International Journal of Infectious Diseases 17 (2013) e199–e205

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short parenteral antibiotic treatment for adult septic arthritis after successful drainage☆

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ARTICLE INFO

Article history:
Received 31 August 2010
Received in revised form 28 April 2011
Accepted 27 December 2011

Corresponding Editor: Vikas Trivedi, Meerut, India

Keywords:
Septic arthritis
Antibiotic treatment
Parenteral
Drainage
Functional outcome

SUMMARY

Objectives: To assess the risk factors for recurrence of septic arthritis with an emphasis on the duration of antibiotic treatment, to gather data for a prospective study on an optimized antibiotic treatment in adults with septic arthritis.

Methods: This was a retrospective single-center study conducted for the period 1996–2008.

Results: A total of 169 episodes of septic arthritis in 157 adult patients (median age 63 years; 65 females) were included. In 21 episodes (21/169, 12%), arthritis recurred after the end of antibiotic treatment. Multivariate analysis showed that Gram-negative infection (odds ratio (OR) 5.9, 95% confidence interval (CI) 1.4–25.3), immune suppression (OR 5.3, 95% CI 1.3–22.0), and lack of surgical intervention were associated with recurrence. The size of the infected joint, the number of surgical drainages (OR 1.3, 95% CI 1.0–1.7), arthrotomy vs. arthroscopic drainage (OR 0.5, 95% CI 0.2–1.8), duration of antibiotic therapy (OR 1.0, 95% CI 0.95–1.05), and duration of intravenous antibiotic therapy (OR 1.0, 95% CI 1.0–1.0) were not. Seven days of intravenous therapy had the same success rate as 8–21 days (OR 0.4, 95% CI 0.1–1.7) and >21 days (OR 1.1, 95% CI 0.4–3.1). Fourteen days or less of total antibiotic treatment had the same outcome as 15–28 days (OR 0.4, 95% CI 0.1–2.3) or >28 days (OR 0.4, 95% CI 0.1–1.6).

Conclusions: In this retrospective study of adults with septic arthritis, the duration of antibiotic therapy, or an early switch from intravenous to oral administration, did not statistically influence the risk of recurrence. Due to study limitations, the data cannot be used directly for antibiotic therapy recommendations for septic arthritis. Prospective randomized trials are warranted to optimize the antibiotic treatment of septic arthritis.

1. Introduction

Septic arthritis is a surgical as well as a medical emergency.[1–4] Although no studies have been published comparing drainage to non-drainage procedures, experts would probably recommend joint drainage, as this condition represents a closed abscess.[1–5] The optimal antibiotic treatment remains controversial since randomized controlled studies, at least in adults, are lacking.[6] We also have yet to determine whether interdigital arthritis and large size joint arthritis should be treated differently. Different antibiotic regimens have been recommended, such as 2 weeks intravenous (IV) therapy for streptococci, 3–4 weeks IV for staphylococci and Gram-negative bacteria,[7,8] and more than 4 weeks for immune suppressed patients or abnormal joints, e.g., severe osteoarthritis.[7] Others recommend parenteral treatment for 2 weeks, followed by another 2 weeks of oral treatment;[5,9] or for 4 weeks without indicating the means of administration.[6] Outpatient antibiotic therapy (OPAT) services have been developed in the USA and Europe to maintain parenteral treatment. In addition, many surgeons prescribe antimicrobials for longer periods without further justification.[1,4]

Parenteral medication should be limited as far as possible.[10] We hypothesize that if surgical drainage is adequately performed, septic arthritis could theoretically be treated with oral antibiotics and for shorter periods of time than reported in the literature.

☆ This manuscript was presented in part at the 20th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria, April 12, 2010; the 70th Annual Congress of the Swiss Orthopedic Society, St. Gallen, Switzerland, July 2, 2010; and the Joint Annual Meeting of the Swiss Society for Infectious Diseases, Swiss Society for Hospital Hygiene, and the Swiss Society for Intensive Care Medicine, Lausanne, Switzerland, September 3, 2010.

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1201-9712/$36.00 – see front matter
http://dx.doi.org/10.1016/j.ijid.2011.12.019

In this retrospective study of adults with septic arthritis, we determined the risk factors for recurrence and sequelae. This retrospective study was not designed to draw direct conclusions regarding antibiotic use in septic arthritis. Therefore our data should not be considered as any form of recommendation regarding the duration or administration route of antibiotic therapy in this neglected field of research.

