Oral Antibiotics are Effective for Highly Resistant Hip Arthroplasty Infections

José Cordero-Ampuero MD, PhD, Jaime Esteban MD, PhD,
Eduardo García-Cimbrelo MD, PhD

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Abstract Infected arthroplasties reportedly have a lower eradication rate when caused by highly resistant and/or polymicrobial isolates and in these patients most authors recommend intravenous antibiotics. We asked whether two-stage revision with interim oral antibiotics could eradicate these infections. We prospectively followed 36 patients (mean age, 71.8 years) with late hip arthroplasty infections. Combinations of oral antibiotics were prescribed according to cultures, biofilm, and intracellular effectiveness. The minimum followup was 1 year (mean, 4.4 years; range, 1–12 years). We presumed eradication in the absence of clinical, serologic, and radiographic signs of infection. Infection was eradicated in all 13 patients with highly resistant bacteria who completed a two-stage protocol (10 with methicillin-resistant *Staphylococci*) and in eight of 11 patients treated with only the first stage (and six

of nine with methicillin-resistant *Staphylococci*). Infection was eradicated in six of six patients with polymicrobial isolates (of sensitive and/or resistant bacteria) who completed a two-stage protocol and in five of seven with polymicrobial isolates treated with only the first surgery. The Harris hip score averaged 88.1 (range, 70–98) in patients who underwent reimplantation and 56.8 (range, 32–76) in patients who underwent resection arthroplasty. Long cycles of combined oral antibiotics plus a two-stage surgical exchange appear a promising alternative for infections by highly resistant bacteria, methicillin-resistant *Staphylococci*, and polymicrobial infections.

Level of Evidence: Level IV, 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 has 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.

J. Cordero-Ampuero (✉)
Cirugía Ortopédica y Traumatología, Hospital Universitario La Princesa, Océano Antártico 41, Tres Cantos, 28760 Madrid, Spain
e-mail: jcordera@telefonica.net

J. Esteban
Microbiología, Fundación Jiménez Díaz-UTE, Madrid, Spain

E. García-Cimbrelo
Cirugía Ortopédica y Traumatología, Hospital Universitario La Paz, Madrid, Spain

Introduction

The incidence of highly resistant bacterial infections has been increasing recently [12, 13], probably because of the massive use of antimicrobials. Published series of arthroplasty infections describe a lower likelihood of eradicating infection when it is caused by multiresistant organisms [1, 14–16, 20, 23, 27]. Some of these studies report rates of eradication of infection but do not evaluate the functional orthopaedic outcomes of the patients [1, 14, 16, 20, 23, 27]. Eradication of infection and functional outcomes in polymicrobial infections have been less studied [14, 18, 20].

Hip arthroplasty infections are usually treated surgically with intravenous antibiotics for 3 to 6 weeks [15, 20, 27]. Alternative treatments with long cycles of oral antibiotics have been recently proposed [1, 4, 6, 14, 23, 26], but some of these papers report a mixture of chronic and acute infections [1, 26] and/or results with prosthesis retention

[1, 4, 23, 26]. Several papers suggest a low risk of recurrence (ranging from 0% to 6%) [6, 22] with oral antibiotics plus two-stage surgery in chronic infections. A protocol based on oral antibiotics would allow treatment on an outpatient basis, short hospital stays, cost savings, and improved quality of life for patients [6].

We raised the following questions: (1) Are oral antibiotics combined with two-stage exchange effective for eradicating hip arthroplasty infections caused by highly resistant bacteria? (2) Are oral antibiotics combined with two-stage surgery effective for eradicating hip arthroplasty infections caused by methicillin-resistant *Staphylococci*? (3) Are oral antibiotics combined with two-stage exchange effective for healing polymicrobial hip arthroplasty infections? (4) What are the Harris hip scores at followup in patients with eradicated hip arthroplasty infections by highly resistant bacteria and in patients with eradicated polymicrobial infections?

