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ORIGINAL PAPER

Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience

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Abstract
Purpose The optimal duration of concomitant antibiotic therapy after surgical intervention for implant-free chronic osteomyelitis is unknown. No randomized data exist. Available recommendations are based on expert's opinion. We evaluated the duration of post-surgical antibiotic treatment related to remission of chronic osteomyelitis.

Methods This was a retrospective single-centre study at Geneva University Hospitals with a minimal follow-up of two years after treatment. We used multivariate logistic regression analysis with exclusion of pediatric cases and of implant-related chronic osteomyelitis.

Results A total of 49 episodes of implant-free chronic osteomyelitis in 49 adult patients were studied. The median number of surgical interventions was two (range, 1–10). The median duration of post-debridement antibiotic treatment was eight weeks (range, 4–14 weeks). Thirty-nine patients (80%) were in remission after a minimal follow-up of two years. In multivariate logistic regression analysis, one week of intravenous therapy had the same remission as two to three weeks (0.2, 0.1–1.9) or ≥ 3 weeks (0.3, 0.1–2.4). More than six weeks of total antibiotic treatment equalled ≤ six weeks (0.8, 0.1–5.2).

Conclusions In chronic osteomyelitis in adults, a post-debridement antibiotic therapy beyond six weeks, or an IV treatment longer than one week, did not show enhanced remission incidences. Prospective randomized trials are required to confirm this observation.

Thierry Rod-Fleury and Nathalie Dunkel contributed equally to this work.

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Introduction

Chronic bacterial osteomyelitis is a surgical disease [1, 2]. Various surgical approaches and techniques have been established [2–7] and experience has been acquired among orthopedic surgeons and infectious diseases (ID) specialists worldwide. Whereas expert's opinion and scientific evidence is rich for haematogenous childhood osteomyelitis or implant-related osteomyelitis (surgical site infections), the optimal antibiotic treatment post-debridement for implant-free, non-diabetic osteomyelitis among adults remains unknown [1, 5, 8, 9]. Studies investigated primarily the

choice of antibiotic agents [8–10], rather than their duration or route of administration [8, 9]. Different case series recommend different durations without comparing within or between the reports [5, 9] and international consensus guidelines are currently lacking [8].

Experts usually recommend an intravenous (IV) therapy for four [2] to six weeks [5, 11, 12] followed by an oral course of additional months or weeks. In practice, long postsurgical oral treatment regimens are frequent, ranging from six [8, 10] to ten months [13] or even up to two years [8]. The rationale for an IV course is to achieve high elevated serum concentrations, because bone diffusion is limited for certain groups of antibiotics. To maintain parenteral treatment, outpatient antibiotic therapy (OPAT) services [8] have been developed in the United States [14] and Europe [11, 15]. At the same time, parenteral medication should be limited as far as possible in order to save unnecessary costs, prevent catheter-related complications and to increase patient and nursing comfort. The estimated proportion of complications attributed to prolonged IV course are around 15% [9, 11]. Moreover, the basis for long periods of supplementary oral treatment evolved from cases of relapsing osteomyelitis in the 1970s, which may be less frequent today due to improved surgery and newly available antibiotics [14]. Yet still, there are no clinical studies or documented records indicating the superiority of the four- to six-week course over shorter durations [5].

We hypothesize that if surgery is adequately performed, IV antibiotics can be switched to oral administration a few days later and that a prolonged duration beyond six weeks is unlikely to be beneficial [5]. In their recent review regarding duration of antibiotic treatment for osteomyelitis, Haidar et al. listed small individual reports in animals and humans that obtained remission of osteomyelitis with antibiotic durations ranging from one to four weeks [5], but did not provide their own data. In this retrospective study, we determine antibiotic duration in relation to the remission of chronic osteomyelitis. We consider this pilot analysis as a prerequisite for future prospective randomized trials.

Methods

Setting and data collection

The Orthopedic Service of Geneva University Hospitals is a tertiary centre with a septic subunit consisting of 22 acute care beds. A dedicated team of orthopaedic surgeons, infectious disease specialists, diabetologists, nurses and physiotherapists treat patients with osteo-articular infections. Hyperbaric oxygen is not used.

