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Two weeks versus four weeks of antibiotic therapy after surgical drainage for native joint bacterial arthritis: a prospective, randomised, non-inferiority trial

Ergys Gjika,[1] Jean-Yves Beaulieu,[1] Konstantinos Vakalopoulos,[1] Morgan Gauthier,[1] Cindy Bouvet,[1] Amanda Gonzalez,[1] Vanessa Morello,[1] Christina Steiger,[1] Stefanie Hirsiger,[1] Benjamin Alan Lipsky,[2,3] Ilker Uçkay [2,4]

ABSTRACT

Objective The optimal duration of postsurgical antibiotic therapy for adult native joint bacterial arthritis remains unknown.

Methods We conducted a prospective, unblinded, randomised, non-inferiority study comparing either 2 or 4 weeks of antibiotic therapy after surgical drainage of native joint bacterial arthritis in adults. Excluded were implant-related infections, episodes without surgical lavage and episodes with a follow-up of less than 2 months.

Results We enrolled 154 cases: 77 in the 4-week arm and 77 in the 2-week arm. Median length of intravenous antibiotic treatment was 1 and 2 days, respectively. The median number of surgical lavages was 1 in both arms. Recurrence of infection was noted in three patients (2%): 1 in the 2-week arm (99% cure rate) and 2 in the 4-week arm (97% cure rate). There was no difference in the number of adverse events or sequelae between the study arms. Of the overall 154 arthritis cases, 99 concerned the hand and wrist, for which an additional subgroup analysis was performed. In this per-protocol subanalysis, we noted three recurrences: one in the 2-week arm (97 % cure); two in the 4-week arm (96 % cure) and witnessed sequelae in 50% in the 2-week arm versus 55% in the 4-week arm, of which five (13%) and six (13%) needed further interventions.

Conclusions After initial surgical lavage for septic arthritis, 2 weeks of targeted antibiotic therapy is not inferior to 4 weeks regarding cure rate, adverse events or sequelae and leads to a significantly shorter hospital stay, at least for hand and wrist arthritis.

Trial registration number NCT03615781.

Key messages

What is already known about this subject?
► The treatment of a septic arthritis requires a combination of at least one lavage/debridement and a long-lasting antibiotic administration.
► Usually, this initial antibiotic administration is parenteral during the first 2 weeks.

What does this study add?
► According to our randomised controlled trial, and at least for hand and wrist septic arthritis, total postsurgical antibiotic therapy can be limited to 2 weeks.
► Likewise, the initially systemic (and often empirical) parenteral antibiotic therapy can be switched to targeted oral medication after few days (1–2 days parenterally only).

How might this impact on clinical practice or future developments?
► Future patients with septic (hand and wrist) arthritis and a good evolution after surgical drainage might profit from significantly less antibiotics.
► This might limit potential adverse events, costs and complications of (parenteral) antibiotic therapy.

INTRODUCTION

Native joint bacterial arthritis is frequent and usually associated with considerable morbidity, need for hospitalisation and substantial financial costs.[1–3] While the need for surgical drainage of these infections has been well established,[4 5] the ideal duration and route of administration of antibiotic therapy remains unknown. For almost 40 years, the recommended total duration of postsurgical systemic antibiotic therapy has been 3–6 weeks, with most clinicians prescribing 4 weeks for adults.[3] Unfortunately, this recommendation is based on expert opinion and individual experience, rather than on research studies. Furthermore, clinicians often treat bacterial arthritis at all anatomic sites in the same way, with no distinction between small and large joints.

In the current era of critical shortages of effective antibiotics, antimicrobial stewardship principles suggest that a shorter treatment duration and early switch to targeted oral agents could decrease antibiotic-related adverse events,[1 3 6] costs and possibly emergence of antimicrobial resistance. Retrospective studies,[2] reviews[7] and our own retrospective data[3] suggest that just 2 weeks of targeted systemic antibiotic therapy after surgical drainage may be sufficient, especially for hand joints. In an attempt to provide an evidence base for antibiotic treatment for adult native joint arthritis,[5] we undertook

a prospective, randomised trial to determine if a postsurgical antibiotic course of 2 weeks, together with an early switch to oral targeted systemic antibiotics,[3–5] is non-inferior in inducing remission to the currently recommended 4 weeks.[3]