Materials and Methods

From January 1997 to January 2007, we treated 36 patients diagnosed with late hip arthroplasty infection (Tables 1, 2) with a protocol based on two-stage exchange (reimplantation surgery was not possible in all patients; see subsequently) plus a combination of two oral antibiotics for 6 months. Six additional patients diagnosed with late infection declined to participate in the trial; three rejected any surgical treatment, whereas three others refused the temporary resection arthroplasty and assumed the risks of one-stage surgery.

We defined a late infection if the following two criteria were fulfilled: (1) more than 3 months had passed since primary surgery (all infections were Type IV according to the classification system of Cierny and DiPasquale [5, 9]); and (2) the patient presented multiple (three or more) positive cultures with the same organisms from intraoperative samples (samples taken according to the protocol described subsequently). During the same period of time, 29 other patients did not fulfill the mentioned criteria; 28 were diagnosed with an acute infection (less than 3 months have passed from primary surgery), whereas one patient presented multiple negative cultures despite abundant purulent material obtained during the first surgery.

Surgical reimplantation was not possible in 16 of 36 patients for the following reasons: (1) death after the first surgery in four patients (Patients 11, 13, 33, 35; death from unrelated diseases: two digestive cancer, two ischemic cardiopathy); (2) reimplantation contraindicated in four patients (ipsilateral hemiplegia in Patients 8 and 15, severe dementia in Patient 26, terminal renal failure in Patient 9); and (3) refusal of reimplantation surgery by eight patients (Patients 2, 3, 17, 20, 22, 27, 28, 34; they had mild or no

pain and were afraid of recurrence) (Table 1). Thus, 20 of the 36 (56%) patients had the intended two-stage procedure, whereas 16 had only the first stage. However, all patients described were treated after their first stage with a combination of two oral antibiotics for 6 months.

There were 23 females with a mean age of 72.0 years (range, 46–90 years) and 13 males with a mean age of 71.4 years (range, 56–83 years). Systemic and local conditions of patients were classified according to Cierny and DiPasquale [5] (Tables 1, 2). The minimum followup after the first procedure was 1 year (mean, 4.4 years; range, 1–12 years) (Table 1). The study was approved by the Institutional Review Board and carried out in accordance with the World Medical Association Declaration of Helsinki. All patients gave oral and written informed consent to participate in this study after being informed of benefits, risks, and other treatment alternatives.

We took five tissue samples from different macroscopically suspicious bone and deep soft tissues during the first surgery [21, 24] and processed each for aerobic and anaerobic bacteria [2] (Tables 1, 2). Methicillin-resistant *Staphylococcus* sp, extended-spectrum β -lactamase-producing *Enterobacteriaceae*, *Enterococcus* sp, and *Pseudomonas aeruginosa* were classified as highly resistant organisms [3, 17]; they were isolated in 24 patients. Thirteen of 36 patients presented two or more different isolates (polymicrobial infection). Five new cultures were taken during the second surgery to check response to the therapy.

After the first surgery, patients received a short course (less than 5 days in all cases) of empiric intravenous antibiotics (cefazolin + gentamicin + clindamycin) until the cultures and susceptibility tests were available. Two simultaneous oral antibiotics with biofilm and intracellular effectiveness were then used on an outpatient basis for 6 months [6–8, 19, 22] (Tables 1, 2). Oral antibiotics were selected according to in vitro susceptibility tests of individual bacterial isolates. Dosages were in the high range for each drug and not adjusted to individual weights as follows: 300 mg rifampin every 8 hours (25 patients), 750 mg ciprofloxacin every 12 hours (14 patients), 160–400 mg trimethoprim-sulfamethoxazole every 12 hours (13 patients), 600 mg clindamycin every 8 hours (seven patients), 1000 mg fosfomicin every 8 hours (six patients), 200 mg ofloxacin every 8 hours and 500 mg levofloxacin every 12 hours (five patients), 600 mg linezolid every 12 hours (one patient), and 100 mg doxycycline every 8 hours (one patient).

