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How to cite

LAUPER, Nicolas et al. Native septic arthritis is not an immediate surgical emergency. In: Journal of Infection, 2018. doi: 10.1016/j.jinf.2018.02.015

This publication URL: https://archive-ouverte.unige.ch/unige:104798
Publication DOI: 10.1016/j.jinf.2018.02.015

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PII: S0163-4453(18)30134-8
DOI: 10.1016/j.jinf.2018.02.015
Reference: YJINF 4098

To appear in: *Journal of Infection*

Received date: 3 May 2017
Revised date: 21 January 2018
Accepted date: 7 February 2018

Please cite this article as: Nicolas Lauper MD , Marie Davat MD , Ergys Gjika MD , Camillo Müller MD , Wilson Belaieff MD , Didier Pittet MD, MS, CBE , Benjamin A. Lipsky MD, FACP, FIDSA, FR Didier Hannouche MD , Ilker Uçkay MD , Native septic arthritis is not an immediate surgical emergency , *Journal of Infection* (2018), doi: 10.1016/j.jinf.2018.02.015

Highlights

- Acute native joint bacterial arthritis is an emergency for arthrocentesis or surgical lavage
- The degree of this emergency is not known
- Our strudy suggest that a delay of several days does not influence infection remission or post-infectious sequels

Native septic arthritis is not an immediate surgical emergency

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Word count: 3857 words + 3 Tables

Running title: Surgical delay in arthritis drainage

#The material presented in the paper has not been previously published, nor has it been submitted elsewhere for publication. The data presented are the work of all authors listed. None of the authors have any conflict of interest or financial interest in connection with this work. All authors have seen, approved, and contributed to the manuscript. There was no funding for this study.

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Keywords: *septic arthritis; emergency surgery; functional outcome; treatment*

ABSTRACT

Summary Acute native joint septic arthritis is generally considered a surgical emergency, requiring drainage within hours, including during night, weekend or holiday shifts. However, there are few data supporting the need for the disruption caused by this degree of urgency.

Methods We performed a retrospective review of all adult patients seen in our medical center from 1997-2015 with culture-proven septic arthritis and noted the epidemiology of sequelae, and their possible association with a delay in surgical drainage.

Results Of 204 septic arthritis episodes, 46 (23%) involved interdigital hand and foot joints. Large joints involved included the knee (n=67), shoulder (48), hip (22), ankle (8), acromio-clavicular (5), elbow (4), wrist (3), and sterno-clavicular (1) regions. All patients underwent surgical drainage of the joint and received targeted systemic antibiotic therapy. Sequelae of varying severity occurred in 83 patients (41%): recurrences (n=15); secondary arthrosis (30); persistent pain (9); Girdlestone procedure (9); arthrodesis (9); amputation (8); stiffness (8); and Chronic Regional Pain Syndrome (2). By multivariate Cox regression analysis factors did *not* predict sequelae included: age; treatment with systemic corticosteroids; pre-existing clinical or radiological arthropathy; total duration of antibiotic therapy; type of joint; and, number of surgical interventions. Similarly, there was no association of sequelae with the number of days of pre-hospitalization joint symptoms (hazard ratio 1.0, 95% confidence interval 0.99-1.01) or hours spent in the emergency department (HR 1.0, 0.9-1.2). Notably, patients who had joint lavage within 6 hours of presentation had similar functional outcomes as those with lavage done at 6-12 hours, 12-24 hours, or >24 hours after presentation.

Conclusions Our data suggest that for native septic arthritis, in the absence of clinical sepsis immediate joint drainage does not appear to reduce the risk of sequelae compared with delayed drainage.

Introduction

Acute native joint septic arthritis is typically considered a medical emergency, requiring urgent surgical intervention to help reduce cartilage damage and to preserve good long-term joint function [1-10]. Both surgeons and physicians are taught that they should ensure joint drainage is performed within hours after hospital admission, even in the absence of clinical evidence of sepsis or during night, weekend or holiday shifts. Emergent surgical treatment of patients with septic arthritis, independent of the time elapsed between the onset of symptoms and admission, may actually be detrimental, especially for elderly bedridden patients. Furthermore, mobilizing the specialists to properly drain a septic joint can be time-consuming and costly. Although this recommendation has been widely and repeatedly made in the surgical literature, there are few data supporting the need for urgent surgical lavage of a septic joint [4-8].