2. Methods

2.1. Setting

The Orthopedic Service of Geneva University Hospitals has 135 acute care beds and a dedicated infectious diseases (ID) specialist.[11] Lavage for any septic arthritis is usually performed on admission as a surgical emergency. In severe infection or an unfavorable course (clinical and biological),[12] a surgical re-intervention is performed according to the decision of the responsible surgeon. The choice of antibiotic agents and the duration of their administration depend on the surgeon and the ID physician in charge of the individual patient.

2.2. Data collection

The Laboratory of Bacteriology and the hospital's Administrative Coding Office databases were retrospectively searched for adult native joint arthritis during the period January 1996 to December 2008. Forty-two variables for each episode were assessed pertaining to demographic characteristics, immune suppression, microbiology, surgical and antibiotic treatment, and outcomes. A surgeon (LT) and a physician (IU) independently recorded each variable on an Excel spreadsheet. In the case of discordance, a consensus was negotiated.

Patients were followed-up until December 31, 2010, i.e., 3 years after the inclusion of the last patient. The study was approved by the Hospital's ethics committee (No. 08-017R). No informed consent was requested.

2.3. Microbiology procedures

Aspirate material from suspected infected joints was cultured using microbiology procedures that were unchanged during the study period; these procedures were based on the Clinical and Laboratory Standards Institute (CLSI) guidelines.[13] To enhance specificity, only cultures positive on agar plates with significant growth were considered. Growth in enrichment broth was ignored.

2.4. Inclusion criteria and definitions

The definition of an infectious arthritis required the presence of intra-articular pus and a surgical and antibiotic treatment targeted to joint infection. Culture-negative septic arthritis cases were included because their omission would introduce a substantial selection bias. Bacteremia was defined as a documented positive blood culture with the same pathogen as that of the arthritis in cases where blood cultures had been sampled before the antibiotic treatment. Patients with an abscess in the surrounding soft tissue were included if the abscess could be excised or drained in toto during the first surgical intervention.

2.5. Exclusion criteria

Patients with the following conditions were excluded: arthritis due to other reasons, e.g., rheumatoid arthritis, crystal-induced arthropathy (even in the presence of concomitant infection), patients known or diagnosed during follow-up for rheumatic polyarthritis or other autoimmune diseases, patients with an episode of respiratory or gastrointestinal infection in the past 2 months (possibility of reactive arthritis) or gout, viral arthritis, preexisting implant material in the infected joint, and amputation as the primary therapeutic approach. Finally, infections with pathogens for which the literature suggests long-lasting antibiotic treatments or does not indicate surgical drainage were excluded: tuberculosis, other mycobacteria, fungi,[14] brucellosis,[15] borreliosis,[16] gonococcal arthritis,[17] nocardiosis,[18] and *Mycoplasma spp*. Also excluded were cases of secondary arthritis due to an underlying infection for which a total antibiotic treatment of more than 2 weeks is recommended: endocarditis, Lemierre's syndrome,[19] spondylodiscitis,[20] or suspected osteomyelitis[21] outside the joint wall.

2.6. Subgroup analyses

Two separate subgroup analyses for large joint arthritis and arthritis due to *Staphylococcus aureus* were added to the general analyses. Large joints were defined as: hip, knee, shoulder, sternoclavicular, sacroiliac, and the ankle joints.

2.7. Clinical outcomes

Cure was defined as complete clinical, laboratory, and microbiological resolution of arthritis after a minimum active follow-up time of 6 weeks following the end of antibiotic treatment.

Recurrence was defined as new clinical signs of infection with the same microorganism 2 weeks or more after the end of treatment for the first episode. Sequelae were persisting non-infectious handicaps (debilitating pain, limitation of joint movements) that were not resolved despite adequate physiotherapy and analgesia. The sequelae were not pre-existing and had to be attributed to the infection.

2.8. Statistical analyses

Group comparisons were performed using the Pearson Chi-square test or the Wilcoxon rank sum test. Logistic regression with cluster control (random effect) was used to determine associations with the outcomes recurrence and sequelae. Each of these analyses was separately repeated for the subgroups of large joint arthritis and arthritis due to *S. aureus*. Independent variables with a p-value of ≤ 0.05 in the univariate analysis were introduced stepwise into a multivariate analysis. Exceptions were variables for surgical interventions and antibiotic treatment, which were automatically included in the final model. We included 6–10 predictor variables per outcome event.[22] Key variables were checked for collinearity and interaction, the latter by interaction terms and Mantel–Haenszel estimates. According to these criteria, included variables were: joint type, immune suppression, pathogens, number of surgical interventions, duration of IV antibiotic treatment, and duration of total antibiotic therapy. All remained in the final model.