Databases from the Hospital's Administrative Coding and the Septic Orthopaedic Cohort were retrospectively searched for osteomyelitis among adult orthopaedic patients free of implants from January 1999 to November 2008. Patients were followed-up until 30 November 2010. Eighty-three variables for each episode were assessed related to demographic characteristics, immune suppression, microbiology, surgical and antibiotic treatment modalities and outcomes. An orthopaedic surgeon (TR) and a biologist with experience in clinical research (ND) independently recorded each variable on an EXCEL®-sheet. In case of discordance, a consensus was negotiated with the infectious disease physician with experience in osteo-articular infections (IU). The severity of underlying co-morbidities was assessed by the Charlson co-morbidity index [16].

The microbiological procedures were unchanged during the study period and based on the CLSI guidelines [17]. The study was supported by the Hospital's Ethics Committee (No. 08-017R). No informed consent of the included patients was requested.

Criteria and definitions

Our definition of a chronic osteomyelitis was based on a surgical [2] (rather than internistic) understanding of osteomyelitis with bone alterations and abscesses. It required a minimal symptom duration of three months, radiological alterations in favour of osteomyelitis, bone abscesses, and the identification of the same bacteria in three intraoperative bone samples. Only the first episode of osteomyelitis at the same localization was recorded; patients presenting relapsing episodes were excluded. The presence of a sinus tract or histology was no prerequisite to include the patient in the study. Exclusion criteria were: pediatric patients (defined as $\leq$ 17 years); presence of an implant in the infected bone; cure by amputation [14, 18]; diabetic foot osteomyelitis, vertebral or skull osteomyelitis, involvement of fingers or toes only, infection in a bone modified by prior radiotherapy [10] or osteomyelitis with pathogens for which the literature provides long-lasting antibiotic treatments (tuberculosis [19], other mycobacteria, fungi, or brucellosis).

Remission was defined as complete clinical resolution of the former infection after a follow-up of two years. Mechanical sequels were allowed in the definition "remission". Recurrence meant new signs of infection at least two weeks after the end of treatment for the first episode. Immune suppressed patients were considered those with diabetes mellitus, HIV infection with a CD4 count of $\leq$ 200 cells/mm^3, or those requiring chronic steroid therapy for autoimmune and rheumatic disorders.

Statistical analyses

Group comparisons were performed using the Pearson χ^2, Fisher's exact or Wilcoxon rank sum tests. Logistic regression determined associations with outcome remission. To adjust for case mix, a multivariate analysis was included with continuous variables regarding surgical interventions and antibiotic treatment. In a second step, the duration of antibiotic treatment was categorized with cut-offs at four, six, and 12 weeks for total therapy; and at one and three weeks for intravenous therapy. We included six to ten predictor variables per outcome event [20]. Variables were checked for collinearity and interaction; the latter by Mantel-Haenszel estimates and likelihood ratio tests. We assessed a possible linearity of antibiotic duration and remission by linear and logistic regression analyses with categorized variables. This procedure was performed first with untransformed variables, and repeated with quadratic and logarithmic (ln) transformations of these variables.

P values≤0.05 (two-tailed) were regarded as significant. STATA software (9.0, STATA, USA) was used.

Results

Patients and bones

During the study period a total of 49 chronic osteomyelitis episodes, corresponding to the study criteria, could be determined. Nineteen patients had received a previous course of unsuccessful antibiotic therapy; however, none of them underwent prior surgery. Median age of the patients was 41 years; nine were females. Sixteen patients (32%) were immune-compromised, of which ten were due to diabetes mellitus, one due to advanced HIV infection, and the rest for chronic steroid medication. Forty-three (85%) patients presented no peripheral arterial disease; only two revealed a grade III or IV arterial insufficiency. Median CRP value at admission was 18 mg/L (range, 3–194 mg/L). Seventeen cases had normal CRP values (≤ 10 mg/L).

The majority of infections concerned long bones (n=32; 65%), with diaphyseal involvement in 28 cases. The distribution was as follows: tibia (n =17), femur (6), radius (4), fibula (4), humerus (3), ulna (2), ischium (2), clavicle (1), talus (1), and calcaneum (9). Thirty-two episodes (65%) had a sinus tract on admission, of which 24 were discharging on admission. According to the Cierny-Mader classification [21], the majority of infections (39; 80%) were Cierny grade IV.

Radiological sequestra were witnessed in 15 cases (31%), while X-rays indicated pathologic evidence in 90%. Histological results were available for 42 cases (85%) mentioning microorganisms in 16% and inflammation in 78%.

