

## ORIGINAL ARTICLE

# Antibiotic Therapy for 6 or 12 Weeks for Prosthetic Joint Infection

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## ABSTRACT

**BACKGROUND**

The management of prosthetic joint infection usually consists of a combination of surgery and antimicrobial therapy. The appropriate duration of antimicrobial therapy for this indication remains unclear.

**METHODS**

We performed an open-label, randomized, controlled, noninferiority trial to compare 6 weeks with 12 weeks of antibiotic therapy in patients with microbiologically confirmed prosthetic joint infection that had been managed with an appropriate surgical procedure. The primary outcome was persistent infection (defined as the persistence or recurrence of infection with the initial causative bacteria, with an antibiotic susceptibility pattern that was phenotypically indistinguishable from that at enrollment) within 2 years after the completion of antibiotic therapy. Noninferiority of 6 weeks of therapy to 12 weeks of therapy would be shown if the upper boundary of the 95% confidence interval for the absolute between-group difference (the value in the 6-week group minus the value in the 12-week group) in the percentage of patients with persistent infection within 2 years was not greater than 10 percentage points.

**RESULTS**

A total of 410 patients from 28 French centers were randomly assigned to receive antibiotic therapy for 6 weeks (205 patients) or for 12 weeks (205 patients). Six patients who withdrew consent were not included in the analysis. In the main analysis, 20 patients who died during follow-up were excluded, and missing outcomes for 6 patients who were lost to follow-up were considered to be persistent infection. Persistent infection occurred in 35 of 193 patients (18.1%) in the 6-week group and in 18 of 191 patients (9.4%) in the 12-week group (risk difference, 8.7 percentage points; 95% confidence interval, 1.8 to 15.6); thus, noninferiority was not shown. Noninferiority was also not shown in the per-protocol and sensitivity analyses. We found no evidence of between-group differences in the percentage of patients with treatment failure due to a new infection, probable treatment failure, or serious adverse events.

**CONCLUSIONS**

Among patients with microbiologically confirmed prosthetic joint infections that were managed with standard surgical procedures, antibiotic therapy for 6 weeks was not shown to be noninferior to antibiotic therapy for 12 weeks and resulted in a higher percentage of patients with unfavorable outcomes. (Funded by Programme Hospitalier de Recherche Clinique, French Ministry of Health; DATIPO ClinicalTrials.gov number, NCT01816009.)

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N Engl J Med 2021;384:1991-2001.

DOI: 10.1056/NEJMoa2020198

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PROSTHETIC JOINT INFECTIONS ARE ASSOCIATED with considerable morbidity. The treatment of this condition is challenging and costly.<sup>1</sup> The management of prosthetic joint infection involves both surgery and antimicrobial therapy. The classic surgical options include one-stage or two-stage implant exchange, resection arthroplasty (with or without arthrodesis), or débridement with implant retention. Treatment failure occurs in 11 to 35% of patients.<sup>1,2</sup>

The duration of antibiotic therapy in patients with prosthetic joint infection is primarily based on expert recommendations rather than evidence.<sup>3,4</sup> Patients usually receive long courses of antibiotic therapy, which can be up to 6 months for staphylococcal infections.<sup>1,5</sup> However, several studies suggest that shorter courses may be appropriate for most cases of prosthetic joint infection or osteomyelitis<sup>2,6-8</sup> and may be associated with reductions in the duration of hospital stay, incidence of adverse events, and emergence of microbiologic resistance.<sup>8</sup> We conducted the Duration of Antibiotic Treatment in Prosthetic Joint Infection (DATIPO) trial to compare the efficacy and safety of a short course of antibiotic treatment (6 weeks) with those of a longer course (12 weeks) in patients with prosthetic joint infections that had been caused by various pathogens and managed with appropriate surgical procedures.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The DATIPO trial was an investigator-initiated, multicenter, open-label, parallel-group, randomized, controlled, noninferiority trial. The trial protocol, available with the full text of this article at NEJM.org, was approved by the appropriate French ethics committee (Comité de Protection des Personnes de Tours). All the patients provided written informed consent. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### PATIENTS

Patients were eligible to participate in the trial if they were 18 years of age or older and had prosthetic joint infection (hip or knee) that had been managed with an appropriate surgical procedure (either one-stage or two-stage implant exchange or débridement with implant retention). Prosthetic joint infection was identified by the presence of at least one clinical symptom (pain, fever,

fistula, outflow around the scar, erythema, or swelling) and a microbiologically documented infection.

The criterion for microbiologic identification of the causative agent from surgical samples was a minimum of two bacterial cultures of different samples obtained during the same surgical procedure that yielded the same pathogen. If the pathogen was any skin bacteria (e.g., coagulase-negative staphylococcus or *Cutibacterium acnes*, corynebacterium, lactobacillus, or micrococcus), at least three cultures yielding the same pathogen were required for identification. We excluded patients who were receiving an effective antibiotic therapy that had been initiated more than 21 days before screening; had undergone more than one prosthesis replacement strategy for sepsis at the affected joint; had prosthetic joint infection that was caused by mycobacterium, actinomyces, a fungal pathogen, or brucella; had a life expectancy of less than 2 years; or were currently included in another randomized trial. Additional details of the eligibility criteria are provided in the Supplementary Appendix, available at NEJM.org, and the protocol.