METHODS
We performed a single-centre (at Geneva University Hospitals), prospective, unmatched, unblinded, randomised, interventional study from 1 March 2015 to 10 March 2018, with database closure on 18 May 2018. Inclusion criteria among patients diagnosed with native joint bacterial arthritis were: age ≥18 years; underwent at least one articular lavage (by arthrotomy or arthroscopy; with or without synovectomy); and treatment with systemic antibiotic therapy. Of note, we allowed the inclusion of episodes with previous antibiotic therapy during at maximum 48 hours prior to the first lavage and episodes with concomitant crystalline disease. Patients with an abscess in surrounding soft tissue were equally allowed to participate, but only if the abscess could be excised or drained in toto. Exclusion criteria were: recurrent bacterial arthritis; non-bacterial arthritis; history of allergies to multiple antibiotics; receiving long-term antibiotic prophylaxis because of immune-suppression; presence of left-side endocarditis; incomplete joint lavage or >4 surgical lavages; plan for repetitive arthrocentesis as a therapeutic approach[5]; concomitant spondylodiscitis or osteomyelitis;[8] plan for arthrodesis or amputation; foot arthritis in a patient with diabetes mellitus[9]; presence of necrotiing fasciitis; intravertebral arthritis[8]; patient with or planned for a Girdlestone procedure[10 11]; patient who underwent a bone marrow transplantation; undergoing active oncological chemotherapy; or presence of foreign material in close vicinity to the infected joint. We also excluded infections for which published literature recommends either an unusually long, or a short duration of antibiotic therapy, for example, infection with mycobacteria,[12] actinomycetes, gonococci, meningococci, fungi, brucellosis, mycoplasma or nocardia.[13]

We defined bacterial arthritis as the presence of: clinical findings of joint infection (wound discharge, redness, warmth and new pain); and, at least two positive microbiological culture or Gram-strained smear[14] or PCR of joint, pus or synovial tissues. Elevated serum inflammatory markers, positive histology of synovial tissue, elevated intra-articular white cell counts[11] or abnormal radiological images were not required. We defined immune-suppression as the patient having undergone an organ transplantation, taking chronic corticosteroid medication equivalent to ≥15 mg prednisolone daily, requiring renal dialysis, having diabetes mellitus, active cancer, liver cirrhosis of at least CHILD class C, severe chronic alcoholism, untreated HIV disease and agranulocytosis.

We defined sequelae as persisting non-infectious handicaps after adequate physiotherapy, ergotherapy (sensory-integrative therapy) and analgesia that was not pre-existent and attributed to the recent infection. We asked all patients to indicate their pain on a Likert scale, with responses ranging from 0 (least) to 10 (greatest).

Study conduct
We assigned eligible hospitalised patients, following a specified randomisation procedure (1:1, by computer-generated random numbers) to therapy with systemic antibiotic agents for either 2 weeks (±3 days) or 4 weeks (±3 days). Treating surgeons, in consultation with an infectious diseases expert,[15] selected the agents in the antibiotic regimen from a list of options we provided them. Initial therapy was empirical and was started after collecting intraoperative samples for culture. Treating clinicians could amend the antibiotic regimen (agent(s) or route of administration) according to the microbiological results and clinical evolution of infection. During the first days of therapy, the most frequently administered (empiric) antibiotic regimens were of the following given by intravenous route: co-amoxiclav; cefazolin; cefuroxime; cefepime; ertapenem; imipenem; piperacillin/tazobactam; vancomycin; or daptomycin. Definitive therapy was based on of culture and sensitivity results, with a targeted oral antibiotic regimen selected from among the following agents: ciprofloxacin; levofloxacin; clindamycin; co-trimoxazole; doxycycline; linezolid; rifampicin; or fusidic acid. The timing for switching to oral therapy was at the discretion of the treating clinicians and depended on the global evolution of the patient and the infection. The treating surgeons decided on: the arthrotomy or arthroscopy techniques; the timing of any emergency intervention[4]; whether to do synovectomy; and when to repeat joint lavages. We avoided using intra-synovial antibiotic infusions or irrigations with local antiseptics. Twelve months after enrollment of the last patient, we searched the hospital databases to determine if any of the enrolled patients had been seen in outpatient clinics for problems related to the operative site. Online supplementary appendix S1 shows the original protocol (in French).

Patient and public involvement
We involved all study participants on hospitalisation for surgical drainage of septic arthritis by asking them directly. We informed them orally in their native language and provided French-language study documents. We moreover accompanied all patients until the test-of-cure visit, and beyond, if necessary. During accompaniment, the patients were always free to ask for additional information and clinical results. This was also the case for the study team that was free to ask to the patients. No information was withheld. Although not a formal part of the study protocol, we think that the patients will help and promote the study idea in their respective communities. On a larger scale, the study team shall inform the public, that is, with interviews in the local press. In contrast, patients and public had not been involved in the design of the study. The study team had developed this prospective-randomised study according to their clinical experience, academic interest, retrospective own data and on a scientific literature research. According to national ethical requirements, we will not provide a scientific copy of the final publication to every study participant, unless he or she wished to receive it specifically.