We intended to analyze duration of antibiotic treatment variables within three strata (instead of dichotomous variables) in order to reveal more details. The strata of the categorical variables were around the median value, with inferior and superior limits relying on the 33% and 66% percentiles, rounded up to clinically practical duration times. According to this approach, the total duration of antibiotic therapy was divided into the following three strata: 0–14 days, 15–28 days, and more than 28 days. This approach was similar for parenteral antibiotic therapy with the strata 0–7 days, 8–21 days, and more than 21 days.

We assessed a possible linearity of the duration of antibiotic administration and recurrence of infection by linear and logistic

regression analysis with categorized variables. This procedure was performed first with untransformed antibiotic duration variables, and repeated with quadratic and logarithmic (ln) transformations of these variables. Furthermore, we investigated the presence of a potential threshold beneath which the duration of antibiotic administration could be associated with an enhanced risk of recurrence by graphical plotting of all recurrent cases in relation to their antibiotic duration.

p-Values of ≤0.05 (two-tailed) were considered significant. STATA software (9.0, STATA, USA) was used.

3. Results

3.1. Patients

A total of 212 native joint arthritis episodes were found. Of these, 43 were excluded due to loss to follow-up ($n = 4$); amputation ($n = 22$); secondary arthritis due to spondylodiscitis ($n = 6$), Lemierre's syndrome ($n = 1$), pneumonia ($n = 1$), or endocarditis ($n = 2$); and arthritis due to tuberculosis ($n = 1$), other mycobacteria ($n = 2$), *Nocardia sp* ($n = 1$), *Brucella sp* ($n = 1$), *Neisseria meningitidis* ($n = 1$), or *Mycoplasma sp* ($n = 1$).

A total of 169 arthritis episodes in 157 patients (median age 63 years, interquartile range (IQR) 39–78 years; 65 females) remained in the final analysis. In 65 episodes (65/169, 38%), patients were immunocompromised: diabetes mellitus ($n = 34$), steroid medication ($n = 22$), HIV disease ($n = 4$), and solid organ transplantation ($n = 5$).

3.2. Infected joints

One-hundred fifty-nine arthritis episodes involved a single joint, seven involved two joints, and three involved three joints. There were 126 episodes (126/169, 75%) of large joint arthritis and 43 episodes (43/169, 25%) of interdigital joint arthritis (Table 1). The large joints included: knee ($n = 51$), hip ($n = 21$), shoulder ($n = 32$), ankle ($n = 9$), sternoclavicular ($n = 2$), elbow ($n = 2$), and sacroiliac joints ($n = 1$). Interdigital arthritis involved the following joints: metatarsophalangeal ($n = 23$), interphalangeal ($n = 18$), Lisfranc ($n = 1$), and cuneometatarsal ($n = 1$).

3.3. Origin of infection and documented bacteremia

For 58 arthritis episodes (58/169, 34%), the focus of infection could not be determined. The remaining 111 causes were: traumatic ($n = 31$), surgical site infection after ligament surgery or intra-articular steroid injections ($n = 31$), intravascular drug abuse ($n = 16$), wound infections ($n = 20$), and hematogenous seeding from remote infections ($n = 13$). For the episodes with iatrogenic or traumatic cause, the median delay between the event and the onset of symptomatic arthritis was 14 days (IQR 2–41 days). Half of the patients had documented bacteremia (46 episodes positive out of 97 episodes with blood cultures sampled).

3.4. Pathogens

There were 130 episodes involving Gram-positive bacteria (130/169, 77%) and 26 involving Gram-negative bacteria (26/169, 15%). In 18 episodes (18/169, 11%) no pathogen could be identified. Ten patients had mixed Gram-positive and Gram-negative infections. Eighty-eight episodes (88/169, 52%) were due to *S. aureus*, of which 17 were methicillin-resistant strains (MRSA). Community-acquired MRSA was not encountered. Thirty-eight episodes (38/169, 22%) were due streptococci: *S. pyogenes* ($n = 13$), *S. agalactiae* ($n = 7$), and others. *Escherichia coli* ($n = 5$) and *Pseudomonas aeruginosa* ($n = 5$) were the most frequent Gram-negative pathogens.