### RANDOMIZATION AND INTERVENTIONS

An independent statistician prepared a computer-generated 1:1 randomization list using permutation blocks of variable sizes, stratified according to the initial surgical procedure (one-stage or two-stage implant exchange or débridement with implant retention), infected joint (hip vs. knee), and episode of infection (first vs. at least the second). Day 0 (baseline) was the first day of effective antibiotic treatment, defined as the administration of active antibiotics for the type or types of bacteria causing the infection, as determined with the use of phenotypic methods for antimicrobial susceptibility testing. The days that empirical antibiotic therapy was administered before the results of susceptibility testing were available were counted if the antibiotic therapy was determined retrospectively to be active.

Randomization was performed by trained staff members with the use of a secure, centralized, interactive, Web-based response system within the first 21 days after day 0. The patients were randomly assigned to receive 6 weeks or 12 weeks of antibiotic therapy as soon as possible after the surgical procedure. The patients and the clinicians who administered the interventions were aware of the trial-group assignments;

however, primary outcome events were validated by an adjudication committee of three independent specialists (one infectious diseases specialist, one orthopedic surgeon, and one bacteriologist) who were unaware of the trial-group assignments. The electronic case-record form was included in the secure, interactive, Web-based response system that was available at each trial center, as provided and managed by the staff of the Methodology, Biostatistics, and Data Management Unit of Tours University Hospital, who were not involved in patient recruitment.

The empirical treatment that was administered before the results of susceptibility testing were available, as well as the definitive treatment, was chosen by the treating physician according to guidelines of Société de Pathologie Infectieuse de Langue Française<sup>9</sup> or the Infectious Diseases Society of America,<sup>5</sup> without knowledge of whether the duration of antibiotic treatment was 6 weeks or 12 weeks. No maintenance or suppressive antibiotic therapy was administered after the scheduled end of treatment. The choice of surgical procedure was guided by recommendations made by Société Française de Chirurgie Orthopédique et Traumatologique or the American Academy of Orthopaedic Surgeons. Additional information on the methods of the trial is provided in the Supplementary Appendix.

#### ASSESSMENTS AND OUTCOMES

Results of clinical assessments and patient-reported outcome measures were recorded at enrollment and at 6, 12, 24, and 52 weeks after day 0 and at 104 weeks after the planned completion date of antibiotic therapy. Telephone follow-up took place at 9, 36, and 76 weeks after day 0.

All events of treatment failure that occurred within 2 years after the end of antibiotic therapy were recorded. There were three categories of treatment failure: persistent infection, defined as the persistence or recurrence of infection with the initial causative bacteria, with an antibiotic susceptibility pattern that was phenotypically indistinguishable from that at enrollment; new infection, defined as treatment failure with a new bacterium, with or without the presence of the initial causative bacteria; and probable failure, defined as the absence of bacteriologic documentation and the presence of certain macroscopic clinical signs of infection (e.g., fistula) and possibly histologic signs (e.g., presence of neutrophils). Detailed definitions of the categories

of treatment failure are provided in the Supplementary Appendix. All confirmed or suspected failure events that were identified during follow-up were subsequently verified by the independent adjudication committee. The members of the committee determined the category of each suspected treatment failure by consensus. The outcomes of patients with confirmed or suspected failure were reviewed separately by the three members of the adjudication committee. In case of disagreement, consensus among the committee members was obtained during a telephone meeting. The committee reviewed data for 112 patients. Immediate agreement among the three committee members was reached for 67 patients, and consensus was needed for 45.

The primary outcome was persistent infection within 2 years after the end of antibiotic therapy. Secondary outcomes were new infection, probable treatment failure, hospital length of stay (from day 0), functional outcome, and safety outcomes. The functional outcome was established with the use of the Merle d'Aubigné and Postel score for the hip<sup>10</sup> and the Knee Society score<sup>11</sup> (see the Supplementary Appendix). Safety outcomes included serious adverse events and laboratory values during treatment and follow-up.

#### STATISTICAL ANALYSIS

Assuming that persistent infection would occur in 15% of the patients in both trial groups, we estimated that a sample size of 410 patients (205 patients per group) would give the trial 80% power to show noninferiority of 6 weeks of antibiotic therapy to 12 weeks of therapy, with a noninferiority margin of 10 percentage points, at a one-sided alpha level of 0.025. The main analysis of the primary outcome was performed in the modified intention-to-treat population that included all the patients who had undergone randomization, except those who withdrew consent for participation or who died; missing outcomes for the patients who were lost to follow-up were considered to be persistent infections, as planned in the protocol. We determined that noninferiority of 6 weeks of therapy to 12 weeks of therapy would be shown if the upper boundary of the 95% confidence interval for the absolute between-group difference (the value in the 6-week group minus the value in the 12-week group) in the percentage of patients with persistent infection within 2 years was not greater than 10 percentage points. We performed two

sensitivity analyses of the primary outcome. In one, we adjusted the main analysis for stratification variables (initial surgical procedure, infected joint, and episode of infection), and in the other, data from the patients who were lost to follow-up or died were removed. Additional details are provided in the Statistical Analyses section in the Supplementary Appendix.

