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Late sequelae of osteoarticular infections in pediatric patients

A single-center study

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Abstract

To review the orthopedic sequelae of pediatric patients diagnosed with osteoarticular infections (OAIs) and identify significant differences between those with and without sequelae.

Medical charts between 2010 and 2016 from a tertiary-care pediatric hospital were reviewed to collect demographic and clinical data for this retrospective case series. The main inclusion criteria were:

1. age (≤10 years old);
2. absence of sickle cell anemia and immunocompromising disease or medication;
3. a minimum follow-up of 12 months with radiographs; and
4. diagnosis of osteomyelitis of long bones and/or septic arthritis.

The following late sequelae were observed and aggregated: osteal deformations that led to limb-length discrepancies (LLD) superior to 5 mm, abnormal articular angulations of more than 5°, and symptomatic chondropathies visible on imaging studies after 1 year. The patients were divided into 2 subgroups: with and without sequelae. Chi-Squared tests were used for categorical variables and Mann–Whitney *U* tests for continuous data to identify statistically significant differences between the 2 subgroups.

Among 401 patients with osteomyelitis and/or septic arthritis, 50 (12.5%) were included (24 girls and 26 boys). There were 36 (72%) cases of osteomyelitis, 8 (16%) cases of septic arthritis, and 6 (12%) cases of combined infection (3 acute/subacute and 3 chronic cases). Five (10%) patients had orthopedic sequelae at the latest follow-up. The total duration of antibiotic treatment ($P = .002$), infectious disease follow-up ($P = .002$), and the presence of sequestra ($P = .005$) were significantly different between subgroups. There were no statistically significant differences between the 2 subgroups for the other variables, but some trends could be discerned. Only 4/50 patients developed a sequestrum, 2 of which were in the orthopedic sequelae subgroup. Furthermore, initial C-reactive protein (CRP) values were higher in the sequelae subgroup, as were the CRP values at hospital discharge. The orthopedic follow-up was also longer in the sequelae subgroup. Finally, the delay between the onset of symptoms and the beginning of antibiotic treatment was longer in the sequelae group.

Patients with orthopedic sequelae had a longer antibiotic treatment and infectious disease follow-up, and were more likely to have presented with a sequestrum.

Level of evidence: IV – case series.

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All procedures performed this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments, or comparable ethical standards. The study was approved by the institutional review board of the CHU Sainte-Justine. The ethics committee did not require informed consent for this retrospective case series review with appropriately anonymized data. Patient confidentiality was ensured throughout the data access, collection, and storage process.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Abbreviations: CHU = Sainte-Justine: Centre hospitalier universitaire (University Hospital Center) Sainte-Justine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IQR = interquartile range, LLD = limb-length discrepancy, MRSA = methicillin-resistant *Staphylococcus aureus*, OAI = osteoarticular infection, OSSA = oxacillin-sensible *Staphylococcus aureus*, PCR = polymerase chain reaction.

Keywords: joint infection, orthopedic sequelae, osteomyelitis, pediatric bones, septic arthritis

1. Introduction

Osteoarticular infections (OAIs) are infections of the bone (osteomyelitis) and joint (septic arthritis). They are frequent in pediatric patients, with an incidence rate of 2 to 13 per 100,000 children annually in developed countries for osteomyelitides, and half of that incidence rate for septic arthritides.[1] Nonetheless, recent literature focusing on the late sequelae of OAI has been sparse.[2] In septic arthritis of the hip, for example, delayed diagnosis may lead to chondrolysis,[3] premature or asymmetrical closing of the triradiate cartilage, acetabular dysplasia, and premature or asymmetrical closure of the proximal femoral physis; potentially leading to abnormal angulation and limb-length discrepancy (LLD).[4,5] Damage to the epiphyseal vascular supply may result in avascular necrosis of the femoral head and metaphysis, causing joint destruction, hip instability, and even dislocation and pseudoarthrosis of the femoral neck.[4,6,7] Similar sequelae were also reported in other joints. For example, septic arthritis of the shoulder can cause humeral shortening and subluxation;[8] in long bones, osteomyelitis can result in epiphysiodesis and LLD as well as angular limb deformity.[9]

Several factors have been associated with a higher risk of developing late sequelae after OAI, including: initial delay in diagnosis and treatment,[2,6–8,10–13] inadequate pharmacological and surgical treatment,[14] (younger) age,[6,7,9,15,16] pathogen virulence,[13,17–19] and laboratory results.[11,20] In osteomyelitis, long-term sequelae are associated with the three-dimensional extent of the physeal injury, duration of interference with growth (i.e., treatment delay), and the age of the patient at the time of the injury.[17,21,22] Indeed, osteomyelitis involving the physes of younger patients increases risk, as these patients are at an earlier stage of their growth.[23] Additionally, in acute hematogenous *Staphylococcus aureus* OAI in children, prolonged fever, bacteraemia, and delayed source control are recognized risk factors for sequelae.[13]

The primary objective of this study was to review OAI cases in skeletally immature patients without comorbidities and to report the prevalence of orthopedic sequelae resulting from physeal insult or chondrolysis. The secondary aim of this study was to identify any differences between the subgroups with and without sequelae.