Table 1
Characteristics and comparisons between large joint and interdigital joint arthritis (all types of arthritis, $N = 169$)

	Large joint arthritis (hip, knee, shoulder, ankle) ($n = 126$)	Interdigital joint arthritis (foot and hand) ($n = 43$)	Comparison, *p*-value[a]
Patients			
Female sex	44 (35%)	21 (49%)	
Median age, years	58	71	
Single joint infection	118 (94%)	41 (95%)	
Immune suppression[b]	49 (39%)	16 (37%)	
Diabetes mellitus	23 (18%)	11 (26%)	
Origin of arthritis			
Drug abuse	16 (13%)	0 (0%)	0.014
Ulcer/wound	4 (3%)	16 (37%)	0.001
Surgical site/intra-articular injection	24 (19%)	7 (16%)	
Infection			
Maximal median C-reactive protein, mg/l	191	50	0.001
Staphylococcus aureus	67 (53%)	21 (49%)	
Gram-negative pathogens	23 (18%)	3 (7%)	
Surgical treatment			
Lack of any surgical intervention	3 (2%)	6 (14%)	0.004
Median number of surgical interventions	2	1	0.008
Arthrotomy compared to arthroscopy	87 (69%)	22 (51%)	
Resection[c] compared to arthroscopy	10 (8%)	14 (33%)	0.001
Antibiotic treatment			
Median duration of antibiotic treatment, days	42	36	0.001
Median duration of intravenous treatment, days	14	6	0.001
Outcomes			
Recurrence of infection	12 (10%)	9 (21%)	
Definite sequelae at long-term follow-up	29 (23%)	15 (35%)	
Median length of hospital stay, days	22	18	

[a] Only significant *p*-values ≤0.05 (two-tailed) are displayed.
[b] Immune suppression: diabetes mellitus, steroids, organ transplantation, and HIV disease.
[c] Resection: excision arthroplasty, arthrodesis, or other orthopedic surgery not limited to drainage.

3.5. Surgical treatment

All but nine patients (9/169, 5%) underwent a surgical intervention, with a median delay of 7 days after the onset of infection (IQR 2–15 days). In 87 episodes (87/169, 51%), patients underwent a single drainage, in 39 episodes (39/169, 23%) two drainages, and in the remaining cases between three and 13 interventions. Surgical re-intervention occurred after a median delay of 3 days (IQR 2–8 days). In 27 episodes (27/160, 17%), surgical drainage was arthroscopic, in 109 episodes (109/160, 68%) by arthrotomy, and in 24 episodes (24/160, 15%) arthrotomy with resection or arthrodesis.

3.6. Antibiotic treatment

All patients received systemic antibiotic therapy. No antibiotics were added to the irrigating solutions. The duration and the choice of antibiotic agents were not changed by the different ID consultants over the study period (Chi-square tests; $p > 0.2$). For 18 episodes (18/169, 11%), antibiotic treatment was empirical.

3.7. Choice of antibiotic agents

For parenteral therapy, flucloxacillin, amoxicillin/clavulanic acid, and glycopeptides were the most frequently prescribed agents, and ciprofloxacin/rifampin (22 episodes, 13%) for oral treatment. Quinolones were used alone or in combination in 64 episodes (38%), clindamycin in 43 (25%), co-trimoxazole in nine (5%), and linezolid in five episodes (3%). In 32 staphylococcal infections (32/88, 36%), rifampin was used in combination therapy. Oral treatment consisted of beta-lactam antibiotics in only 24 episodes (24/169, 14%).

3.8. Duration of antibiotic treatment

The median duration of total antibiotic therapy was 6 weeks; 12 episodes were treated for ≤14 days (12/169, 7%), 26 episodes for between 15 and 28 days (26/169, 15%), and 131 episodes for >28 days (131/169, 78%). The patient groups receiving total short (≤14 days) or long-term (>28 days) antibiotic treatments did not differ substantially in demographic or surgical characteristics, final outcomes, or joint type (Tables 1 and 2).

The median duration of parenteral therapy was 14 days; 65 episodes (65/169, 38%) were treated IV for a maximum of 7 days, 46 episodes (46/169, 27%) for between 8 and 21 days, and 58 episodes (58/169, 34%) for >21 days. All patients treated for <14 days had IV therapy throughout. Documented bacteremic infections were treated parenterally for longer than non-bacteremic episodes (median 22 days vs. 7 days, $p = 0.002$).