We performed a per-protocol analysis that excluded patients who were lost to follow-up, died, were enrolled in the trial but did not meet one eligibility criterion, received prolonged antibiotic therapy for an indication other than the prosthetic joint infection (which would interfere with the assessment of the primary outcome), or did not complete the assigned course of antibiotic therapy at the scheduled time ( $\pm 6$  days). We also performed a post hoc analysis in which only persistent infections that were diagnosed after 6 weeks of antibiotic therapy were counted, because the treatment received by the patients differed only after week 6. In the analyses of the binary outcomes, the results are presented as the point estimate for the between-group differences in the percentage of patients with treatment failure, and the two-sided 95% confidence interval of the difference was calculated with the use of the Wilson score method without continuity correction.<sup>12</sup>

In all primary outcome analyses, we estimated the differences in risk in unadjusted models and models adjusted for stratification factors. Post hoc analyses were performed with a linear model with robust standard errors to assess the consistency of the between-group differences in subgroups defined according to the stratification variables. In the analyses of safety outcomes, the results are presented as the number and percentage of patients with an adverse event according to trial group. Confidence intervals for secondary outcomes and subgroup analyses were not adjusted for multiple comparisons. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R version 4.0.2.

## RESULTS

### PATIENTS

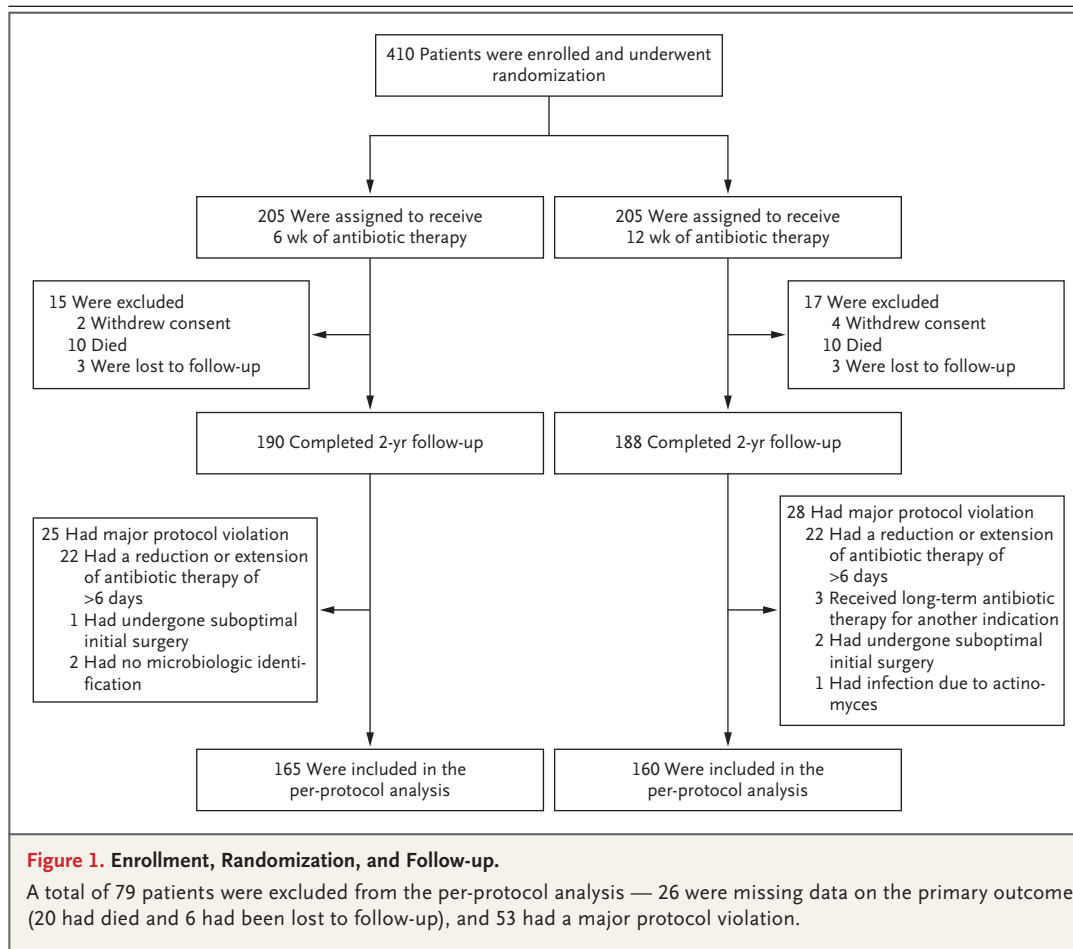
Between November 29, 2011, and January 22, 2015, a total of 410 patients underwent randomization across 28 trial sites in France, including 14 university hospital sites (median number of

