997, Haddad et al. 1999, Kilgus et al. 2002).

The use of extended antibiotic treatment has been suggested to avoid relapses and recurrence of intracellular bacteria, so we used 6 months of antibiotic treatment following Drancourt's protocols (Drancourt et al. 1993, Stein et al. 1998, Costerton 2005). Moreover, infection was not considered to have been eliminated until clinical and analytical normalization after first surgery, so re-implantation was delayed until objective proof of healing, as recommended by some authors (Haddad et al. 1999, Mont et al. 2000, Hoad-Reddick et al. 2005). Prescribing oral antibiotics on an outpatient basis makes it easier to lengthen the time interval between surgeries.

2 years is the minimum length of follow-up to consider an infection resolved. The average follow-up of 4 years in this study is comparable with figures for other published series (Lieberman et al. 1994, Hofmann et al. 2005). These patients are always at risk of relapse, however, and it is advisable to monitor them indefinitely.

15 of the 16 hips healed, which compares favorably with one-stage results (84% cure, 8–10% relapse) (Raut et al. 1994, Callaghan et al. 1999) and is similar to outcomes published for the two-stage strategy (85–95% eradication rate, 7–22% recurrence) (McDonald et al. 1989, Colyer and Capello 1994, Garvin et al. 1994, Lai et al. 1996, Tsukayama et al. 1996, Younger et al. 1997, Haddad

et al. 1999, Hsieh et al. 2004, Kraay et al. 2005). The clinical and functional results in re-implanted patients were satisfactory, but the overall functional results were not so positive because of a high proportion of resection-arthroplasty. Girdlestone is not an ideal end-situation, but it was accepted in some of these patients.

23 of the 24 knees in this study healed, which is similar to the figures published for a two-stage approach: 3% recurrence with aspiration between stages (Mont et al. 2000), cure rates of 89–91% (Wilde and Ruth 1988, Booth and Lotke 1989, Goldman et al. 1996) and 6.5–15% recurrent infection (Haleem et al. 2004, Hoad-Reddick et al. 2005, Hofmann et al. 2005). 7 of our patients needed a third surgery for additional debridement, in 6 of them between resection and re-implantation and in 1 after re-implantation, but all had a good outcome. To perform a second debridement is rarely necessary in hips, but it is recommended for knees in case of doubt (Mont et al. 2000, Hoad-Reddick et al. 2005) because of its success. We were able to implant a new TKA in 21 patients, and their functional results so far are satisfactory or fair. A resection-arthroplasty of the knee was the final undesirable situation in two patients for medical reasons, and their functional result was poor.

Two additional advantages of the proposed treatment come from the use of oral antibiotics. Firstly, outpatient-based treatment leads to a marked reduction in overall healthcare costs (patients remain hospitalized for only one week after each surgery) (Mader et al. 2002). Secondly, patient and family discomfort (social costs) are greatly alleviated because of these short stays in hospital. The weakest point of this approach, and the main cause of patients' complaints, is the prolonged time between resection and re-implantation (Hsieh et al. 2004). Even so, all patients were able to walk short distances with external aids during this period either with no pain (hip patients), or with pain controlled by non-narcotic analgesics (knee patients).

Oral combinations of intracellularly and biofilm-effective antibiotics in combination with two-stage exchange surgery appears to be a promising alternative for treating chronic hip and knee arthroplasty infections. It shortens hospitalization, lowers costs, and reduces patient discomfort.

Contributions of authors

JCA: designed the study. JCA and EGC: gathered the data. JCA, JE, and EGC: analyzed the data. JCA and JE: wrote the paper. JCA, EGC, LM, and RE: ensured the accuracy of the data.

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