Sample size considerations, outcome parameters and statistical analyses
The primary outcome for this study was the rates of remission of infection. Remission was defined as the complete absence of clinical, laboratory or radiological findings after a minimal follow-up of 2 months after treatment. Secondary endpoints were: remission in the subgroup of hand and wrist septic arthritis; the occurrence of adverse events related to antibiotic therapy; and the development of non-infectious sequelae of bacterial arthritis. Using a non-inferiority design, with an alpha level of 5%, a power of 80%, expected remission rates of 96% in both study arms,[2 3] we calculated that we needed 48 patients in each group to establish a non-inferiority margin of 10%. We planned interim analyses beginning after enrolment of the first 40 cases. Our intention-to-treat (ITT) population was composed of all randomised patients, while the per-protocol (PP) population
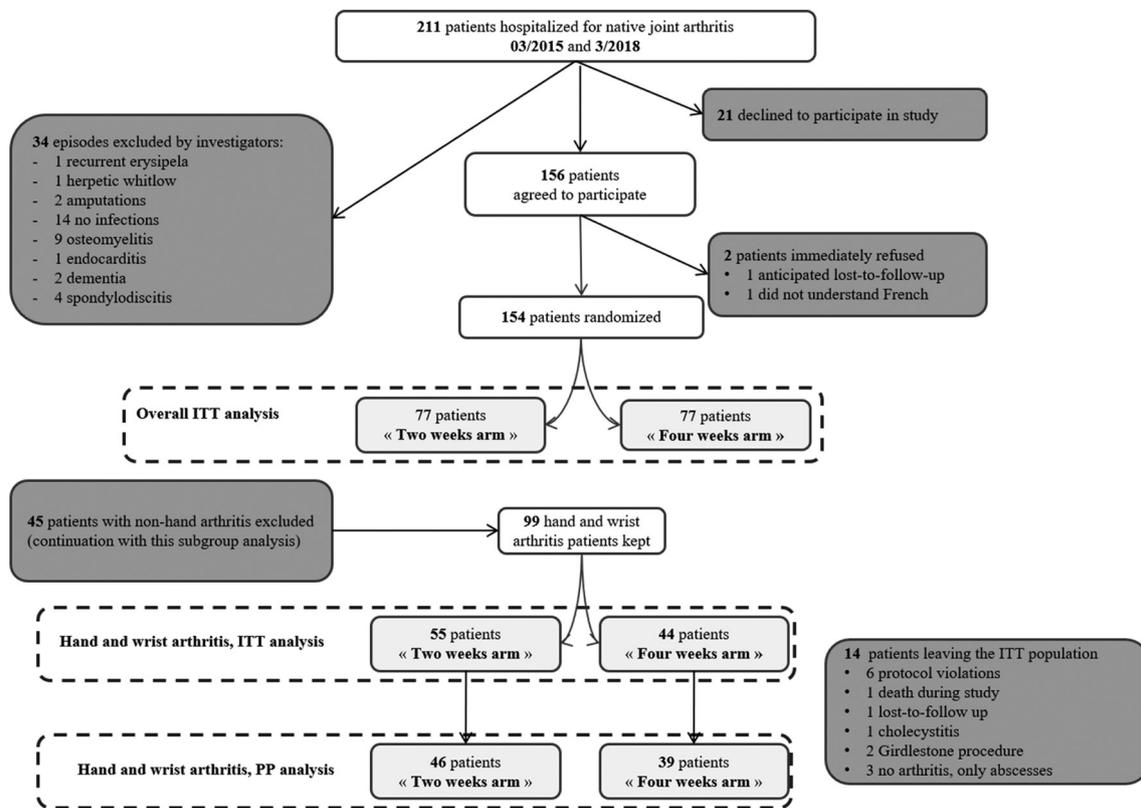
Figure 1 Study flow chart of patients. ITT, intention-to-treat.

included patients who completed the study without any major protocol deviation. Due to the predominance of hand arthritis cases, we performed a subgroup analysis for hand arthritis only, which included the fingers, hand and wrists. We compared treatment groups using the Pearson χ^2 or the Wilcoxon rank-sum test. Due to the small number of failures, we elected not to perform multivariate analyses. We used STATA software (V.9.0) and considered p values (two tailed) ≤0.05 as significant.

RESULTS

Patients (entire study population; ITT analysis)

Among 211 native joint arthritis cases, 154 (analysis in 154 different patients) were eligible for inclusion for the ITT analyses. Overall, we excluded 34 of 211 patients and episodes due to various exclusion criteria, while the number of patients refusing to participate in the study was only 21 (21/211; 10%) (see figure 1).

Clinically, these refusing patients and those excluded by investigators were a very heterogeneous group without clear anamnestic patterns or objectively common comorbidities (*data not shown*). Among the study patients, 77 were randomised to the 4-week treatment arm and 77 to the 2-week treatment arm. Demographic characteristics were similar for the patients in the two groups (see table 1, left part).

The actual median duration of antibiotic therapy in the 2-week arm was 14 days, and in the 4-week arm it was 28 days. Overall, 59 patients were women (38%), and the median age of all patients was 51 years. While many patients lacked comorbidities, 15 (10%) were chronically immune-compromised (due to diabetes mellitus (n=13), advanced cirrhosis (n=2), active cancer (n=3), solid organ transplant (n=1), steroid medication (n=2) or a combination of immune-suppressive conditions. In addition, six patients had an active psychiatric comorbidity and nine illicitly used drugs. The median American Society of

Anesthesiologists' Score[16] for all enrolled patients was 2 points (IQR: 2–2 points).