patients per trial site, 7; interquartile range, 3 to 19) — 205 patients were assigned to the 6-week group and 205 to the 12-week group. Consent was withdrawn after randomization by 2 patients in the 6-week group and by 4 patients in the 12-week group, and these patients were not included in the analyses. Therefore, the trial involved 404 patients (203 in the 6-week group and 201 in the 12-week group) (Fig. 1). Baseline characteristics were balanced between the two trial groups (Table 1). The initial surgical management of prosthetic joint infection among the 404 patients was débridement with implant retention in 167 (41.3% [82 patients in the 6-week group and 85 in the 12-week group]), one-stage implant exchange in 150 (37.1% [77 patients in the 6-week group and 73 in the 12-week group]), and two-stage implant exchange in 87 (21.5% [44 patients in the 6-week group and 43 in the 12-week group]). Some between-group differences were noted with respect to the infecting pathogen at baseline; *Staphylococcus aureus* was identified in 38.0% of the patients in the 6-week group and in 30.0% of those in the 12-week group, and coagulase-negative staphylococcus was noted in 29.5% and 35.2%, respectively (Table 1).

### ANTIBIOTIC THERAPY AND ADHERENCE

The antibiotic treatments received by the patients are listed in Table 1, with additional details provided in Tables S1 through S3 in the Supplementary Appendix. Among the 380 patients who received at least one oral antibiotic agent, the most frequently used agents were rifampin (267 patients [70.3%]) and fluoroquinolone (260 [68.4%]); a total of 194 patients (51.1%) received both. Parenteral methicillin or cephalosporin was used during the initial intravenous phase of treatment in 136 of the 221 patients with prosthetic joint infection due to methicillin-susceptible staphylococci. The distribution of antibiotic agents was similar in both groups.

The median duration of intravenous administration was similar in the two groups (9 days; interquartile range, 5 to 15). The median total duration of antibiotic therapy was 42 days (interquartile range, 42 to 43) in the 6-week group and 84 days (interquartile range, 84 to 84) in the 12-week group. Overall, 16 of 192 patients (8.3%) in the 6-week group and 28 of 194 (14.4%) in the 12-week group reported an omission of at least one antibiotic dose.



**PRIMARY OUTCOME**

In the main modified intention-to-treat analysis, 20 patients who died during follow-up (all from causes that were considered by the adjudication committee members to be unrelated to prosthetic joint infection) were excluded, and missing outcomes for 6 patients who were lost to follow-up were considered to be persistent infection. Persistent infection occurred in 35 of 193 patients (18.1%) in the 6-week group and in 18 of 191 patients (9.4%) in the 12-week group (Table 2). The difference in the risk of persistent infection (6-week group vs. 12-week group) was 8.7 percentage points (95% confidence interval [CI], 1.8 to 15.6), which did not meet the criterion for noninferiority. The results were similar after adjustment for stratification variables (difference, 9.0 percentage points; 95% CI, 2.3 to 15.7). The results of the other modified intention-to-treat and per-protocol analyses were consistent with the results of the main analysis (Table 2).

Details on the microorganisms that caused persistent infections are provided in Table S4.

The results of the post hoc subgroup analyses consistently favored the 12-week group, and we did not find any inconsistency across the subgroups (Fig. 2). The results of the post hoc analysis of persistent infection according to the infected joint are provided in Tables S5 and S6.

**SECONDARY OUTCOMES**

Treatment failure due to a new infection (new bacteria with or without the initial bacteria) occurred in 13 of 190 patients (6.8%) in the 6-week group and in 20 of 188 patients (10.6%) in the 12-week group (difference, -3.8 percentage points; 95% CI, -9.7 to 2.0). Details on the microorganisms that caused new infections are provided in Table S7. Probable treatment failure occurred in 8 of 192 patients (4.2%) in the 6-week group and in 7 of 190 patients (3.7%) in the 12-week group (difference, 0.5 percentage points; 95%