Pathogens

Current bacterial cultures were positive on a median of three out of four intraoperative samples. *Staphylococcus aureus* was predominant and involved in 29 cases (9 methicillin-resistant), followed by streptococci: *Streptococcus agalactiae* (4), *Streptococcus pyogenes* (2) and milleri group (3). Other Gram-positives were *Enterococcus faecalis* (1). Among Gram-negatives, we diagnosed osteomyelitis due to *Proteus* spp (6), *Pseudomonas aeruginosa* (6), *Enterobacter cloacae* (3), *Klebsiella* spp (3), and *Escherichia coli* (1). No anaerobic pathogen was detected. In 14 cases (29%), osteomyelitis was polymicrobial. The pathogens were moderately resistant. Resistances to clindamycin, ciprofloxacin or rifampicin (for *S. aureus*) were observed in 33%, 29% and 8%, respectively.

Surgical treatment

All patients underwent surgical treatment with a median of two surgical interventions in the operating theatre (range, 1–10 surgeries). In 13 episodes, there was a single intervention; in 11 episodes two interventions. The distribution of interventions was as follows: debridement and lavage (49 cases), insertion or removal of antibiotic beads (16), intramedullar reaming (7), use of vacuum-assisted devices (2) and use of external fixation in four cases (median duration 9 weeks). Overall, six patients required a later implant in order to achieve bone stability after clinical remission. Skin and muscular grafts were needed in ten and 13 cases, respectively.

Antibiotic treatment

All patients received systemic antibiotic therapy and no severe adverse events were recorded. No antibiotics were added to the irrigating solutions. Gentamicin beads were used in 16 cases for a median duration of three weeks. For parenteral therapy, fluclocaxillin, amoxicillin/clavulanic acid and vancomycin were the most prescribed agents; and ciprofloxacin/rifampicin [10] and clindamycin for oral treatment.

The median duration of total antibiotic therapy was eight weeks (range, 4–14 weeks); eight episodes were treated for less than four weeks, nine episodes between four and six weeks, 20 between seven and 12 weeks, and 12 episodes for>12 weeks. The median duration for parenteral therapy was eight days (range, 0–42 days); ten episodes were treated intravenously for a maximum of seven days, 13 between two and three weeks, and 16 episodes for more than three weeks.

Outcomes

A total of 39 episodes (80%) remained in remission; among these however 31 with long-term mechanical sequels of lower degree. The median duration of hospital stay was six weeks and the median study follow-up time was 7.2 years (range, 2–10 years). Ten cases recurred after a median delay of ten months. Interestingly, among them four were due to a different pathogen (3 methicillin-resistant, 1 methicillin-susceptible *S. aureus*) than the one identified at first diagnosis. Demographic characteristics were equally distributed between patients with remission and recurrence, with one exception. Immune suppression was statistically more prevalent in the recurrence group (Table 1).

Multivariate analysis

Because of the heterogeneity of the study population and therapeutic approaches, we performed a multivariate logistic regression analysis to adjust for this case mix.

No demographic or surgical variable showed significant association with remission (Table 2). Of note was the observation that steroid-induced immune suppression showed a trend for more frequent recurrence in the univariate, but not in the multivariate analysis. Diabetes mellitus did not influence this trend. No antibiotic related parameters revealed statistical association with remission: One week of intravenous therapy had the same success as two to three weeks (odds ratio 0.2, 95% confidence interval 0.1–1.9) or more than three weeks (0.3, 0.1–2.4). Regarding total antibiotic therapy, a duration stratified at a cut-off of six weeks was insignificant. Compared to less than six week's therapy, a prolonged antibiotic administration beyond six weeks revealed an odds ratio of 0.8, 95%CI 0.1–5.2. When stratifying the variable "total antibiotic duration" into more detail, four weeks of total antibiotic treatment had the same outcome as four to six weeks (0.8, 0.1–14.8), seven to 12 weeks (1.1, 0.1–14.4) or more than 12 weeks (0.8, 0.1–12.3). We equally failed to detect linearity or a threshold level for antibiotic duration and remission.

Our final model yielded a non-significant goodness-of-fit test and a receiver operating curve (ROC) value of 0.8 (95% confidence interval, 0.6–0.9).