3.9. Outcomes

3.9.1. Cure and follow-up time

A total of 104 episodes (104/169, 62%) were cured without sequelae. Whether or not sequelae occurred could not be determined in 21 cases. The median follow-up time was 3.6 years (IQR 1.5–6.0 years). There were no secondary infections following arthritis among the study patients.

3.9.2. Recurrence of infection and sequelae

Twenty-one patients revealed a recurrent arthritis (21/169, 12%) after a median delay of 71 days. Of these, 12 (12/126, 10%) concerned large joint episodes and nine (9/43, 21%) interdigital joint arthritis ($p = 0.05$). Among the nine patients without surgical intervention, five showed recurrence (5/9, 56%).

Table 2
Characteristics and comparison of the patient groups with cure, recurrence, and sequelae after native joint arthritis (all types of arthritis, $N = 169$)

	Recurrence ($n = 21$)	Non-recurrence ($n = 148$)	Comparison, p-value[a]	Non-sequelae ($n = 125$)	Sequelae ($n = 44$)	Comparison, p-value[a]
Patients						
Female sex	7 (33%)	58 (39%)		44 (35%)	13 (30%)	
Median age, years	71	62		62	61	
Large size joint arthritis[b]	12 (57%)	114 (77%)	0.050	81 (65%)	29 (66%)	
Immune suppression[c]	15 (71%)	50 (34%)	0.001	18 (14%)	25 (57%)	0.001
Diabetes mellitus	8 (38%)	26 (18%)	0.029	13 (10%)	13 (30%)	0.003
Organ transplantation	3 (14%)	2 (1%)	0.001	0 (0%)	1 (2%)	
Infection						
Maximal median C-reactive protein, mg/l	118	172		172	154	
Documented bacteremia	8 (38%)	38 (26%)		33 (26%)	13 (30%)	
Gram-positive pathogens	10 (48%)	120 (81%)	0.001	87 (70%)	30 (68%)	
Staphylococcus aureus	8 (38%)	80 (54%)		54 (43%)	23 (52%)	
Methicillin-resistant *S. aureus*	5 (24%)	12 (8%)	0.025	15 (12%)	5 (11%)	
Gram-negative pathogens	7 (33%)	19 (13%)	0.015	17 (14%)	8 (18%)	
Surgical treatment						
Lack of any surgical intervention	5 (24%)	4 (3%)	0.000	NA	NA	
Median number of surgical interventions	2	1	0.019	1	2	
Arthrotomy compared to arthroscopy	11 (52%)	98 (66%)		79 (63%)	20 (45%)	0.040
Resection[d] compared to arthroscopy	1 (5%)	23 (16%)		6 (5%)	18 (41%)	0.000
Antibiotic treatment						
Median duration of antibiotic treatment, days	42	42		42	42	
Median duration of intravenous antibiotic treatment, days	10	14		14	10	
Empirical antibiotic treatment	4 (19%)	14 (9%)		10 (8%)	8 (18%)	
Outcome						
Median length of hospital stay, days	16	22		22	26	

NA, not applicable.
[a] Only significant p-values ≤0.05 (two-tailed) are displayed.
[b] Large joints: hip, knee, shoulder, sternoclavicular, and the ankle joints.
[c] Immune suppression: diabetes mellitus, steroids, organ transplantation, and HIV disease.
[d] Resection: excision arthroplasty, arthrodesis, or other orthopedic surgery not limited to drainage.

Forty-four patients (44/169, 26%) had sequelae: Girdlestone hip ($n = 4$), arthrodesis ($n = 3$), limitation of mobility ($n = 3$), amputation due to functional impairment ($n = 2$), secondary osteoarthritis ($n = 1$), and persistent pain at last follow-up ($n = 31$). Among the nine patients without surgical intervention, two had sequelae (2/9, 22%).

3.10. Multivariate analyses of risk factors for adverse outcomes

3.10.1. Recurrence of infection

In the multivariate analysis, lack of surgical intervention was the most important risk factor for recurrence (odds ratio (OR) 21.9, 95% confidence interval (CI) 2.07–333.9), followed by Gram-negative arthritis (OR 5.9, 95% CI 1.4–25.3) and immune suppression (OR 5.3, 95% CI 1.3–22.0) (Table 3). The final model was more than acceptable with a non-significant goodness-of-fit test and a receiver operating curve (ROC) value of 0.87 (95% CI 0.78–0.96).