**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline and Antibiotic Treatments during the Trial.\***

Characteristic	6-Wk Therapy (N=203)	12-Wk Therapy (N=201)
Age — yr†	68.4±11.7	69.5±10.7
Male sex — no./total no. (%)	143/203 (70.4)	130/201 (64.7)
History of prosthetic joint infection — no./total no. (%)‡	30/203 (14.8)	29/201 (14.4)
Baseline surgical procedure — no./total no. (%)		
Débridement with implant retention	82/203 (40.4)	85/201 (42.3)
One-stage prosthetic joint implant exchange	77/203 (37.9)	73/201 (36.3)
Two-stage prosthetic joint implant exchange	44/203 (21.7)	43/201 (21.4)
Affected joint — no./total no. (%)		
Hip	129/203 (63.5)	126/201 (62.7)
Knee	74/203 (36.5)	75/201 (37.3)
BMI§	29.9±5.8	29.9±6.2
Coexisting medical condition — no./total no. (%)		
Obesity§	91/192 (47.4)	78/186 (41.9)
ASA score ≥3¶	51/178 (28.7)	60/179 (33.5)
Clinical presentation — no./total no. (%)		
Infection after surgery	68/203 (33.5)	66/201 (32.8)
Acute blood-borne infection	46/203 (22.7)	37/201 (18.4)
Fever	83/196 (42.3)	62/196 (31.6)
Fistula	81/201 (40.3)	76/192 (39.6)
Median time between symptom onset and surgical procedure (IQR) — days	17 (5–85)	18 (5–110)
CRP level at diagnosis of infection — mg/liter**	108.4±99.0	113.2±100.8
Positive blood culture — no./total no. (%)	29/203 (14.3)	23/201 (11.4)
Mono-microorganism — no./total no. (%)	166/203 (81.8)	170/201 (84.6)
Multidrug resistance — no./total no. (%)††	17/196 (8.7)	19/192 (9.9)
Pathogens identified — no./total no. (%)‡‡		
<i>Staphylococcus aureus</i>	90/237 (38.0)	70/233 (30.0)
Coagulase-negative staphylococcus	70/237 (29.5)	82/233 (35.2)
Streptococcus species	32/237 (13.5)	26/233 (11.2)
Gram-negative organisms	21/237 (8.9)	26/233 (11.2)
Other pathogens§§	24/237 (10.1)	29/233 (12.4)
Antibiotic treatment		
Median duration of intravenous administration (IQR) — days¶¶	9 (5–15)	9 (5–15)
≥1 Oral antibiotic agent — no./total no. (%)	191/203 (94.1)	189/201 (94.0)
Rifampin	144/191 (75.4)	123/189 (65.1)
Quinolone	137/191 (71.7)	123/189 (65.1)
Clindamycin	35/191 (18.3)	52/189 (27.5)
Trimethoprim-sulfamethoxazole	22/191 (11.5)	34/189 (18.0)
Amoxicillin with or without clavulanic acid	19/191 (9.9)	21/189 (11.1)