Renal, hepatic, and hematologic functions were checked monthly during the entire treatment period by means of blood analyses (parameters controlled: creatinine, urea nitrogen, serum glutamic oxaloacetic and pyruvic transaminases, γ -glutamyl transferase, total erythrocyte count, hemoglobin, leukocyte count, platelet count).

Table 1. Patients with only first surgery: age, gender, Cierny type, infected arthroplasty, microbiology, antibiotic treatment, followup, and outcome (infective and orthopaedic)

Patient number	Age (years)	Gender	Cierny type	Infected arthroplasty	Cultured bacteria	Oral antibiotics	Followup (years)	Healing of infection	Harris hip score
2	78	Female	C	Link Lubinus	MRSCN	Rifampin + levofloxacin	2	Yes	58
3	80	Male	B-s	Link Lubinus	MRSCN	Clindamycin + fosfomicin	2	Yes	45
8	72	Female	C	Traiber autoblocking stem	MRSA, <i>Corynebacterium</i> sp, <i>Providencia stuartii</i>	Trimethoprim-sulfametoxazole + fosfomicin	7	No (multiple fistula)	56
9	69	Female	C	JRI Furlong-HAP	MRSCN	Rifampin + ciprofloxacin	1	No (multiple fistula)	32
11	83	Male	C	JRI Furlong-HAP	MRSCN	Rifampin + ciprofloxacin	1	Yes	Not available
13	79	Female	C	JRI cemented Furlong	MSSCN	Ciprofloxacin + clindamycin	1	Yes	Not available
15	74	Female	C	Traiber autoblocking stem	MRSA, <i>Pseudomonas aeruginosa</i>	Clindamycin + trimethoprim-sulfametoxazole	3	Yes	58
17	74	Female	B-s	JRI Furlong-HAP	MRSCN, <i>Proteus mirabilis</i>	Linezolid + fosfomicin	3	Yes	58
20	82	Male	C	Wagner long-stem	<i>Enterococcus faecalis</i>	Rifampin + ciprofloxacin	6	Yes	63
22	80	Female	B-s	JRI Furlong-HAP	MSSCN	Rifampin + ciprofloxacin	7	Yes	58
26	89	Female	C		MRSCN	Rifampin + ciprofloxacin	7	Yes	58
27	70	Male	B-s	DePuy Charnley	MSSCN	Rifampin + trimethoprim-sulfametoxazole	12	Yes	76
28	65	Female	B-s	DePuy Charnley	MSSCN, <i>Proteus mirabilis</i> , <i>Corynebacterium</i> sp	Rifampin + ofloxacin	11	Yes	65
33	78	Female	C	Traiber Thompson	<i>Pseudomonas aeruginosa</i> , <i>Proteus mirabilis</i> , <i>Enterococcus faecalis</i>	Rifampin + trimethoprim-sulfametoxazole	1	Yes	Not available
34	90	Female	B-s	Traiber autoblocking stem	MSSCN, <i>Candida albicans</i>	Rifampin + trimethoprim-sulfametoxazole + ketoconazole	1	Yes	54
35	81	Male	C	JRI Furlong-HAP	MRSCN, <i>Escherichia coli</i> , <i>Bacteroides fragilis</i>	Ciprofloxacin + amoxicillin-clavulanic acid	1	No	Not available

MRSA = methicillin-resistant *S aureus*; MSSCN = methicillin-sensitive coagulase-negative Staphylococcus; MRSCN = methicillin-resistant coagulase-negative Staphylococcus.