In a previously published study of antibiotic treatment of septic arthritis [9], we found that the incidence of long-term adverse sequelae of this infection was 26%. By regression analysis we found no variable that was significantly associated with sequelae, suggesting that treatment modalities play less of a role in determining outcomes than the patient's baseline characteristics. This previous study was not, however, specifically designed to address that issue. In the current large follow-up study, our aim was to investigate the effect of delay in the first surgical drainage of septic arthritis on long-term functional and radiological outcomes. We did not investigate the separate issue of mortality in cases of haemodynamically compromising sepsis [10,11].

Methods

Setting

The Geneva University Hospitals is a large general and referral medical center with an Orthopedic Service of 135 acute care beds. Our usual procedure for treating patients hospitalized for septic arthritis is to perform a joint lavage as a surgical emergency, on all days and during all shifts. At the surgeon's preference, this lavage may be performed by either an arthroscopic or open arthrotomy approach. As we have previously documented, in cases of severe infection or in those expected to have an unfavorable course, the surgeons usually perform a re-intervention, often with a synovectomy [12]. For pain relief patients are routinely treated with paracetamol and ibuprofen [13], and with morphine or tramadol prescribed when needed. These medications are not selected for their anti-inflammatory effects, and we avoid administering corticosteroids [14] for adults with septic arthritis.

Study design

We conducted a retrospective, single-center cohort study based on reviewing the records of all adult patients hospitalized with acute native joint septic arthritis between January 1997 and November 2015 who had follow-up for at least 3 months. To exclude cases of arthritis caused by viral pathogens [15], crystal-related or immune-triggered diseases, we included only patients whose infections were characterized by purulent synovial fluid and growth of bacteria from an intraoperative joint specimen. We did include patients with crystalline disease concomitant with proven septic arthritis [16]. To avoid likely confounders, we excluded patients with the following conditions: recurrent arthritis [9]; contraindication to surgical drainage [9,12]; active rheumatic polyarthritis or rheumatic fever; presence of a joint implant [17]; contiguous osteomyelitis at the time of hospitalization; vascular necrosis; bone neoplasm; idiopathic bone marrow edema; adjacent bone trauma; hemophilia; haemochromatosis; sickle cell disease; Perthes disease; amputation as the primary therapeutic

approach [18]; infection believed to be viral, fungal, mycobacterial [19], mycoplasmal, gonococcal, brucellar, parasitic [20], nocardial [21]; and, pediatric cases.

One or more of three surgeons (NL, MD, DS) and an infectious diseases consultant with expertise in osteoarticular infections (IU) used an Excel® spreadsheet to independently record data on each patient's demographics, treatment, and outcomes. They resolved any disagreements between reviewers by consensus. We recorded the following key outcomes of interest: estimated duration of work leave; radiological changes of the joint; need for subsequent joint surgery for mechanical reasons; infectious recurrences; and, pain or reduced function of the affected joint during daily activities. We defined the occurrence of any one of these variables as a "sequela" after the end of first scheduled treatment. Treatment or complications occurring during the initial episode of septic arthritis were not defined as sequelae. For example, an additional surgical intervention during the initial hospitalization for treatment of acute septic arthritis was not counted as a sequela. We elected to use the above-cited objective parameters rather than a questionnaire that we previously developed [5]. This was to avoid the risk of misinterpreting subjective parameters during the long retrospective look-back period of this study. We closed the databases on 30 December 2016.

Statistical analyses

We compared groups using the Pearson-χ^2-test or the Wilcoxon-ranksum-test. We used Cox regression to determine if there were any associations with the outcome sequelae. Each episode of septic arthritis was censored when one of the following occurred: the patients's last follow-up visit to our hospital; patient death; subsequent corrective surgery; or, infection recurrence. To determine if there were independent risk factors, we introduced in a stepwise fashion each variable that achieved a p value ≤ 0.2 by univariate analysis into multivariate