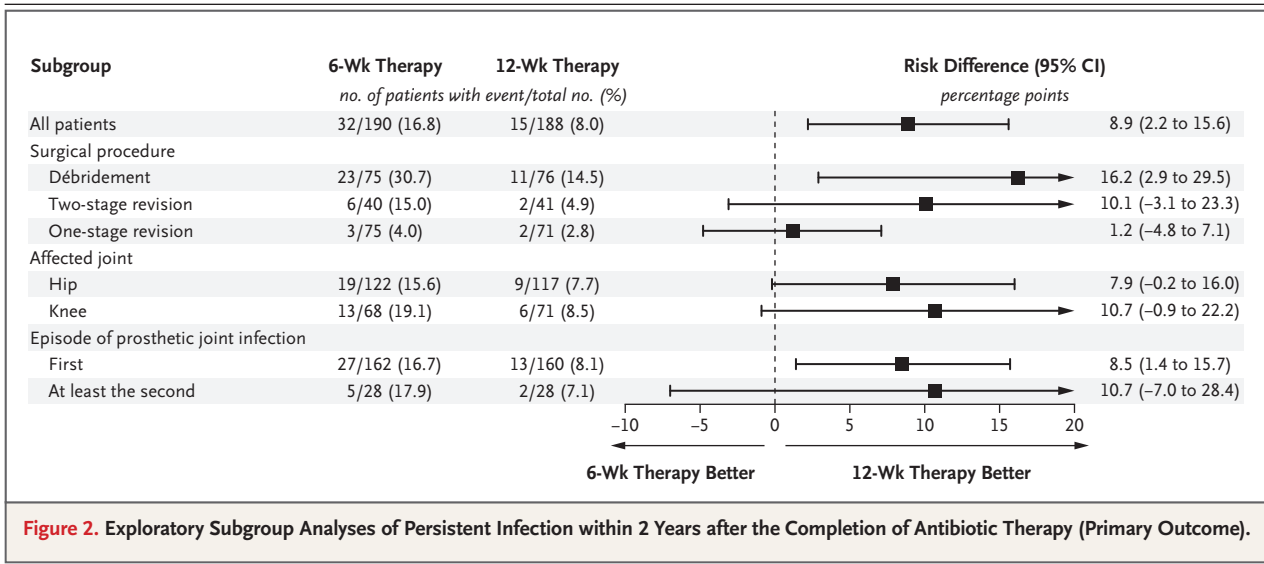
**Table 1. (Continued.)**

- \* Plus-minus values are means ±SD. Stratification variables at randomization included history of prosthetic joint infection, baseline surgical procedure, and affected joint. IQR denotes interquartile range.
- † Data on age were available for 203 patients in the 6-week group and 201 patients in the 12-week group.
- ‡ History of prosthetic joint infection was defined as having had at least one previous episode.
- § Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Obesity was defined by a BMI greater than 30. Data on BMI were available for 192 patients in the 6-week group and 186 patients in the 12-week group.
- ¶ An American Society of Anesthesiologists (ASA) score of 1 denotes a normal healthy patient, 2 a patient with mild systemic disease, 3 a patient with severe systemic disease, 4 a patient with severe systemic disease that is a constant threat to life, 5 a patient in a moribund state, and 6 a patient declared brain-dead.
- || Data on the time between symptom onset and surgical procedure were available for 198 patients in the 6-week group and 188 patients in the 12-week group. Among the patients who underwent débridement with implant retention, the median time between the onset of symptoms and surgical procedure was 5 days (IQR, 3 to 10) among 82 patients in the 6-week group and 5 days (IQR, 3 to 11) among 83 patients in the 12-week group.
- \*\* Data on C-reactive protein (CRP) level were available for 164 patients in the 6-week group and 147 patients in the 12-week group.
- †† Multidrug resistance was defined as an isolate that is not susceptible to at least one agent in at least three antimicrobial classes.
- ‡‡ A total of 68 patients had a polymicrobial infection (37 in the 6-week group and 31 in the 12-week group), so patients may have had more than one pathogen identified at baseline. A total of 237 pathogens were identified in the 6-week group, and 233 pathogens were identified in the 12-week group.
- §§ Other pathogens included anaerobic bacteria, enterococcus, and other gram-positive bacteria.
- ¶¶ Data on duration of intravenous route of antibiotic treatment were available for 192 patients in the 6-week group and 194 patients in the 12-week group.
- ||| Patients may have received more than one oral antibiotic agent.

**Table 2. Difference in Risk of Persistent Infection within 2 Years after the Completion of Antibiotic Therapy (Primary Outcome) in the Modified Intention-to-Treat and Per-Protocol Analyses.**

Analysis	6-Wk Therapy	12-Wk Therapy	Risk Difference	Adjusted Risk Difference*
	<i>no. of patients with event/total no. (%)</i>		<i>Percentage points (95% CI)</i>	
<b>Modified intention-to-treat</b>				
Main analysis in which missing outcomes for patients who were lost to follow-up were considered to be persistent infections and data from patients who died removed†	35/193 (18.1)	18/191 (9.4)	8.7 (1.8–15.6)	9.0 (2.3–15.7)
Sensitivity analyses in which data from patients who were lost to follow-up or died were removed†				
Analysis in which all persistent infections were counted	32/190 (16.8)	15/188 (8.0)	8.9 (2.2–15.6)	9.1 (2.6–15.5)
Post hoc analysis in which only persistent infections that were diagnosed after 6 weeks of antibiotic therapy were counted‡	29/187 (15.5)	13/186 (7.0)	8.5 (2.1–15.1)	8.8 (2.5–15.0)
<b>Per-protocol§</b>				
Analysis in which all persistent infections were counted	29/165 (17.6)	11/160 (6.9)	10.7 (3.6–17.9)	10.6 (3.7–17.5)
Post hoc analysis in which only persistent infections that were diagnosed after 6 weeks of antibiotic therapy were counted¶	27/163 (16.6)	11/160 (6.9)	9.7 (2.7–16.8)	9.7 (2.9–16.5)

- \* In a sensitivity analysis, the risk difference was adjusted for the stratification variables at randomization (initial surgical management strategy, infected joint, and episode of infection).
- † In each trial group, 3 patients were lost to follow-up and 10 patients died.
- ‡ Treatment failure occurred before 6 weeks in 3 patients in the 6-week group and in 2 patients in the 12-week group.
- § The per-protocol analyses included all patients who underwent randomization, except those who were lost to follow-up, died, were enrolled in the trial but did not meet one eligibility criterion, received prolonged antibiotic therapy for an indication other than the prosthetic joint infection, or did not complete the assigned course of antibiotic therapy at the scheduled time (±6 days). In the 6-week group, 38 patients were excluded from the per-protocol analysis, including 3 patients with treatment failure. In the 12-week group, 41 patients were excluded from the per-protocol analysis, including 4 patients with treatment failure.
- ¶ Treatment failure occurred before 6 weeks in 2 patients in the 6-week group and in no patient in the 12-week group.



**Figure 2.** Exploratory Subgroup Analyses of Persistent Infection within 2 Years after the Completion of Antibiotic Therapy (Primary Outcome).

CI, -3.8 to 4.8). The median duration of hospital stay was 14 days (interquartile range, 8 to 19) in the 6-week group and 13 days (interquartile range, 8 to 19) in the 12-week group. Changes in the Merle d'Aubigné and Postel hip score and the Knee Society score between baseline (day 0) and week 104 are reported in Figures S1 and S2.