Discussion

We report our experience in the management of 49 episodes of chronic implant-free osteomyelitis among adult orthopaedic patients. Our remission incidence of 80% was similar to the literature [10], where remission "rates" vary between 60% [14] and 90% [4, 7, 15] with a peak around 80% [8, 9]. Of note, high remission reports are often seen in

Table 1 Characteristics and comparison of the patient groups with recurrence and remission after treatment of osteomyelitis

Patients, n=49	Recurrence, n=10	Comparison, p value[a]	Remission, n=39
Female sex	1		8
Median age	48 years		40 years
Median Charlson Index	2 points		1 point
Immune suppression[b]	6	0.039	10
- Diabetes mellitus	3		7
- Insulin-dependent diabetes mellitus	0		4
Infection			
CRP value on admission	22 mg/L		16 mg/L
Purulent discharge of sinus tract	5		19
Presence of sequestra	1		14
Polymicrobial infection	6		8
Staphylococcus aureus	5		15
- Methicillin-resistant *S. aureus*	1		7
Gram-negative pathogens	1		12
Treatment			
Median no. of surgical interventions	2		2
- Use of gentamicin beads	2		14
- Intramedullar reaming	1		6
Median duration of antibiotic treatment	56 days		56 days
Median duration of IV antibiotic treatment	16 days		8 days
Outcomes			
Median length of hospital stay	65 days		44 days

[a] Only significant p values ≤ 0.05 (two-tailed) are displayed

[b] Immune suppression = Diabetes mellitus, steroids, HIV disease

Table 2 Associations of variables with remission of osteomyelitis (logistic regression)

Variable associated with remission	Univariate analysis Odds ratio (95% confidence interval)	Multivariate analysis Odds ratio (95% confidence interval)
Age (continuous variable)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
-Age between 30 and 60 years[a]	1.1 (0.2–6.6)	n.a.
-Age over 60 years[a]	0.5 (0.1–2.7)	n.a.
Charlson Index (continuous variable)	0.8 (0.5–1.2)	n.a.
-Index with more than 2 points[b]	0.6 (0.1–2.9)	n.a.
Immune suppression[c]	**0.2 (0.1–0.9)**	0.2 (0.1–1.1)
-Diabetes mellitus	0.5 (0.1–2.5)	n.a.
CRP on admission (continuous variable)	1.0 (1.0–1.0)	n.a.
Long bone osteomyelitis	0.7 (0.2–3.4)	n.a.
Staphylococcus aureus	0.7 (0.2–3.1)	n.a.
No. of surgical interventions	0.7 (0.5–1.0)	0.7 (0.5–1.0)
-2 to 3 surgical interventions[d]	0.6 (0.1–3.8)	0.2 (0.1–2.9)
-More than 3 surgical interventions[d]	0.3 (0.1–1.9)	0.1 (0.1–1.8)
Use of gentamicin beads	2.2 (0.4–12.0)	n.a.
Intramedullary reaming	1.6 (0.2–15.4)	n.a.
Duration of antibiotic treatment (contin.variable)	1.0 (0.98–1.03)	1.0 (0.98–1.03)
- ≤6 weeks compared to >6 weeks	0.8 (0.2–3.1)	0.8 (0.1–5.2)
- 4 to 6 weeks compared to ≤4 weeks	0.3 (0.1–3.5)	0.8 (0.1–14.8)
- 6 to 12 weeks compared to ≤4 weeks	0.6 (0.1–6.0)	1.1 (0.1–14.4)
- >12 weeks compared to ≤4 weeks	0.7 (0.1–9.5)	0.8 (0.1–12.3)
Duration of IV therapy (continuous variable)	1.0 (0.96–1.03)	0.8 (0.96–1.05)
- 8 to 21 days compared to ≤7 days	0.3 (0.1–1.6)	0.2 (0.1–1.9)
- More than 21 days compared to ≤7 days	0.3 (0.1–2.1)	0.3 (0.1–2.4)

Variables in bold are statistically significant (two-tailed p value < 0.05)

n.a.=not available, multivariate analysis not performed

[a] Age groups compared to the group of less than 30 years old

[b] Charlson index compared to the group with ≤2 points

[c] Immune suppression=Diabetes mellitus, steroid medication, HIV disease

[d] Compared to a single surgical intervention

studies with short follow-up times [3], in acute haemotogenous osteomyelitis in children, or small sample sizes [4, 6, 7]. In general, comparison of treatment modalities in osteomyelitis should be interpreted with precaution, since reports are not based on standardized treatment regimens of osteomyelitis episodes that include variable definitions such as bones, pathogens, host factors and different chronicity of drainage [8, 9].