models. An exception to this procedure was that we always included the variables for surgical interventions, antibiotic treatment, and time delays in our final model. Based on these criteria, variables included in the multivariate analysis and retained in the final model were: age; use of corticosteroid medication; infection with *Staphylococcus aureus*; pre-existing arthropathy; number of surgical interventions; duration of intravenous antibiotic treatment; total duration of antibiotic therapy; and, time delays to surgical drainage. We assessed any time delays as categorical and continuous variables, i.e., a delay between admission and surgery was expressed in hours, in days, and as the time to the best of the patient's recollection from the onset of arthritis and the first surgery. In order to exclude treatment biases throughout the study period, we stratified the study period into 1997-1999, 2000-2004, 2005-2009 and 2010-2015. To further exclude biases related to the chief surgeon in charge of the septic orthopedic unit, we created a dichotomous variable corresponding to the years of service of the chief surgeon (periods 1997-2012 and 2013-2015). We did the same regarding the dedicated infectious diseases physician (periods 1997-2000, 2001-1006, and 2007-2015). We also graphically plotted the time delay against any sequelae. We included 8 predictor variables per outcome event and checked key variables for collinearity and for interaction (by Mantel-Haenszel estimates and interaction terms). We used STATA software (9.0, STATA™, USA) and considered *p* values (two-tailed) ≤0.05 as significant.

Literature search

To seek information on any previous publications examining outcomes and sequelae of septic arthritis, we performed a non-systematic literature search of papers published in PubMed from 1995 to 2015. We used the MeSH terms "native," "septic arthritis", "surgery", and "delay" in combination with "sequels", "sequelae", "impairment" or "functional outcome" and retrieved all English-language publications. We hand-searched references of retrieved

papers for additional relevant articles. We excluded articles about implant-related infections and those that reported on fewer than 20 cases.

Results

Patients' characteristics

We identified 345 episodes admitted with suspicion of septic arthritis. Of these, 97 were probably not bacterial (absence of microbiological proof of bacterial arthritis and absence of historic context of intraarticular bacterial infection) and rather corresponded, according to clinical evaluation by infectiology and rheumatology specialists, to non-bacterial etiologies such as gout (n=16), chondrocalcinosis (14), advanced osteoarthritis (11), rheumatologic diseases (6), reactive arthritis (4), ruptured Baker cysts (3) or undetermined reasons (43). Among the remaining 248 suspected bacterial cases, 44 (18%) were culture-negative and were excluded from the main analyses. Finally, we included 204 culture-positive episodes (204/248; 82%) into the study. The median age of the patients was 63 years (range 18-97); 70 (34%) were women. There was an immune compromising condition in 72 (35%) of the patients, the most common being: diabetes mellitus (n=37); active cancer (12); chronic treatment with corticosteroid medication (9); untreated human immunodeficiency virus (HIV) disease (9); renal dialysis (9); advanced cirrhosis (6); solid organ transplantation (5); alcohol dependency (4) and, pregnancy (1). In 20 patients there was more than one immune suppressing condition. There were documented psychiatric problems in 38 patients, among whom 22 abused intravenous drugs. A total of 95 (47%) patients reported having a profession that required daily physical activity, and 111 (54%) reported problems in the affected joint prior to infection, of whom 56 (27%) had documented osteoarthritis (arthrosis). Other relevant preexisting complaints included: ligament ruptures (n=9); chondrocalcinosis (4); gout (4);

previous fractures (13) or bone cysts (2). Overall, 170 (71%) of the patients stated that they were “mobile in daily life” prior to infection.

Involved joints

The involved joint was an interdigital hand or foot joint in 46 (23%) patients. Large joints involved included the knee (n=67), shoulder (48), hip (22), ankle (8), acromio-clavicular (5), elbow (4), wrist (3), and sterno-clavicular (1) joints. The median serum C-reactive protein level upon admission was 180 mg/L (normal values in our hospital are 10 mg/L) and 82 patients (40%) of all enrolled patients were bacteremic. The median intra-articular leucocyte count was 40,000 cells/mm^3 and microscopists noted various types of crystals (mostly calcium pyrophosphate) in 25 episodes. In 109 patients (53%), a Gram-stained smear of an intraoperative specimen demonstrated microorganisms (16). Pre-drainage administration of systemic antibiotic therapy was documented in 73 patients (36%). The origin of the joint infection remained unknown in 63 septic arthritis episodes (31%). In 111 patients, septic arthritis was due to nosocomial surgical site infections (n=48), whereas trauma/bites appeared to be causative in 29 cases, and 11 episodes were related to intravenous drug abuse. The remaining cases were caused by haematogenous seeding from a remote site of infection, e.g. catheter-related (3) or urological sepsis (8).