Infections

The origin of infection varied greatly, including: surgical site infections[17] (n=12); cat bites (n=16); cat scratches (n=2); dog bites (n=14); rat bite (n=1); human bites (n=3); infection of gouty tophus (n=1); intravenous drug abuse (n=9); direct trauma (n=48)[18]; and Baker cyst rupture (n=1). In 47 cases, the origin was unknown. Bacteraemia was documented in six episodes (4%). There were no apparent seasonality[19] or outbreak situations. On admission, the overall median serum C reactive protein level was 30 mg/L and the median pain score 5 points (out of 10). The joints infected were: finger (n=95); wrist (n=3); knee (n=14); shoulder (n=7); ankle (n=3); elbow (n=1); hip (n=1); metatarsal (n=28); combination of wrist and ankle (n=1); and another combination of ankle and elbow (n=1). In 16 of the 154 episodes (10%), the infected joints had a prior known pathology: osteoarthritis (arthrosis) (n=6), cyst (n=2), rheumatological inflammation (n=4), psoriasis (n=1), meniscal lesion (n=1), recurrent subluxation (n=1) and chronic rotator calf injury (n=1). The infected joints also harboured intraarticular crystals in six cases (4%)[11]: calcium pyrophosphate in four, calcium apatite in one and urate in one. The median preoperative intracellular leucocyte count was 41 200 cells/mm^3, and the percentage of polynuclear leukocytes was 95%.[11] Culture results of intraoperative specimens revealed 31 different microbiological patterns. *Staphylococcus aureus* was the most commonly isolated pathogen, found in 48 episodes (31%); none of the strains was a methicillin-resistant strain. Streptococci were involved in 22 cases,[20] Gram-negative pathogens in 35 episodes (including 19 due to *Pasteurella* spp,[18] and skin commensals (coagulase-negative staphylococci, micrococci, corynebacteria or cutibacteria) in seven cases and the rest consisted of other

Table 1 Characteristics of patients treated with 2 weeks versus 4 weeks of systemic antibiotic therapy after surgical drainage of native joint septic arthritis (all arthritis cases on the left vs hand and wrist arthritis only on the right; both populations are intention-to-treat)

All arthritis cases n=154	Duration of antibiotic therapy			Only hand arthritis cases n=99	Duration of antibiotic therapy		
	4 weeks n=77	2 weeks n=77	P value *		4 weeks n=44	2 weeks n=55	P value *
Female sex	31 (40%)	28 (36%)	0.62	Female sex	17 (35%)	20 (42%)	0.82
Median age	52 years	48 years	0.23	Median age	50 years	45 years	0.49
Immune-suppression†	7 (9%)	8 (10%)	0.79	Immune suppression†	4 (9%)	5 (9%)	1.0
Bacteraemia	2 (3%)	4 (6%)	0.37	Bacteraemia	0 (0%)	0 (0%)	–
Median ASA Score[16]	2 (IQR: 1–2)	2 (IQR: 1–2)	0.13	Median ASA Score[16]	2 (IQR: 1–2)	2 (IQR: 1–2)	0.05
Pain score on admission (median)	five points	five points	0.33	Pain score on admission (median)	five points	five points	0.31
Antibiotics before first surgery	21 (27%)	21 (27%)	0.95	Antibiotics before first surgery	12 (28%)	15 (29%)	0.92
Duration of presurgical antibiotics (median)	0 day	0 day	0.90	Duration of presurgical antibiotics (median)	0 day	0 day	0.49
Staphylococcus aureus	23 (30%)	25 (32%)	0.73	*Staphylococcus aureus* infection	11 (25%)	18 (33%)	0.40
Streptococci	19 (25%)	12 (16%)	0.16	Streptococci	12 (27%)	8 (16%)	0.12
Gram negative(s)	19 (25%)	16 (21%)	0.56	Gram-negative pathogens	15 (34%)	14 (25%)	0.35
Number of surgical lavages (median)	1 (IQR: 1–3)	1 (IQR: 1–3)	0.13	Number of surgical lavages (median)	1 (IQR: 1–3)	1 (IQR: 1–3)	0.11
Duration of intravenous therapy (median)	2 days	1 day	0.01	Duration of intravenous therapy (median)	2 days	1 day	0.02
Complete microbiological remission	75 (97%)	76 (99%)	0.56	Complete microbiological remission	42 (95%)	53 (96%)	0.82
Duration of sick leave (median)	36 days	28 days	0.31	Duration of sick leave (median)	36 days	27 days	0.29
Number of outpatient attendances (median)	6 controls	7 controls	0.05	Number of outpatient attendances (median)	7 controls	7 controls	0.70
Length of hospital stay (median)	6 days	4 days	0.01	Length of hospital stay (median)	4 days	3 days	0.01
Mechanical or neurological sequelae	33 (54%)	27 (47%)	0.47	Mechanical or neurological sequelae	21 (53%)	23 (48%)	0.67
Antibiotic-related adverse events	5 (6%)	2 (3%)	0.25	Antibiotic-related adverse events	2 (5%)	2 (4%)	0.82

*Pearson χ² test or Wilcoxon rank-sum tests, as appropriate.