Table 2. Patients with two-stage surgery: age, gender, Cierny type, infected arthroplasty, microbiology, antibiotic treatment, period between surgeries, followup, and outcome (infective and orthopaedic)

Patient number	Age (years)	Gender	Cierny type	Infected arthroplasty	Cultured bacteria	Oral antibiotics	Period between surgeries (months)	Followup (years)	Healing of infection	Harris hip score
1	73	Male	B-1	Zimmer HG	MRSA	Rifampin + ciprofloxacin	6	2	Yes	79
4	73	Female	B-s	JRI Furlong-HAP	MSSCN	Fosfomicin + trimethoprim-sulfametoxazole	7	6	Yes	91
5	78	Female	B-s	Traiber autoblocking stem	ESBL <i>Escherichia coli</i> , <i>Micrococcus</i> sp	Rifampin + ciprofloxacin + trimethoprim-sulfametoxazole	7	3	Yes	98
6	57	Male	A	Link Pippino	MSSCN	Rifampin + ciprofloxacin	6	4	Yes	92
7	71	Female	B-s	JRI Furlong-HAP	MRSCN	Rifampin + fosfomicin	23	7	Yes	91
10	78	Female	B-s	JRI cemented Furlong	MSSCN, ESBL <i>Enterobacter cloacae</i>	Rifampin + ciprofloxacin	13	4	Yes	92
12	65	Male	A	JRI Furlong-HAP	MRSCN	Doxycycline + rifampin	11	7	Yes	97
14	62	Male	A	DePuy Chamley	<i>Streptococcus agalactiae</i>	Clindamycin	3	2	Yes	70
16	70	Female	A		MRSCN	Rifampin + levofloxacin	9	2	Yes	94
18	80	Female	B-s	Johnson S-ROM	MRSCN	Rifampin + trimethoprim-sulfametoxazole	4	4	Yes	98
19	79	Male	C	Zweymüller	MRSA, <i>Enterococcus faecalis</i>	Rifampin + clindamycin + trimethoprim-sulfametoxazole	6	2	Yes	74
21	57	Female	B-s	Wagner long-stem	MRSCN, <i>Streptococcus mitis</i>	Rifampin + ciprofloxacin	14	5	Yes	81
23	69	Female	B-s	Traiber autoblocking stem	Mixed anaerobic bacteria	Rifampin + ciprofloxacin	9	6	Yes	88
24	56	Male	B-s	Wagner long stem	MRSCN	Fosfomicin + clindamycin	14	5	Yes	98
25	46	Female	B-1	Stryker-Howmedica ABG-I	MRSCN	Rifampin + trimethoprim-sulfametoxazole	4	2	Yes	75
29	46	Female	A	DePuy Chamley	MSSCN	Rifampin + ofloxacin	9	11	Yes	86
30	78	Female	B-s	DePuy Solution	MSSA, MSSCN, <i>Corynebacterium</i> sp	Rifampin + trimethoprim-sulfametoxazole	21	10	Yes	87
31	62	Female	B-s	DePuy Chamley	MSSCN	Rifampin + ofloxacin	4	8	Yes	84
32	77	Male	B-s	JRI Furlong-HAP	ESBL <i>Escherichia coli</i>	Ciprofloxacin + trimethoprim-sulfametoxazole	6	1	Yes	95
36	63	Male	B-s	Stryker ABG-II	MRSA	Clindamycin + trimethoprim-sulfametoxazole	6	1	Yes	91

MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*; MSSCN = methicillin-sensitive coagulase-negative *Staphylococcus*; MRSCN = methicillin-resistant coagulase-negative *Staphylococcus*; ESBL = extended-spectrum beta-lactamase.

During the first surgical stage, we removed the entire implant and all cement, aggressively débrided the soft tissues, and irrigated all tissues with 12 L of a saline solution containing 120 mL of 10% iodine (Betadine®; Viatrix Manufacturing, Merignac, France; final concentration, 1/1000). We did not use spacers.

Patients remained in the hospital for 1 week. They received intravenous antibiotics until the results of cultures were obtained (less than 5 days in all patients) and then two simultaneous oral antibiotics were begun as described. Reimplantation surgery was delayed until there were no clinical signs of infection (complete wound healing, no erythema, swelling, or edema) and the erythrocyte sedimentation rate (ESR) was less than 20 and the C-reactive protein (CRP) was less than 0.8.