Causative pathogens

Half of all episodes (105/204; 51%) were monomicrobial infection caused by *S. aureus*. Of these isolates 14 (13.3%) were methicillin-resistant strains (MRSA), only one of which was community-acquired. Streptococci caused 56 infectious episodes (27%), 18 of which were *S. pyogenes* and 10 *S. agalactiae*. Gram-negative pathogens were present in 35 (17%) of cases,

the most common of these etiologic agents being *Escherichia coli* (11) and *Pseudomonas aeruginosa* (5).

Treatment

All patients underwent both surgical interventions and treatment with pathogen-targeted systemic antibiotic therapy. No local antibiotic were added to the joint irrigation.

Surgical. Lavage was performed arthroscopically in 28 episodes (14%), and by arthrotomy in 176 episodes (86%). Surgical re-intervention was undertaken in 42 episodes (21%), after a median delay of 3 days (range, 1-26). The median number of "second look" surgeries was 1 (range, 0-11 interventions). The median delay between the reported onset of arthritis and the first joint surgery was 6 days (range, 0-214). The overall median delay between admission to the hospital and joint lavage was 18 hours (range 1 hour-19 days), including conditions of nosocomial acquisition. For nosocomial cases in patients already hospitalized for another reason, the median delay until surgery was 2 days, and for those entering via the emergency department it was 7 hours (range, 1-23).

Antibiotic. Overall, patients received a total of 117 different oral or parenteral antibiotic regimens. Flucloxacillin, glycopeptides and amoxicillin-clavulanate were the most frequently prescribed agents for parenteral use, while ciprofloxacin and clindamycin were the most frequently used for oral therapy. The median duration of systemic antibiotic therapy was 42 days (range, 5-123), of which a median of 14 days was given intravenously (range, 0-91 days).

Outcomes

The median overall follow-up time was 1.8 years (range, 0.25-18.67). During the follow-up period 41 patients (20%) died, but death was related to sepsis in only patient. Seventy-eight patients (38%) needed reeducation. The median duration of sick leave taken by patients for their septic arthritis infection was 37 days (range, 19-200). At the end of follow-up 189 episodes (189/204, 93%) were in remission. Proven infectious recurrences with the same pathogen occurred in only 15 patients (7%), of whom five had adjacent osteomyelitis. There were no secondary joint infections caused by another pathogen following the first episode of arthritis. However, 83 patients (41%), including the 15 with a recurrence, had at least one sequelae; these included osteoarthritis (arthrosis) (in 30), persistent pain at last follow-up (9), requirement for a Girdlestone hip procedure (9), arthrodesis (9), amputation (8), stiffness (8), or Chronic Regional Pain Syndrome (2). Seven patients suffered from two or more sequelae. Standard X-rays taken during and after the patients' hospitalization were available for 126 episodes. Clear radiological evidence of osteoarthritis was seen in only 3 patients (2%) on admission, but was apparent among 48 patients (38%) after treatment ($p<0.001$).

Comparisons and case-mix adjustments

In Table 1 we have compared the patient populations with and without sequelae. Variables that were significantly associated with sequelae were: immune-suppression; sedentary lifestyle or profession; pre-existing arthropathy; and, new radiological osteoarthritis. Of note, the time delay between admission and surgery was not significantly related to the development of sequelae. A plot we constructed comparing delay of surgery against functional impairment demonstrated no threshold associated with the occurrence of sequelae (not shown).

Due to the heterogeneous patient population, we adjusted for case-mix by multivariate Cox regression analysis (see Table 2). None of the variables we investigated was significantly associated with sequelae. Specifically, there was no association with age, use of corticosteroid medication, pre-existing clinical or radiological arthropathy, total duration of antibiotic administration, treatment with parenteral (versus oral) antibiotic therapy, or number of surgical interventions. Likewise, there was no association of sequelae with the duration of symptoms in days (hazard ratio 1.0, 95% confidence interval 1.0-1.0) or the delay in hours within the emergency department (hazard ratio 1.0, 95% confidence interval 0.9-1.2). A delay before joint drainage of less than 6 hours had the same effect as delays of 6-12 hours, 12-24 hours, or greater.

Literature search

Our search found a total of 27 papers that met our criteria; for the 15 that addressed our study question (i.e., the effect of delay in joint drainage on outcomes) we summarized key data in Table 3. Among 733 cases from a variety of settings in the reports we included, the most common causative pathogen was *S. aureus*, followed by streptococci. The studies reported sequelae in between 16% and 63% of cases, with an average rate of about 35%. Of note, four of the studies reported a delay in treatment as a cause of sequelae.