No antibiotic-related parameters revealed a statistical association with recurrence: ≤7 days of IV therapy had the same effect as 8–21 days (OR 0.4, 95% CI 0.1–1.7) and >21 days of IV treatment (OR 1.1, 95% CI 0.4–3.1); ≤14 days of total antibiotic treatment had the same outcome as 15–28 days (OR 0.4, 95% CI 0.1–2.3) and >28 days (OR 0.4, 95% CI 0.1–1.6). We failed to detect linearity or a threshold level for antibiotic duration and risk of recurrence.

3.10.2. Subgroups of large joint arthritis and arthritis due to S. aureus

The same trends were noted in a sub-analysis for large joint arthritis, but the variables did not reach formal statistical significance (Table 3). The separate analysis of the subgroup of *S. aureus* arthritis was not different from the global analysis. While immune suppression was again revealed as a significant risk factor (OR 3.4, 95% CI 1.2–10.4), ≤7 days of IV therapy had the same effect as 8–21 days (OR 0.4, 95% CI 0.1–1.8) and as >21 days of IV treatment (OR 1.6, 95% CI 0.5–5.1), and ≤14 days of total antibiotic treatment was similar to 15–28 days (OR 0.4, 95% CI 0.1–3.6) and >28 days (OR 0.4, 95% CI 0.1–2.2).

3.10.3. Sequelae

In the multivariate analysis, only resection (OR 7.9, 95% CI 1.2–54) and immune suppression (OR 3.6, 95% CI 1.5–8.7) were associated with sequelae. No antibiotic-related parameters influenced sequelae (Table 4). The same trends were observed for large size joint arthritis compared to interdigital arthritis. The variables did not reach statistical significance (data not shown).

4. Discussion

We report our experience in the management of 169 episodes of septic native joint arthritis in patients hospitalized in an orthopedic service. The minimum clinical follow-up was long, recurrence occurred in only 12% of the cases, and the final statistical model was accurately adapted.

A lack of surgical intervention revealed a 21-times higher risk of recurrence than at least one surgical intervention. None of the other surgical parameters analyzed was associated with a risk of recurrence. This is congruent with the orthopedic literature indicating no differences between arthroscopy and arthrotomy for the initial drainage of knee,[2] hip,[23] and other joint septic arthritis.[4,24] We could not determine any ideal antibiotic duration. Antibiotic-related ORs and corresponding 95% CIs were often around one, indicating no difference. Thus, ≤7 days of IV therapy had the same effect as >21 days of IV treatment; also a maximum 14 days of antibiotic treatment had the same outcome as >28 days. Of note, all our patients received antibiotic medication. Hence we are unable to estimate a recurrence risk with surgery alone. The total duration of antibiotic treatment had no influence on the risk of recurrence, in contrast to parameters that are inherent to patient baseline characteristics, such as immune suppression.[9,25] While age and diabetes mellitus did not influence outcome, steroid

Table 3
Predictors of recurrence in all type of arthritis and large joint arthritis (random-effect controlled logistic regression)