During the second stage, we again débrided the wound and implanted a new cemented prosthesis with antibiotic-laden cement Copal® (polymethylmethacrylate with 1 g clindamycin and 1 g gentamicin; Biomet Merck GmbH, Ried b Kerzers, Switzerland) (Table 2). We did not obtain frozen histologic sections during the reimplantation surgery.

After the second surgery, patients remained in the hospital for 1 week. Intravenous prophylactic cefazolin was used for 5 postoperative days as we do in any nonseptic revision arthroplasty [11].

Patients were checked clinically, serologically, and radiographically at 2, 4, 8, 12, 16, 20, and 24 weeks after the second surgery. Thereafter, clinical, serologic (CRP, ESR), and radiographic checks were obtained every 6 months.

We defined eradication of infection as an absence of clinical, serologic, and radiographic signs of infection during the entire followup. For this purpose, the following 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 an ESR greater than 20 and/or a CRP greater than 0.8. Radiographic signs suggestive of infection were definite loosening, progressive migration of the implant, progressive radiolucent lines, and/or progressive osteolysis. Each radiograph was evaluated by two independent observers, one of us (JCA), the main treating surgeon, and one radiologist (different radiologists through the years) from the radiology departments of the involved hospitals (La Princesa and La Paz).

We evaluated all patients at last followup with the Harris hip score [10].

Results

Infection was eradicated in 13 of 13 patients with hip arthroplasties infected by highly resistant bacteria and who completed a two-stage protocol (Table 2). By contrast,

infection was eradicated in eight of 11 patients with highly resistant bacteria treated with only the first-stage operation (Table 1). Of the 24 hip arthroplasty infections caused by highly resistant bacteria, 21 of 24 were eradicated by oral antibiotics plus at least a first stage (all 12 hip arthroplasty infections caused by sensitive bacteria were eradicated) (Tables 1, 2).

The 10 patients infected by methicillin-resistant *Staphylococci* and treated with a two-stage protocol (Table 2) presented an eradicated infection. On the other side, six of nine patients treated with only the first surgery and with methicillin-resistant *Staphylococci* were cured (Table 1). Analyzing the whole subgroup of 19 infections caused by methicillin-resistant *Staphylococci*, 16 of these 19 were eradicated by oral antibiotics plus at least a first-stage operation.

Infection was eradicated in six of six hip arthroplasties infected by polymicrobial isolates and treated with a two-stage protocol (Table 2). By contrast, infection was eradicated in five of seven patients with polymicrobial isolates treated with only the first surgery (Table 1). When considering globally the 13 hip arthroplasty infections with polymicrobial isolates in the intraoperative cultures, 11 were eradicated by oral antibiotics plus at least a first-stage surgery.

Reimplantation was performed in 13 of the 24 patients with highly resistant bacteria; their Harris hip score at the end of followup averaged 89.5 (range, 74–98) (Table 2). The other 11 of 24 patients with highly resistant bacteria but without reimplantation had a mean Harris hip score of 53.5 (range, 32–63) (Table 1). Among the 19 patients infected by methicillin-resistant *Staphylococci*, 10 of 19 were successfully reimplanted (mean Harris hip score, 87.8) (Table 2) and nine of 19 remained in resection arthroplasty (mean Harris hip score, 52.1) (Table 1). Reimplantation was performed in six of 13 polymicrobial infections; their Harris hip score at the end of followup averaged 86.7 (range, 74–98) (Table 2). This score averaged 58.2 (range, 54–65) in the seven of 13 patients who remained in resection arthroplasty (Table 1).