#### SAFETY OUTCOMES

During follow-up, 220 serious adverse events were recorded in 149 patients (78 patients in the 6-week group and 71 patients in the 12-week group). The most common serious adverse events were events related to the operative site, musculoskeletal events not related to the operative site, cardiovascular events, neurologic events, and serious reactions to antibiotics (14 events, mainly allergy or acute kidney disease) (Table 3). During the 2-year follow-up, 20 patients died (10 each in the 6-week and 12-week groups). The causes of death, all of which were considered to be unrelated to prosthetic joint infection, are listed in Table 3.

Nonserious adverse events (mainly gastrointestinal disorders and mycosis) were more common in the 12-week group than in the 6-week group. At least one nonserious adverse event was recorded in 216 patients — 96 of 203 patients (47.3%) in the 6-week group and 120 of 201 patients (59.7%) in the 12-week group ( $P=0.01$ ) (Table S8). *Clostridioides difficile*-associated diarrhea occurred in 2 of 203 patients (1.0%) in the

6-week group (1 serious and 1 nonserious) and 1 of 201 patients (0.5%) in the 12-week group (nonserious). Tendinopathy was reported in 4 patients (2.0%) in the 6-week group and in 5 patients (2.5%) in the 12-week group (all nonserious).

#### DISCUSSION

Among patients with microbiologically confirmed prosthetic joint infection that had been previously managed with a standard surgical procedure, antibiotic therapy for 6 weeks was not shown to be noninferior to antibiotic therapy for 12 weeks and resulted in unfavorable outcomes in a higher percentage of patients. We did not find clinically significant between-group differences with respect to serious adverse events, *C. difficile* infection, duration of hospital stay, or functional outcomes.

The strengths of our trial included good retention during the 2-year follow-up and good adherence to the randomly assigned course of antibiotic therapy. The patients in this trial came from many distinct types of participating centers (e.g., university hospitals, private care centers, and general hospitals), which improves the generalizability of the findings. Furthermore, the percentage of cured patients is consistent with earlier published data.<sup>13,14</sup>

Our trial has some limitations. First, most of the treatment failures in the 6-week group occurred among the patients who had undergone



**Table 3. Serious Adverse Events According to Trial Group.**

Event	6-Wk Therapy	12-Wk Therapy
Patients with $\geq 1$ serious adverse event — no. of patients/total no. (%)	78/203 (38.4)	71/201 (35.3)*
Serious adverse events — no. of events/total no. (%)		
Operative site–related event	28/116 (24.1)	24/104 (23.1)
Antibiotic-related event†	8/116 (6.9)	6/104 (5.8)
Episode of <i>Clostridioides difficile</i> –associated diarrhea	1/116 (0.9)	0/104
Intravenous catheter complication	1/116 (0.9)	1/104 (1.0)
Neurologic event	6/116 (5.2)	8/104 (7.7)
Cardiovascular event‡	16/116 (13.8)	10/104 (9.6)
Respiratory event	3/116 (2.6)	1/104 (1.0)
Gastrointestinal event	1/116 (0.9)	4/104 (3.9)
Renal event	4/116 (3.4)	0/104
Diabetic event	2/116 (1.7)	2/104 (1.9)
Genitourinary event	3/116 (2.6)	5/104 (4.8)
Musculoskeletal event, not related to operative site§	15/116 (12.9)	24/104 (23.1)
Skin- or soft-tissue–related event, not related to operative site	4/116 (3.4)	2/104 (1.9)
Anemia	4/116 (3.4)	1/104 (1.0)
Frailty-related event¶	1/116 (0.9)	0/104
Other event	9/116 (7.8)	6/104 (5.8)
Death from any cause	10/116 (8.6)	10/104 (9.6)

\* P=0.52.

† The antibiotic-related events reported here met the definition of a serious adverse event. These events included pruritic rash, anorexia, acute kidney disease, and nausea (nonserious adverse events are reported in the Supplementary Appendix).

‡ Most cardiovascular events involved ischemic cardiomyopathy, infective endocarditis, and arrhythmic cardiomyopathy.

§ Most musculoskeletal events involved arthritis and back pain.

¶ A frailty-related event was considered to be a fall and readmission as a result of an inability to live at home.

|| The cause of death was unknown in 7 patients (4 in the 6-week group and 3 in the 12-week group), stroke in 3 patients in the 12-week group, cancer in 3 patients (2 in the 6-week group and 1 in the 12-week group), cardiogenic shock in 3 patients in the 6-week group, septic shock in 2 patients in the 12-week group, terminal liver cirrhosis in 1 patient in the 12-week group, and suicide in 1 patient in the 6-week group.