Discussion

Among the 204 cases of septic arthritis hospitalized at our medical center over 18 years we found that 41% had at least one long-term sequela related to the infection. This finding is in line with most of the previously reported series in the literature, but the published results vary and depend on the severity of the infections reported (Table 3). Of note, however, we found no evidence that the time between onset of symptoms or diagnosis of infection and the first

surgical lavage was related to the likelihood of developing sequelae. All of our stratified analyses, including duration of symptoms, time delay between admission and first surgery (in hours or days, or as categorical or continuous variables) showed that these parameters were not associated with future problems affecting the infected joint. Specifically, a delay between diagnosis and surgery of less than 6 hours was associated with the same functional outcomes as delays of 6-12 hours, 12-24 hours, or longer. As a result of these findings, we have become more reluctant to urge every patient with septic arthritis to undergo emergency surgery, especially if the patient is already under antibiotic coverage, has no clinical evidence of sepsis or long-lasting symptoms, or if mobilizing the necessary team and operating room time is difficult.

The rational for immediate lavage appears to be based on animal studies conducted in the last century. Observations from rabbit and bovine models of staphylococcal arthritis demonstrated that the cartilage is rapidly destroyed: >45% chondrocyte death at 40 hours [22] and 50% cartilage loss in three weeks [23]. This destruction appears to be associated with a variety of mediators, such as synovial RANKL expression, mast cells and pro-inflammatory cytokines [14]. Furthermore, activated leucocytes, the synovium and infecting bacteria produce destructive enzymes. These, coupled with a recently detected delayed immune response, suggest damage will continue even if there are no viable bacteria in the joint [24]. Studies in experimental animals suggest that antibiotic treatment reduces joint damage if administered within 12 hours post-infection. Corticosteroids and non-steroidal anti-inflammatory drugs such as naproxen can reduce collagen loss by another 50%, compared with antibiotic treatment alone [13]. Experimental models demonstrate that one day of antibiotic delay can lead to a 37% loss of joint collagen, despite adequate medication dosing [23].

What is the clinical evidence in humans? The available literature has primarily investigated the duration of patient symptoms prior to surgery, rather than the time they spent waiting in the emergency department. Many patients with septic arthritis may wait several days or weeks [10], with [25,26] or without antibiotic treatment, before being admitted for joint surgery. In our region, 42% of all infected patients were already receiving antibiotic therapy before they underwent emergency orthopedic surgery [27]. In clinical studies, the cut-off time before the occurrence of deleterious effects on the joint has usually been set at 2 or 3 weeks, not hours or a few days (Table 3). To cite examples, Vispo-Seara et al. demonstrated that advanced cartilage damage in patients infected by *S. aureus* or various bacteria was significantly correlated with a cut-off of longer than 2 weeks between onset of infection and surgery [3]. To the contrary, an extensive literature review of pneumococcal arthritis by Ross et al. did not find that a time delay before surgery was associated to poor functional outcome [28]. Angly et al. identified the cartilage damage observed intraoperatively was the most important risk for long-term joint sequelae. While they did not report any specific delay threshold, their median delay was 4 days (range, 1-550 days) [29]. Balabaud et al. reported that the mean delay before surgery was significantly shorter (12 days) in patients who had good functional results after knee infection compared to cases classified as failures (23 days), but it was not possible to define a specific temporal cut-off value [30]. Klinger et al. suspected that patients with shoulder septic arthritis had better scores if their symptoms had begun ≤2 weeks prior to surgery [31], while the Oxford group identified a cut-off of ≥3 week's delay before surgery as predictive for the need for femoral head excision [1]. Interestingly, the recommendation by experts is that a delay of >3 weeks usually requires the implant to be removed in cases of acute prosthetic joints infection [17].