	Univariate analysis: All arthritis	Multivariate analysis: All arthritis	Univariate analysis: Large joint arthritis[a]	Multivariate analysis: Large joint arthritis[a]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Female sex	0.8 (0.3–2.0)		NA	
Age	1.0 (1.0–1.0)		NA	
Hip joint	0.3 (0.1–2.2)		NA	
Knee joint	1.3 (0.5–3.3)		NA	
Shoulder joint	0.4 (0.1–1.8)		NA	
Ankle joint	0.9 (0.1–7.3)		NA	
Lack of surgical intervention	11.3 (2.7–46.2)	21.9 (2.07–333.9)	5.1 (0.4–60.7)	
Number of surgical interventions	1.2 (1.0–1.4)	1.3 (1.0–1.7)	1.2 (1.1–1.5)	1.4 (1.1–1.8)
Arthrotomy compared to arthroscopy	0.5 (0.2–1.8)		0.5 (0.1–1.7)	
Resection[b]	0.2 (0.1–1.8)			
Duration of total antibiotic treatment	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
15–28 days compared to ≤14 days	0.4 (0.1–2.3)	0.4 (0.1–5.8)	NA	
>28 days compared to ≤14 days	0.4 (0.1–1.6)	0.1 (0.1–1.6)	NA	
Total duration of intravenous therapy	1.0 (1.0–1.0)		1.0 (1.0–1.1)	1.0 (1.0–1.1)
8–21 days compared to ≤7 days	0.4 (0.1–1.7)	0.7 (0.1–5.1)	0.4 (0.1–4.1)	0.8 (0.1–18.5)
>21 days compared to ≤7 days	1.1 (0.4–3.1)	1.2 (0.5–6.2)	2.4 (0.6–9.8)	4.3 (0.5–41.1)
Total duration of oral antibiotics	1.0	(Reference)	1.0	(Reference)
Empirical antibiotic treatment	2.3 (0.7–7.6)		1.4 (0.2–12.4)	
Immune suppression[c]	3.6 (1.3–9.9)	5.3 (1.3–22.0)	4.5 (1.2–17.7)	14.3 (1.2–176.2)
Steroid medication	1.1 (1.1–1.2)		1.1 (1.0–1.1)	
Organ transplantation	12.2 (1.9–77.8)		10.3 (0.6–175.8)	
Staphylococcus aureus	0.6 (0.2–1.6)		0.4 (0.1–1.4)	
Methicillin-resistant *S. aureus*	4.2 (1.3–14.1)		4.6 (1.0–21.0)	
Gram-negative pathogens	4.2 (1.4–12.5)	5.9 (1.4–25.3)	6.4 (1.7–23.2)	5.8 (1.2–28.1)

OR, odds ratio; CI, confidence interval; NA, not applicable due to substantial interaction.
[a] Large joints: hip, knee, shoulder, sternoclavicular, and the ankle joints.
[b] Resection: excision arthroplasty, arthrodesis, or other orthopedic surgery not limited to drainage.
[c] Immune suppression: diabetes mellitus, steroid medication, organ transplantation, and HIV disease.

Table 4
Predictors of sequelae in native joint arthritis (random-effect controlled logistic regression)

	Univariate analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
Female sex	0.65 (0.3–1.2)	
Age	1.0 (1.0–1.0)	
Recurrence of infection	3.8 (1.1–12.6)	
Delay infection onset to first surgery	1.0 (1.0–1.0)	
Lack of any surgical intervention	2.4 (0.3–17.4)	0.9 (0.1–13.3)
Number of surgical interventions	1.1 (0.9–1.3)	1.2 (1.0–1.5)
Arthrotomy compared to arthroscopy	0.8 (0.2–2.3)	
Resection[a] compared to arthroscopy	8.5 (2.1–33.6)	7.9 (1.2–54)
Duration of total antibiotic treatment	1.0	1.0
15–28 days compared to ≤14 days	0.3 (0.1–1.5)	0.4 (0.1–4.4)
>28 days compared to ≤14 days	0.2 (0.1–1.0)	0.3 (0.1–2.4)
Total duration of intravenous therapy	1.0 (0.9–1.0)	
8–21 days compared to ≤7 days	1.0 (0.4–2.3)	
>21 days compared to ≤7 days	0.4 (0.2–1.0)	
Immune suppression[b]	2.8 (1.3–5.8)	3.6 (1.5–8.7)
Steroid medication	1.0 (0.9–1.1)	
Staphylococcus aureus	1.2 (0.6–2.6)	
Methicillin-resistant *S. aureus*	1.8 (0.5–6.7)	
Gram-negative pathogens	2.0 (0.8–5.7)	
Large joint arthritis[c]	0.5 (0.2–1.1)	

OR, odds ratio; CI, confidence interval.
[a] Resection: excision arthroplasty, arthrodesis, or other orthopedic surgery not limited to drainage.
[b] Immune suppression: diabetes mellitus, steroid medication, organ transplantation, and HIV disease.
[c] Large joints: hip, knee, shoulder, sternoclavicular, and the ankle joints.

medication[3] and organ transplantation were among the strongest predictors of recurrence.

The lack of influence of the different antibiotic modalities was equally noted in the subpopulation of patients with large weight-bearing joint arthritis compared to interdigital arthritis, and for *S. aureus* infections. There were no differences including or excluding interdigital arthritis. Studies on antibiotic modalities in interdigital septic arthritis are rare,[3,26] and the literature does not provide any data proving that interdigital septic arthritis would be different to treat than large joint arthritis.