In our multivariate analysis, no variable was significantly associated with remission, albeit the presence of non-diabetic immune suppression showed a tendency for an inverse relationship. Overall, the duration of total post-debridement antibiotic treatment or of its initial parenteral part was not associated with the remission incidences. As continuous variables, antibiotic-related odds ratios and corresponding confidence intervals were often around one, indicating equality. As categorized variables, four weeks of total antibiotic treatment had the same outcome as four to six weeks or more than 12 weeks. Less than six weeks were equal to more than six weeks. Therefore, six weeks (if not less) post-debridement could be sufficient. In the literature, authors treating for three [22] to six months [10] report the same remission incidences as other authors treating for six weeks or less.

Recent retrospective data suggest that regimens with an early switch to oral antibiotics with good bioavailability are as effective as prolonged parenteral regimens; as we could confirm in our study. One week of intravenous (IV) therapy had the same success as two to three weeks or more.

For osteoarticular infections, several antibiotic agents have already proven clinical efficacy upon oral intake: quinolones [10], linezolid, clindamycin, and fusidic acid combined with rifampin. These drugs have an oral bioavailability of over 90% [23]. As clinical examples, Cordero-Ampuero et al. cured 36 arthroplasty infections with oral antibiotics administered from the start [24], and Eyichukwu et al. reported successful treatment of chronic osteomyelitis after surgery and short-term sensitivity-based IV course of two to three days, followed by oral administration [13]. A recent Cochrane review included five trials comparing oral vs. IV antibiotics for chronic osteomyelitis in adults. There was no statistically significant difference in the remission rate [9].

Our study has the following limitations: (i) It was a retrospective, single-center study with a small and heterogeneous population. Especially, the small sample size is an important issue and may hide differences that would have been seen if the analyses were performed

with a more numerous patient population. For instance, a larger sample size would have made it possible to separate those treated with gentamicin beads and the immuno-compromised from the others. This would have improved the quality of our work. However, such a sample size has never been achieved in the literature for implant-free osteomyelitis to the best of our knowledge. According to our estimation, a study population of at least 300 patients would be required to perform such separated analyses. Of note, our case series of implant-free chronic osteomyelitis is one of the largest series described in adults. (ii) Follow-up time could be too short. Recurrences of osteomyelitis after several years, if not decades, have been reported [22], and there is no internationally accepted minimal follow-up duration. Some authors argue that chronic osteomyelitis never heals, and the best you can achieve would be to control the infection or to get patients asymptomatic. In the literature, minimal follow-up times range from three months [3] to one year [7–10, 24] or to two years [4, 15]. Tice et al. showed that 78% and 95% of all osteomyelitis recurrences occur within six and 12 months, respectively [14]. Hence, we consider our individual minimal and median follow-up times of two and seven years as a strong point of our study. (iii) Patients with recurrences treated in another hospital may have been undetected. However, Geneva University Hospitals are by far the largest and only public hospitals in the area; we therefore consider this possibility as low. (iv) The completeness of initial surgical debridement is of paramount importance [4]. Surgeons know how extensively they should perform this debridement. There are no retrospective possibilities to estimate the completeness of such a debridement. (v) Staphylococcal small-colony variants are considered as a risk factor for persistence of bone infections. We could not assess their presence, since our specimens had not been stored. (vi) Our definition of chronic osteomyelitis was rather oriented on a surgical point of view rather than on a radiological or internistic definition. Our cases evolved over at least three months, were only primary episodes, revealed the presence of bone abscesses and identified a pathogen in every case. This working definition might be too rigorous. Especially, the need for pathogen identification excludes culture-negative cases. However, we intended to be absolutely sure about chronic infectious osteomyelitis, for which the confirmation of pathogens in at least three bone samples (abscesses) was considered as essential for this manuscript. Of note, the specific literature lacks an internationally accepted definition [8]. (vii) Despite adjustment for case-mix, we cannot completely exclude therapeutic decision bias. Patients, who were doing less well, might have deserved a longer antibiotic treatment. This theoretical bias reinforces the need for prospective trials.

Our findings may have implications to tailor such future randomized trials. If our retrospective results are confirmed, a shorter or oral antibiotic treatment post-debridement could further decrease antibiotic consumption, as well as the related costs, adverse effects and selective pressure for resistant bacterial pathogens.

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