†Immune-suppression=diabetes mellitus, active cancer, cirrhosis CHILD C, organ transplant and steroid medication equivalent to ≥15 mg prednisolone daily.

ASA, American Society of Anesthesiologists.

pathogens. Twenty-one infections were bimicrobial, and there were no polymicrobial cases.

Treatment

In all patients, we performed surgical drainage of the affected joint and administered systemic antibiotic therapy. Surgery was performed by open arthrotomy in all but seven cases (5%), which were drained by arthroscopy. table 1 Enrolled patients were treated with 13 different initial parenteral regimens and 11 different oral follow-on regimens. The most frequently administered parenteral antibiotics were co-amoxiclav (n=71), ceftriaxone (n=3) and vancomycin (n=4). Overall, we administered parenteral β-lactam antibiotics in 107 (69%) cases. In three episodes, the entire antibiotic course was given intravenously, while in 32 cases treatment was with an oral agent from the start. The oral antibiotics prescribed were co-amoxiclav (74), quinolones (26), clindamycin (19), doxycycline (2), co-trimoxazole (3) or a combination of above. The table 2 resumes the antibiotic classes and administration forms, stratified on the study arm and key pathogen groups.

Overall, these allocations were balanced between both arms. We did not prescribe corticosteroids for the treatment of arthritis in any patient, but some were treated for pain with paracetamol, ibuprofen and opioids (in limited cases). The median number of surgical lavages was 1 in both groups. The overall median length of hospital stay was 4 days (IQR: 3-8 days), and it was longer in the short duration treatment arm (6 days vs 4 days; see table 1).

Remission

Of the 154 episodes in the ITT population, 148 (96%) were microbiologically cured after an active median follow-up of 0.5 years (IQR: 0.3–1.1 years) and a passive median follow-up of 2.2 years (IQR: 1.6–2.8 years). Among the six patients who ultimately failed on therapy, three patients (one in the 4-week arm, and two in the 2-week arm) finally revealed new pathogens completely different from the initial agents. We interpreted these episodes as novel episodes in terms of surgical site infections.[17] Hence, the number of true microbiology-based recurrences was three (3/154; 2%) and these occurred after a median delay of 32 days after the end of treatment of the previous episode. There was no difference in the rate of microbiological recurrences between the two treatment groups (see table 1); they occurred in 2 of 77 in the 4-week arm compared with 1 of 77 in the 6-week arm (p=0.58). The three cases with microbiological recurrences involved one case caused by *S. pyogenes*, and two episodes caused by *S. aureus*. Formally, the 90% CIs (two tailed) regarding clinical remission were within the interval (between 0 and the 10% margin) and did not include the margin

Table 2 Main pathogen groups linked to corresponding selected antimicrobial substances and classes (overall ITT analysis)

n=154 Pathogen group	6 weeks Parenteral antibiotics	Oral antibiotics	4 weeks Parenteral antibiotics	Oral antibiotics
Staphylococcus aureus, n=48	Co-amoxiclav (n=14) Clindamycin (n=1) Cefuroxim (n=10)	*Co-amoxiclav (n=17)* *Clindamycin (n=5)* *Levofloxacin (n=3)*	Co-amoxiclav (n=13) Cefazolin (n=2) Cefuroxim (n=7)	*Co-amoxiclav (n=17)* *Clindamycin (n=5)* *Levofloxacin (n=3)*
Streptococci, n=31	Co-amoxiclav (n=11) Penicillin (n=1) Cefuroxim (n=6)	*Co-amoxiclav (n=9)* *Clindamycin (n=3)* *Levofloxacin (n=3)*	Co-amoxiclav (n=7) Cephalosporins (n=3) Cefuroxim (n=4)	*Co-amoxiclav (n=5)* *Clindamycin (n=3)* *Levofloxacin (n=1)*
Gram negatives, n=35	Co-amoxiclav (n=12) Cephalosporins (n=6)	*Quinolones (n=9)* *Co-amoxiclav (n=10)*	Co-amoxiclav (n=8) Cephalosporins (n=8)	*Quinolones (n=3)* *Co-amoxiclav (n=12)*
Pasteurella spp, n=17	Co-amoxiclav (n=6) Cefuroxim (n=2)	*Co-amoxiclav (n=7)* *Levofloxacin (n=1)*	Co-amoxiclav (n=6) Cefuroxim (n=2)	*Co-amoxiclav (n=8)* *Levofloxacin (n=1)*

Of note, the parenteral antibiotics are mostly empirical.