Many publications failed to identify whether or not there was any delay before surgery for septic arthritis [32]. Shorter cut-off durations, such as 3 days, are primarily reported in cases of hand joint infections, and the sequelae of interest are usually digital stiffness [26]. Finally, a study of neonates found worse radiological, but not clinical, outcomes when the overall duration of symptoms prior to presentation was longer, but the authors provided no specific cut-off duration [33]. One common finding of these studies is that the patients were already symptomatic for several days before they were first seen, and the proportion of the time they spent in the hospital was a small part of the total duration of the symptoms, independently of how quickly they underwent surgical lavage. Using multivariate analyses to adjust for case-mix and additional confounders, this study corroborated our expected finding that no specific facet of antibiotic or surgical treatment was associated with the incidence or type of sequelae [9]. Surprisingly, however, outcomes were not worse in patients who had concomitant corticosteroid medication [14] or staphylococcal infection. There is controversy in the published literature about the influence of causative pathogen in sequelae of septic arthritis [34]. A comprehensive review of bacterial arthritis lists the following factors as potentially associated with sequelae: preexisting joint diseases; very young or old age; immune-suppressive medication; hip involvement; polyarticular infection; Gram-negative bacteria infection; a positive blood culture; and, the presence of a joint implant [32]. However, our data do not confirm any of these factors as being associated with sequelae of septic arthritis.

Radiologic changes in cases of arthrosis (osteoarthritis) or adjacent osteomyelitis may occur rapidly. In a study of 96 episodes of septic arthritis among young children, radiological changes in the bone were noted in 21 (22%) by two weeks after presentation, and in a further 10 cases by six weeks [35]; this is similar to the evolution we found in our study. In an evaluation of 72 knee joints, Vispo-Seara et al. found that there was no radiological deterioration in most of the patients, and only five (7%) showed worsening [3]. In contrast,

their clinical outcome was excellent or good [3]. When adjusting for case-mix, these radiological changes may not be associated with any clinical impairment, as noted by other research groups [33].

Our study has limitations, the most important being its retrospective nature. Furthermore, it is a single-center study conducted in a resource-rich setting, which limits the generalizability of our findings. Nevertheless, a randomized trial to address the question of possible association between early surgical intervention and septic arthritis sequelae is impractical and likely to be rejected by an ethical committee. Our study design cannot control for some additional parameters, such as intraoperative severity scores [5,30], functional assessments [36] or radiologic scores [33]. We may also have missed long-term sequelae among patients who were treated at another center after initial surgery at ours. However, because our center is both the referral center and the largest hospital in the region, and the only public hospital, this is unlikely. We also did not investigate rheumatologic approaches, e.g., repetitive arthrocenteses [37], or alternative surgical techniques, e.g., continuous irrigations [4]. Our exclusion of culture-negative cases, recurrent episodes and implant-related arthritis, also limits the generalizability of our results. Indeed, we had identified 345 episodes admitted with suspicion of septic arthritis. Of these, 97 were probably not bacterial and corresponded to other forms of arthritis according to the clinical evaluation of infectiology and rheumatology experts. These 97 cases did not have any proof of bacterial presence in the sampled joints. Among the remaining 248 suspected bacterial cases, only 44 (18%) were culture-negative. Finally, we included 204 culture-positive episodes (204/248; 82%) into the study. However, we also run the statistical analyses with the 248 presumed bacterial cases. The computing of these 44 additional culture-negative cases did not change the occurrence of outcome « sequels » (*data not shown*). Our data do not apply to prosthetic joint associated arthritis [11,17]. Finally, we

cannot exclude bias in terms of confounding by indication, e.g., patients who were doing well could be those who were treated with short antibiotic courses. However, with such a large case-mix in the background, we elected to not use propensity scores to counterbalance confounding by indication.

In conclusion, septic arthritis patients arriving at the hospital usually suffer from their infection for several days. Provided that they do not have signs of clinical sepsis, and especially if they are already receiving empiric antibiotic treatment, subjecting the patient to immediate surgical drainage does not appear to prevent long-term joint-related sequelae. Interventions can safely be organized for the next day, liberating resources during busy night shifts, and enabling patients to be operated by fresh teams the following day and in better medical conditions when co-morbidities pre-operative corrective interventions.

Acknowledgements

We thank the teams of the Geneva University Hospital Laboratory of Bacteriology and the Orthopaedic Service for their invaluable help.

Funding

No specific funding has been received for this study.

Transparency declarations and potential conflicts of interests

There are no grants, financial support or interests, consultancy, commercial or other associations that could lead to a conflict of interest regarding this study. IU has received unconditional research donation from Innocoll with no relation with the present work. All authors have read and approved the manuscript.