débridement with implant retention, although no heterogeneity was found in the subgroup analysis. Future studies should be directed at a single surgical procedure such as débridement with implant retention or prosthetic joint replacement but not both in the same trial. Second, this trial was open-label, but detection bias was minimized by adjudication of treatment failure by an independent committee whose members were unaware of the trial-group assignments. Because the choice of antibiotics was left to the treating physician, antibiotic treatment was not standardized, which led to the use of a wide variety of molecules, with different routes of administration. Prosthetic joint infection is typically man-

aged with surgery and a prolonged course of antibiotics with an intravenous route of administration (U.S. standard), which has limited evidence of superiority over an oral route of administration. In our trial, the duration of intravenous antibiotic therapy was not standardized and was shorter than the U.S. standard. Nevertheless, a recent randomized trial showed that oral antibiotic therapy was noninferior to intravenous therapy for bone and joint infection.<sup>15</sup> The patients included in our trial received intravenous therapy for a median duration of 9 days (similar in the two groups), and 63.5% of patients received at least 7 days of intravenous therapy. Moreover, 91.0% of the patients received anti-

biotics with good oral bioavailability, such as quinolone, rifampin, clindamycin, and trimethoprim–sulfamethoxazole, and 51.1% received the recommended combination of rifampin and quinolone. The frequency of use of rifampin is consistent with the proportion of patients with staphylococcal infections, current guidelines,<sup>5,15,16</sup> and the findings from a randomized trial that showed the superiority of rifampin use in patients with prosthetic device–related infections.<sup>1</sup> We noted no major differences in the distribution of antibiotics between the two groups, regardless of the microorganism identified. Some imbalance between the trial groups at baseline was noted for the causal pathogens *S. aureus* and coagulase-negative staphylococcus.

We found that the largest between-group difference in treatment failure in favor of 12 weeks of antibiotic therapy over 6 weeks was among the patients who had undergone débridement with implant retention, despite the fact that the surgical procedure involved the exchange of mobile parts, ample irrigation of the joint, and a short time between the onset of infection and surgery (median of 5 days in both groups). A

higher proportion of patients had nonserious adverse events in the 12-week group than in the 6-week group; the difference was mainly due to gastrointestinal side effects and mycosis. Such side effects, although unsurprising, can limit treatment and should be carefully monitored.

This trial showed that a shorter course of 6 weeks of antibiotic therapy did not meet the criterion for noninferiority to a longer course of 12 weeks in the treatment of prosthetic joint infection and resulted in unfavorable outcomes in a higher percentage of patients, most of whom had undergone débridement with implant retention. This difference in risk seemed to be less marked among the patients who had undergone one-stage or two-stage implant exchange, but this observation remains to be explored in a specific randomized trial.

Supported by a grant from Programme Hospitalier de Recherche Clinique, French Ministry of Health (PHRC PO10-06).

Dr. Druon reports receiving royalties from ASTON-SEM. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

#### APPENDIX

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#### REFERENCES

- Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. *JAMA* 1998;279:1537-41.
- Chaussade H, Uçkay I, Vuagnat A, et al. Antibiotic therapy duration for prosthetic joint infections treated by debridement and implant retention (DAIR): similar long-term remission for 6 weeks as compared to 12 weeks. *Int J Infect Dis* 2017; 63:37-42.
- Bernard L, Hoffmeyer P, Assal M, Vaudaux P, Schrenzel J, Lew D. Trends in the treatment of orthopaedic prosthetic

- infections. *J Antimicrob Chemother* 2004; 53:127-9.
4. Cobo J, Miguel LGS, Euba G, et al. Early prosthetic joint infection: outcomes with debridement and implant retention followed by antibiotic therapy. *Clin Microbiol Infect* 2011;17:1632-7.
  5. Osmon DR, Berbari EF, Berendt AR, et al. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2013;56:1-10.
  6. Farhad R, Roger P-M, Albert C, et al. Six weeks antibiotic therapy for all bone infections: results of a cohort study. *Eur J Clin Microbiol Infect Dis* 2010;29:217-22.
  7. Lora-Tamayo J, Euba G, Cobo J, et al. Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial. *Int J Antimicrob Agents* 2016;48: 310-6.
  8. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet* 2015;385:875-82.
  9. Société de Pathologie Infectieuse de Langue Française. Recommendations for clinical practice: osteo-articular infection therapy according to materials used (prosthesis, implants, osteosynthesis). *Med Mal Infect* 2009;39:745-74. (In French.)
  10. d'Aubigne RM, Postel M. Functional results of hip arthroplasty with acrylic prosthesis. *J Bone Joint Surg Am* 1954;36-A:451-75.
  11. Scuderi GR, Bourne RB, Noble PC, Benjamin JB, Lonner JH, Scott WN. The new Knee Society knee scoring system. *Clin Orthop Relat Res* 2012;470:3-19.
  12. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998;17:873-90.
  13. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med* 2004;351:1645-54.
  14. Löwik CAM, Parvizi J, Jutte PC, et al. Debridement, antibiotics, and implant retention is a viable treatment option for early periprosthetic joint infection presenting more than 4 weeks after index arthroplasty. *Clin Infect Dis* 2020;71:630-6.
  15. Li H-K, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med* 2019;380:425-36.
  16. Høiby N, Bjarnsholt T, Moser C, et al. ESCMID guideline for the diagnosis and treatment of biofilm infections 2014. *Clin Microbiol Infect* 2015;21:Suppl 1:S1-S25.

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