*Infections may be polymicrobial and thus the main antibiotics might be larger in spectrum than the main pathogens require.

(−0.7 percentage points (90% CIs −8.5% to +7.0%)). Idem for microbiological remissions (4.3 percentage points (90% CI −1.1% to +9.8%)).

Adverse events and complications

Overall, only eight patients (5%) reported adverse events that were attributed to antibiotic therapy: superficial fungal infection (n=3), allergic rash to amoxicillin or levofloxacin (n=3), severe diarrhoea due to co-amoxiclav (n=1) and dizziness due to clindamycin (n=1). As a consequence of adverse events, we changed the antibiotic or added fluconazole and probiotics in three cases. No patient developed *Clostridium difficile*-associated colitis and none left the study because of an adverse event. One patient developed a urinary tract infection, which we treated with another antibiotic agent inactive against the pathogen causing her bacterial arthritis. The major non-antibiotic-related complications were: haematoma needing revision (n=3), hospital-acquired fall (n=2), new giant cell tumour (n=1), Raynauds' phenomenon (n=1), stroke (n=1), scaphoid necrosis (n=1), influenza (n=1) and basilica vein thrombosis (n=1). The number of complications was similar in patients in the two study arms. Formally, the 90% CI (two tailed) regarding adverse events also excluded the margin (3.8% percentage points (90% CI −1.7% to +9.5%)).

Sequelae

Overall, in 60 episodes (39%), there were mechanical or neurological non-infectious sequelae, including: stiffness (n=16), flexion incapacity and adhesions (n=13; flexion contraction ranging between 5° and 30°), persistent pain (n=12), trigger zone (n=2), persistent dry wound (n=2), scaphoid necrosis (n=1), hypoesthesia (n=1) and Raynaud's phenomenon (n=1). Many of these sequelae did not require any specific therapy, but a minority were severe enough to require corrective actions: tenolysis (n=4), surgical closure of persistent wound (n=1), immunological treatment (n=1), psychiatric follow-up (n=1), persistent vacuum-assisted suctions (n=1), prolonged sensory-integrative therapy (n=1) or prolonged physiotherapy (n=4). Overall, 46 (of the 154) patients had follow-up radiographs and 20 (43%) of these had evidence of 'secondary osteoarthritis' after a median delay of 2 months. The median duration of sick leave (officially granted by the treating physicians or surgeons to the affected patient) was 33 days. Of note, the 90% CI regarding the outcome substantial sequelae failed to fulfil the statistical non-inferiority requirements (6.7% percentage points (90% CI −8.6% to +22.1%)).

Hand and wrist arthritis (ITT analysis)

Among the 154 enrolled cases, 99 (64%) involved the hands or the wrist. Therefore, we decided to perform a subgroup analysis for these patients, of whom 44 were randomised to the 4-week arm and 55 to the 2-week arm. The actual median duration of postlavage antibiotic therapy was 14 days for the 2-week arm and 28 days for the 4-week arm. The interphalangeal joints affected by bacterial arthritis were: thumb (n=15), index finger (n=29), middle finger (n=24), ring finger (n=7) and little finger (n=4). Metacarpal regions involved were: thumb (n=5), index finger (n=9), middle finger (n=1), ring finger (n=0) and little finger (n=1). In four cases, the wrist was involved. This subgroup's patient characteristics (see table 1, right part) and outcomes were similar to those in the overall arthritis population. The most frequent oral antibiotic agents used for hand cases were co-amoxiclav, levofloxacin or clindamycin. The median number of surgical lavages was one. Microbiological recurrence was documented in three patients (4%): one in the 2=week arm and two in the 4-week arm (p=0.44). The proportion of sequelae and adverse events were equal between both arms in the hand arthritis group. However, the duration of intravenous therapy and the total length of hospital stay were shorter in the 2-week arm (see table 1).

PP analysis

Among the 99 episodes composing the ITT population of hand arthritis cases, we removed 17 (17/99; 17%), when constituting the PP population (see figure 1) because of unintended protocol violations or being lost to follow-up. There were no significant differences between patients in the two study arms in the PP population (see table 3 and figure 2).