IU had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1 - Comparing patients with and without sequelae after the treatment of native joint septic arthritis; University of Geneva Hospitals, 1997-2015

n = 204	**No sequelae** **n = 121**	***p* value***	**Sequelae** **n = 83**
Female sex	46 (38%)	ns	24 (29%)
Median age	63 years, IQR 48-75	ns	63 years, IQR 44-75
Interdigital arthritis	24 (20%)	ns	23 (28%)
Pre-existing arthropathy	58 (48%)	0.025	53 (64%)
- Known osteoarthritis (arthrosis)	30 (25%)	ns	26 (31%)

Physically active profession	48 (40%)	0.017	47 (57%)
- Mobile and active lifestyle	112 (93%)	0.001	58 (70%)
Immune suppression[+]	36 (30%)	0.046	36 (43%)
- Diabetes mellitus	17 (14%)	ns	20 (24%)
Psychiatric co-morbidities	18 (15%)	ns	20 (24%)
- Intravenous drug abuse	15 (12%)	ns	7 (8%)
Median serum C-reactive protein level	211 mg/L, IQR 80-316	ns	138 mg/L, IQR 64-311
Median intraarticular leukocyte count	38,873 cells/mm^3	ns	45,785 cells/mm^3
Bacteraemia detected	55 (46%)	ns	27 (33%)
Presence of intraarticular crystals	15 (12%)	ns	10 (12%)
Prior radiological osteoarthritis	38 (31%)	ns	34 (41%)
Positive Gram-stain intraarticular fluid	65 (53%)	ns	44 (53%)
Positive intraarticular culture for:		ns	
- *Staphylococcus aureus*	67 (55%)		38 (46%)
- Streptococci	34 (28%)	ns	22 (27%)
- Gram-negative bacilli	21 (17%)		14 (17%)
Median no. of surgical interventions	1, IQR 1-1	0.003	1, IQR 1-1
- Arthrotomy compared to arthroscopy	104 (86%)	ns	72 (87%)
- Second look procedure	19 (16%)	0.037	23 (28%)

Median duration of antibiotic treatment	39 days, IQR 29-42	ns	42 days, IQR 32-49
- > 28 days compared to ≤ 28 days	92 (76%)	ns	64 (77%)
Median duration of intravenous treatment	13 days, IQR 5-24	ns	16 days, IQR 5-32
- > 10 days compared to ≤ 10 days	68 (56%)	ns	52 (63%)
Median delay: onset to surgery	5 days, IQR 2-10	0.007	7 days, IQR 4-18
- duration > 7 days compared to ≤ 7 days	38 (31%)	0.015	40 (48%)
Median delay admission to surgery	2 days, IQR 1-6	ns	2 days, IQR 1-4
- > 3 days compared to ≤ 3 days	78 (64%)	ns	58 (70%)
Median time admission to surgery	21 hours, IQR 8-52	ns	16 hours, IQR 6-43
Delay in emergency department	7 hours, IQR 5-14	ns	6 hours, IQR 4-12
Recurrence of infection	4 (3%)	0.007	11 (13%)
New radiological osteoarthritis	34 (28%)	0.022	39 (47%)

Categorical variables are displayed as numbers with percentages (%)

Continuous variables are displayed as median values with interquartile ranges (IQR)

*Only significant *p* values ≤ 0.05 (two-tailed) are displayed. ns = not significant

[+]Immune suppression = Diabetes mellitus, steroids, organ transplantation, HIV disease, advanced cirrhosis, dialysis, pregnancy, cancer

Table 2 – Factors associated with sequelae after native joint septic arthritis (Cox regression analysis)

	Univariate analysis	**Multivariate analysis**
n = 204	Hazard ratio (95% confidence interval)	Hazard ratio (95% confidence interval)
Female sex	0.7 (0.5-1.2)	-
Age (continuous variable)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Interdigital arthritis	1.3 (0.8-2.2)	-
Late study period versus early*	1.0 (0.4-2.0)	1.0 (0.5-1.9)
Pre-existing arthropathy	1.5 (0.9-2.1)	1.3 (0.8-2.2)
Immune suppression[+]	1.3 (0.9-2.1)	-
- Prednisolone medication	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Intraarticular fluid leukocyte count	1.0 (1.0-1.0)	-
Bacteraemia detected	1.1 (0.7-1.8)	-
Prior radiological osteoarthritis (arthrosis)	1.3 (0.8-2.1)	1.2 (0.8-2.1)
Positive intraarticular culture for*:*	1.0 (0.7-1.6)	0.8 (0.5-1.4)
- *Staphylococcus aureus*		
- Streptococci	0.8 (0.5-1.4)	-
Gram-negative pathogens	0.8 (0.5-1.5)	
Treatment by late chief surgeon*	0.5 (0.2-1.5)	0.6 (0.3-1.2)
Treatment by late infectious diseases physician*	0.6 (0.3-1.6)	0.6 (0.3-1.5)
Number of surgical	1.0 (0.9-1.1)	1.0 (0.9-1.2)