Synovial penetration of antibiotic agents during parenteral administration is good.[27] Recent retrospective data suggest that regimens with an early switch to oral antibiotics with good bioavailability are as effective as prolonged parenteral regimens, at least for staphylococcal osteomyelitis.[28,29] For bone infections, several antibiotic agents already have proven clinical efficacy: quinolones,[30] linezolid,[31] clindamycin,[32] fusidic acid,[29,30] combined with rifampin.[29,30] These drugs have an oral bioavailability of over 90%.[32] Studies of septic arthritis in children have revealed that a short IV treatment is successful.[6] Prado et al. reported that in 70 children with osteoarticular infections (60% septic arthritis), a regimen of 7 days initial IV antibiotic treatment, followed by 3–5 weeks of oral treatment was sufficient for cure.[33] Kim et al. compared short and longer durations of antibiotic therapy among 20 children. Less than 10 days of parenteral treatment for Gram-positive hip arthritis was sufficient after surgical drainage.[34] Peltola et al. recommended a 10-day course of antimicrobial treatment in a randomized trial comparing 10 days (including a short-term IV therapy) to 30 days for childhood arthritis.[35] Jagodzinski et al. prospectively showed that 3 days of high-dose IV therapy followed by 3 weeks of oral medication cured 70 children.[36] As in our study, an early conversion from parenteral to oral antibiotics after a median of 7 days was equally effective in the treatment of pediatric arthritis among 186 children.[37] This cut-off of 7 days was also confirmed in another trial where 7 vs. 14 days of parenteral antibiotics showed an equal outcome after surgical drainage in 130 cases with infectious arthritis.[38]

For adults, Angly et al. investigated 31 operated patients with interdigital arthritis of the hands. No recurrence of infection occurred after surgery and antibiotics administered for a median of 2 days IV and a median of 17 days orally.[26]

While Gram-negative bacilli are seen in 9–17% of cases of infectious arthritis,[39] the outcome from such infections is reported as good in the older literature. We cannot explain our considerable recurrence risk in this subgroup, besides the fact that we found only 26 episodes, which may be too small a number to allow a conclusion to be drawn. Gram-negative osteoarticular infection is also a hallmark of immune suppression.[3] Therefore it is possible that immune suppression might be a confounding factor with underlying disease. The mean duration of antibiotic therapy for our Gram-negative episodes was 42 days, and we doubt that a prolonged treatment would change the risk of recurrence.

Sequelae in terms of functional impairment were observed in 26% of cases, similar to the studies of Ross et al. with 26% sequelae[9] and Vispo-Seara et al. with 20% sequelae in arthritis patients.[4] In the regression analysis, no antibiotic or clinical parameter was found to be significantly associated with sequelae. Indeed, the literature suggests that cartilaged damage may be the most important factor for a poor functional outcome.[4,26] Cartilage damage itself was significantly correlated with a time delay longer than 2 weeks between the onset of infection and surgery.[4] However we could not confirm this statistical association.

Our study has several limitations: (1) It was a retrospective, single-center study with a heterogeneous patient population and a small sample size. (2) The subgroup analyses, e.g., for *S. aureus* infections or large size joint arthritis, further diminished the sample size. Thus, our results should be interpreted only as a trend, helping to design future prospective randomized trials. We wish to emphasize that our pilot data should not be considered as any form of recommendation regarding the duration or administration route of antibiotic therapy. (3) We included all arthritis cases according to the inclusion criteria, i.e., large and small joints, together with the 18 patients without microbiological documentation of arthritis. Excluding them would have introduced a selection bias to everyday clinical life. Indeed, statistical analyses failed to show any significant differences in the outcome of small and large joint native arthritis. However, for future prospective trials regarding optimal antibiotic therapy, the separation of small and large joint arthritis cases is necessary. (4) We cannot exclude therapeutic decision bias; e.g. the patients who were doing well could be those who had short antibiotic courses. (5) Patients with recurrences treated in another hospital may have been undetected. However, since the Geneva University Hospitals is by far the largest and only public hospital in the area, we consider the possibility very low.

In conclusion, our pilot data, based on a retrospective study with a heterogeneous adult study population, failed to reveal an enhanced recurrence risk regarding the duration of antibiotic therapy, or an early switch from IV to oral administration. Prospective randomized trials are needed to optimize antibiotic treatment in patients with septic arthritis.

Acknowledgements

We are indebted to Gilles Cohen and to Claudine Bréant, Coding Office, for their help in retrieving the data. We thank the teams of the Orthopedic Service and the Laboratory of Bacteriology for their support.

Conflict of interest: No conflict of interest for all authors.

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