The median age was 48 years; 32 (38%) were women, and 9 were immune-suppressed, and the main cause of infection was bites (20 episodes). The predominant pathogens in these infections were *S. aureus* and *Pasteurella multocida* (20 and 12 episodes, respectively). Overall, we treated 39 patients with a 2-week course of antibiotics and 46 with a 4-week course, of which a median of 1 and 2 days was administered intravenously. In the two study arms, the median number of surgical lavages was 1 and the adverse events related to antibiotics were similar. We noted recurrence of bacterial arthritis after stopping antibiotic treatment in the same three patients as in the ITT population (4%): 1 in the 2-week arm (98% remission) and 2o in the 4-week arm (95%; p=0.46). Various sequelae occurred in 50% of the subjects in the 2-week treatment arm compared with 55% in the 4-week treatment arm. Only five (13%) and

Table 3 Characteristics of patients treated with 2 versus 4 weeks of systemic antibiotic therapy after surgical drainage of native joint bacterial arthritis of the hand and the wrist (per-protocol population only)

Hand arthritis (per-protocol analysis) n=85	4 weeks n=39	2 weeks n=46	P value*
Female sex	14 (36%)	18 (39%)	0.76
Median age	52 years	46 years	0.33
Immune-suppression†	4 (10%)	5 (11%)	0.93
Median ASA Score[16]	2 (IQR: 1–2)	2 (IQR: 1–2)	0.05
Serum C reactive protein at admission (median)	15 mg/L	8 mg/L	0.45
Pain score on admission (median)	4 points	5 points	0.15
Antibiotics before first surgery	10 (26%)	14 (30%)	0.63
Delay onset of infection surgery (median)	2 days (IQR: 1–3)	1 day (IQR: 0–2)	0.10
Staphylococcus aureus infection	10 (26%)	16 (35%)	0.36
Streptococci	9 (23%)	7 (15%)	0.36
Gram-negative pathogens	12 (31%)	13 (28%)	0.80
Number of surgical lavages (median)	1 (IQR: 1–1)	1 (IQR: 1–1)	0.23
Treatment with β-lactam antibiotics	28 (72%)	25 (76%)	0.65
Duration of intravenous therapy (median)	2 days	1 day	0.01
Complete microbiological remission	37 (95%)	45 (98%)	0.46
Duration of sick leave (median)	36 days	27 days	0.33
Number of outpatient attendances (median)	7 controls	8 controls	0.77
Length of hospital stay (median)	4 days	3 days	0.01
Mechanical or neurologic sequelae	21 (55%)	23 (50%)	0.52
Antibiotic-related adverse events	2 (5%)	2 (4%)	0.87

*Pearson χ² test or Wilcoxon rank-sum tests, as appropriate.

†Immune-suppression=diabetes mellitus, active cancer, cirrhosis CHILD C, organ transplant and chronic steroid medication.

six (13%) sequelae, respectively, required further and specific interventions (p=0.43). Statistically, our results equally fulfilled the non-inferiority requirements regarding the 10% margin for clinical (two tailed −0.8% percentage points (90% CI −8.5% to +7.0%)) and microbiological remission (4.3% (90% CI −1.1% to +9.8%)), as well as adverse events (0.8% (90%CI −7.0% to +8.5%)); but not regarding substantial sequelae (5.2% (90%CI −13.1% to +23.4%)).

DISCUSSION

In this randomised trial with 154 adult cases of native joint bacterial arthritis, we found no significant difference in rates of clinical remission, adverse events or sequelae in patients treated with 2, compared with 4, weeks of antibiotic therapy after surgical drainage. Moreover, we found no differences in these two arms in analyses of both the ITT and the PP populations, as well as the subgroup of hand arthritis compared with cases in other anatomical sites in group comparisons. Statistically speaking, our study population fulfilled the formal non-inferiority requirements regarding the outcome 'remission' (primary outcome). This was valid for both the ITT and PP analyses, the whole arthritis population and equally separated for the hand arthritis group only. Regarding the secondary outcomes 'adverse events' and 'sequelae', these statistical requirements were only fulfilled for adverse events in all analyses, whereas for substantial sequelae, for example, those with the need for further interventions, our sample size was formally too small. The only exceptions to the similarity in the two treatment arms is that patients in the 4-week arm had a significantly longer length of hospital stay and received a longer duration of parenteral antimicrobial therapy. Only 10% of potentially eligible patients refused to participate in the study, which equally good participation. Moreover, clinically and anamnestically, the refusing patients and those excluded by investigators were a very heterogeneous group without clear patterns of objective common co-morbidities, avoiding an overt refusal bias.