interventions		
- Second look	1.4 (0.9-2.3)	
Duration of antibiotic treatment	1.0 (1.0-1.0)	1.0 (1.0-1.0)
- > 28 days compared to ≤ 28 days	0.6 (0.3-1.0)	-
Duration of intravenous treatment	1.0 (1.0-1.0)	1.0 (1.0-1.0)
- > 10 days compared to ≤ 10 days	0.9 (0.6-1.5)	-
Pre-hospital delay until-surgery	1.0 (1.0-1.0)	1.0 (1.0-1.0)
- duration > 7 days compared to ≤ 7 days	1.0 (0.6-1.5)	-
Delay admission to surgery	1.0 (0.9-1.1)	-
- > 3 days compared to ≤ 3 days	1.1 (0.7-1.8)	-
Delay admission to surgery	1.0 (0.9-1.1)	1.0 (0.9-1.2)
- ≤ 6 hours	-	0.9 (0.4-1.8)
- > 6 hours to ≤ 12 hours	-	0.9 (0.4-2.1)
- > 12 hours to ≤ 24 hours	-	0.8 (0.5-1.4)

[+]Immune suppression = Diabetes, steroid medication, organ transplantation, HIV disease, advanced cirrhosis, dialysis, pregnancy, cancer.

Statistically significant results are displayed ***in italic and bold.***

* Comparisons of the last period with previous ones. Late period = 2010-2015, late chief surgeon of septic orthopaedics = 2013-2015, late infectious diseases physician dedicated for septic orthopaedics = 2007-2015.

Table 3. Clinical outcome of native joint bacterial arthritis. Non-exhaustive English-language literature review 1995-2015

First author / year	No. cases	Population	Setting	Main pathogen	Sequelae	Main reasons for sequelae	Cut-off in delay?
Kaandorp [32] 1997	154	Mixed	Multisite	*S. aureus*	51 (33%)	Preexisting joint disease	none
Vispo-Seara [3] 2002	88	Mixed	University	*S. aureus*	34 (39%)	Delay > 2 weeks	2 weeks
Wang [34] 2003	58	Children	University	*S. aureus*	10 (17%)	*S. aureus*	none
Ross [28] 2003	77	Pneumococcal	Literature review	*S. pneumoniae*	20 (26%)	not reported	not reported
Sinha [26] 2006	26	Hand joints	Regional	streptococci	14 (54%)	Delay > 3 days	3 days
Akinyoola [38] 2006	93	Children	University	*S. aureus*	70 (63%)	Multiple	none
Angly [29] 2007	29	Adult digits	Regional	*S. aureus*	13 (45%)	Cartilage damage	none
Balabaud [30] 2007	33	Adult knees	Regional	*S. aureus*	16 (48%)	Delay > 12 days	none
Matthews [1] 2008	20	Adult hips	University	*S. aureus*	5 (25%)	Hip destruction	3 weeks
Klinger [31] 2010	23	Adult shoulders	University	*S. aureus*	All somehow	Delay > 2 weeks	2 weeks
Yanmış [5] 2011	20	Adult knees	University	*S. aureus*	6 (30%)	Gächter Score ≥ 3	none
Kodomuri [10] 2012	82	Adults	University	*S. aureus*	19 (23%)	Unknown	none
Lee [33] 2015	31	Infant hips	University	*S. aureus*	5 (16%)	Unidentified	none
Makhni [36] 2015	203	Adult knees	Literature review	staphylococci	75 (37%)	Degeneration in x-ray	none

Present study	*204*	*Adults*	*University*	*S. aureus*	*83 (41%)*	*None, unidentified*	*none*

Implant-related infections and papers reporting about less than 20 cases were excluded