Discussion

The presence of highly resistant bacteria is classically considered an increased challenge for the treatment of late arthroplasty infections; in fact, some authors judge these isolates as a contraindication to one-stage exchange [12, 14, 16, 21]. Published papers report relatively low eradication rates and worse functional outcomes when infection is caused by multiresistant organisms [1, 14–16, 20, 23, 27]. Polymicrobial infections have been less studied [14, 18, 20]. A very low risk of recurrence (ranging from 0% to

Table 3. Comparisons of our results with those published in the literature

Study	Highly resistant bacteria	Sensitive bacteria	Methicillin-resistant Staphylococci	Polymicrobial infection	Functional orthopaedic outcomes in highly resistant bacteria
Barberán et al. [1]			31% eradication (prosthesis retention)		
Jackson and Schmalzried [14]		Associated with successful direct exchange	Associated with failure in direct exchange	Associated with failure in direct exchange	
Kilgus et al. [15]		81% successful prosthesis retention/exchange	48% successful prosthesis retention/exchange		48% successful prosthesis retention/exchange
Kordelle et al. [16]			61% successful one-stage exchange		
Salgado et al. [20]			9.2 higher risk of treatment failure		
Soriano et al. [23]	Independent risk factor for treatment failure (prosthesis retention)				
Takahira et al. [25]					Japanese Orthopaedic Association hip score 73.2
Volin et al. [27]		95% eradication	89% eradication		
Walls et al. [28]					50% successful reimplantation
Cordero-Ampuero et al. (current study)	88% eradication	100% eradication	84% eradication	85% eradication	54% successful reimplantation, Harris hip score 89.5

6%) [6, 22] has been communicated with oral antibiotics plus two-stage surgery in chronic infections. Our purposes were to determine whether oral antibiotics would eradicate hip arthroplasty infections caused by highly resistant bacteria, methicillin-resistant Staphylococci, or polymicrobial isolates and to determine the functional outcomes of patients treated for these infections.

Our study is limited by relatively small numbers and dividing the whole series into smaller subgroups with specific bacterial infection results in low statistical power for comparative purposes. Therefore, we present only raw data without further analysis. Despite this, the infections were eradicated in at least 84% of these difficult-to-treat patients and compare favorably with the literature. Thus, we believe the small size of subgroups does not jeopardize the conclusions.

One study [22] reports infection by methicillin-resistant *S aureus* or *Enterococcus* sp as the only independent risk factor for treatment failure (Table 3), whereas we have been able to eradicate infection in 88% of patients with highly resistant bacteria (Tables 1, 2). On the other hand, most authors (Table 3) consider sensitive bacteria as a factor associated with successful direct exchange [14] with 95% eradication of infection after a conventional two-stage protocol [27] or 81% of success after débridement/exchange [15]; our protocol with oral antibiotics compares favorably because infection was eradicated in 100% of 12 patients with sensitive bacteria (Tables 1, 2).

Methicillin-resistant Staphylococcal infection is considered in the literature as the worst microbiologic situation (Table 3); the risk of treatment failure multiplies by 9.2 [20]; débridement with prosthesis retention eradicates infection in only 31% of chronic cases [1]; one-stage exchange eradicates infection in only 61% of patients [16] and is a factor for failure [14]; and a conventional two-stage protocol obtains eradication of infection in 48% to 89% of patients [15, 27]. Our protocol with oral antibiotics plus at least the first-stage surgery obtained results as good as those reported eradicating infection in 84% of patients (Tables 1, 2).

One study [14] reports polymicrobial infection as a factor associated with failure of direct exchange (Table 3); up to 85% of infections with polymicrobial isolates were eradicated in our series (Tables 1, 2).

Methicillin-resistant Staphylococci are not only a problem for eradication, but also for reimplantation with several studies reporting only 48% to 50% pain-free functional prostheses [15, 28] (Table 3). We obtained results only slightly better: 53% successfully reimplanted patients (Table 2). These patients who underwent reimplantation obtained a Harris hip score of 87.8, which is comparable to 73.2 (range, 24–96) in the Japanese Orthopaedic Association hip score after a conventional two-stage protocol [25] (Table 3).

Long cycles of combined oral antibiotics plus a two-stage surgical exchange appears a promising alternative for infections by highly resistant bacteria, methicillin-resistant Staphylococci, and polymicrobial infections; results obtained are at least as good as those published with conventional protocols based on short cycles of intravenous antibiotics.

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