In our review of the literature, we found no randomised clinical trials in adult patients regarding the duration of postsurgical antibiotic therapy in patients with septic arthritis. Various expert groups have recommended different regimens for these cases, such as 2 weeks intravenous therapy for streptococci, 3–4 weeks intravenous for staphylococci and Gram-negative bacteria[21 22] and >4 weeks for immune-suppressed patients or those with
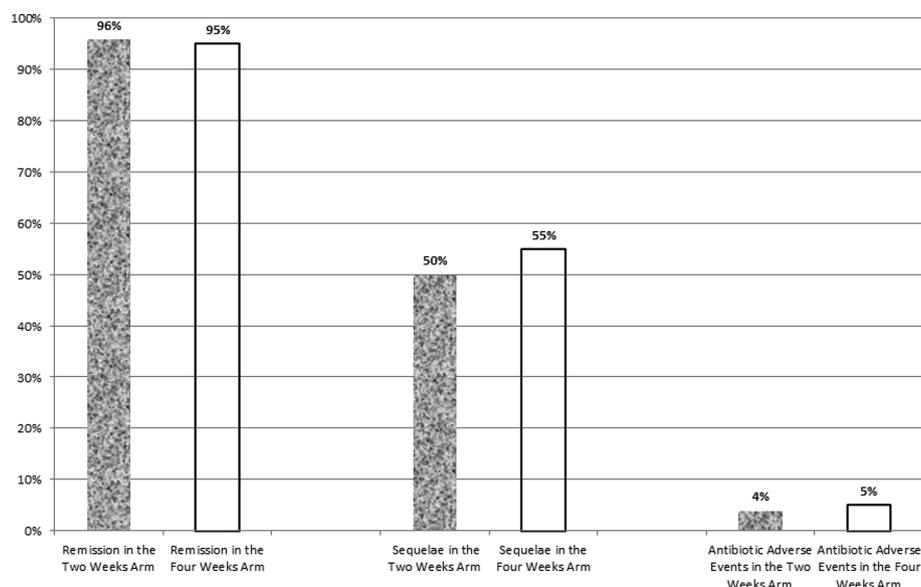

Figure 2 Outcomes of arthritis therapy of the hands and wrists (subgroup analysis). X-axis: study outcome parameters. Y-axis: number of corresponding episodes with proportions and absolute number of cases.

abnormal joints.[21] Others have recommended parenteral treatment for 2 weeks followed by another 2 weeks of oral treatment,[23] or just for a total 4 weeks.[24] Some surgeons prescribe antibiotics for even longer periods without further justification.[25] In the paediatric orthopaedic literature, recommendations are often for a total antibiotic duration of just 2–3 weeks[26–29] or even 10 days.[30] The only investigation of hand bacterial arthritis in the adult population we found was a retrospective study by Meier *et al*[2] that found good outcomes with no more than two surgical interventions and a median antibiotic duration of 14 days in 79% of episodes, similar to what we found in our study.

The results of our trial also support our long-standing policy of providing only a short duration of initial parenteral antibiotic therapy for bacterial arthritis.[3] This contrasts with widespread suggestions for several weeks of parenteral therapy for adult septic arthritis.[21 22] We have found no evidence supporting the need for intravenous antibiotic administration for intrasynovial infections, especially for cases involving smaller joints, such as hand arthritis, that can be drained in toto without missed reservoirs of infection. Even in cases of bone infection, administration of highly bioavailable oral antibiotics can provide acceptable penetration levels,[25] and paediatric arthritis data suggest that an early switch to oral antibiotics is as effective as prolonged parenteral regimens.[26–30] In the aforementioned Meier study of 101 cases of hand arthritis in adults, the transition from the parenteral to oral route occurred 3–5 days after definite surgery in the vast majority of the cases.[2] Finally, very recently, colleagues from Oxford published a large multicentre prospective randomised study with various types of osteoarticular infections, mostly prosthetic joint infections. They could demonstrate the non-inferiority of an early switch to oral targeted medication after 7 days postoperatively.[31] In our study, we switched much earlier after 1–2 days. The lack of prospective randomised trials had made it difficult to change the view of experts' that an initial 2 weeks of parenteral antibiotic therapy is required for all moderate to severe orthopaedic infections. We hope that these recent prospective data, including ours, may make a start in revising that view, at least with hand bacterial arthritis.

Our study has limitations. The majority of arthritis cases involved the hand and wrist (n=99), with only 55 affecting larger joints. While the overall study population entirely fulfilled the sample size requirements for a non-inferiority trial, the subgroup of these 55 patients with larger joint infections did not, making the study underpowered for conclusions regarding non-hand episodes. With this issue in mind, we performed a second interim analysis and considered it unethical to continue the trial just to ensure sufficient numbers (≥250 cases in each study arm) for all subsets of joint infections. Another limitation is that we only compared treatment durations of 2 weeks versus 4 weeks, so we cannot comment on the possible value of shorter (or longer) durations of therapy. While there appears to be little benefit for treating native joint infections with longer than 4 weeks, there are almost no data favouring antibiotic courses shorter than 2 weeks. The third limitation is that the study is performed in a single centre and that it was unblended, demanding for further confirmations in other settings, for example, regarding surgical techniques and approaches.

CONCLUSION

In adult patients who have undergone drainage of native joint bacterial arthritis, we found no difference in rates of clinical remission, adverse events or postinfectious sequelae for those treated with only 2 weeks, compared with 4 weeks' of antibiotic therapy. Our data have statistical validity for hand arthritis cases but are underpowered for other anatomic localisations. As there are many clinical and economic advantages, and apparently no disadvantages, to shorter courses of antibiotic therapy, patients with hand bacterial arthritis might benefit from shorter treatment courses. Similarly, our data support an earlier switch from parenteral to oral antibiotic therapy for these patients, which could help reduce financial costs, length of hospital stay and potentially intravenous line-related complications.

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