2. Methods

2.1. Patient selection

A retrospective case series of OAIs, all treated in a single tertiary pediatric care center between January 2010 and December 2016, was undertaken. The study was approved by the institutional review board of the Centre hospitalier universitaire (University Hospital Center) Sainte-Justine. The inclusion criteria were:

1. a diagnosis of osteomyelitis or septic arthritis, or a combined OAI (acute, subacute, or chronic);
2. the presence of a follow-up radiograph at least 1 year after the initial episode; and
3. subjects aged 10 years or less.

Infections diagnosed less than 3 weeks after initial symptom onset were categorized as acute/subacute, while those with onset later than 3 weeks or presenting a Brodie abscess were labeled chronic. Traditionally, acute OAI includes patients with symptoms for fewer than 2 weeks at the time of diagnosis, while chronic OAI includes patients with symptoms lasting longer than 4 weeks, or who exhibit a Brodie abscess.[24] However, in clinical practice, some patients occasionally do not fit these timelines and are diagnosed at, for instance, 3 weeks. This is especially true in the pediatric population, in which symptoms are harder to discern.[25] Consequently, a 3-week (mid-range) cut-off was chosen by the investigators.

In this study, a diagnosis of OAI was based on a combination of imaging, laboratory, and clinical data – as recommended in recent literature.[26] Patients were diagnosed based on the following: known pathogenic OAI bacteria were identified in joint liquid or pus collected during debridement surgery, through bacterial culture or polymerase chain reaction (PCR); clinical presentation was suggestive of OAI (e.g., nonuse of limb, fever, or septic signs, and symptoms); laboratory results were in line with the diagnosis (high white blood cell and neutrophil counts, high C-reactive protein [CRP], or high erythrocyte sedimentation rate [ESR]); imaging findings were in keeping with OAI; patients responded favorably to antibiotic therapy; evident pus was found at joint aspiration, lavage, or surgical curettage. In some cases, no pathogen was identified through culture or PCR, but bacteria were visible on Gram staining before or after antibiotic treatment was initiated. These patients were diagnosed when they also exhibited signs among those mentioned above.

Patients were diagnosed with septic arthritis when joint aspiration or lavage liquid was purulent or contained a pathogen that was later identified, or when imaging interpretation by a radiologist (of, generally, radiography, magnetic resonance imaging or ultrasonography) unambiguously found a joint infection. Some specific clinical features, such as a complete absence of joint movement, along with laboratory findings suggestive of septic arthritis, helped diagnose the latter.

Patients received an osteomyelitis diagnosis when imaging findings (generally through radiography, magnetic resonance imaging, or nuclear imaging) were unambiguous about the relationship between bone involvement and clinical presentation (e.g., osteolysis or subperiosteal abscess, or bone involvement on scintigraphy). Osteomyelitis was also diagnosed when surgical debridement and exploration confirmed bone involvement.

On an indicative basis, most patients with an OAI at our institution underwent a septic workup, either in our institution or before transfer. They also received an empirical antibiotic treatment. Per the epidemiological data in our region, it was generally cefazolin-based. When and if the pathogens were

identified, narrow-spectrum treatment was initiated. Antibiotic therapy was modified for patients who were not responsive after approximately 48 hours, upon recommendation of an infectious disease specialist. Moreover, patients with imaging findings associated with joint infection, but without a clear diagnosis or too ill for surgery, underwent bedside joint aspiration. Thereafter, patients with joint aspiration results strongly suggestive of septic arthritis who were deemed candidates for surgery underwent joint drainage and lavage in the operating room. Patients with radiological findings suggestive of osteomyelitis who had a subperiosteal or a Brodie abscess large enough for drainage underwent surgical drainage and curettage. Patients who presented with a sequestrum during the course of osteomyelitis underwent debridement to remove necrotic bone. Finally, patients with septic arthritis underwent antibiotic therapy for at least 3 weeks, and those with osteomyelitis underwent same for 4 to 6 weeks. The duration of antibiotic therapy was determined, jointly, by the infectious disease and orthopedic specialists, based on clinical improvement and laboratory results. Decisions to transition from intravenous to *per os* antibiotics were made on a case-by-case basis, according to clinical improvement and laboratory workups.

To assess how classical hematogenous OAI is typically managed, rather than focus on patients predisposed to more severe outcomes, patients exhibiting the following were excluded:

1. postoperative infection;
2. posttraumatic infection;
3. sickle cell anemia;
4. osteomyelitis of flat, irregular, or small bones (e.g., spine, pelvis, jaw, clavicle, or metacarpals);
5. septic arthritis in small joints; and
6. long-standing untreated OAI acquired outside of the country (Canada);
7. immunodeficiency (which included patients with hematologic cancer, other forms of cancer treated with chemotherapy/radiotherapy, or AIDS, as well as patients undergoing long-term immunosuppressive therapy for any medical condition (which included treatments with high doses of corticosteroids); and hereditary immune system deficiencies).

2.2. Data collection

All medical charts with diagnostic codes for osteomyelitis and septic arthritis were retrieved and reviewed. Paper archival records were used for cases preceding 2015. Subsequent records were available electronically. The data collected included: demographic data, significant medical history (such as prematurity and hemophilia), pharmacological and surgical treatment (duration and description), laboratory results (CRP and ESR at hospital admission and discharge, and pathogen identification results), delay from symptom onset and antibiotic treatment (i.e., time elapsed between the onset of symptoms and consultation, and time elapsed between the first consultation and the beginning of antibiotic treatment), number and type of surgical procedures, and follow-up duration. Furthermore, a description of the infection (localization and associated conditions, such as subperiosteal abscess and osteolysis) and related treatment outcome (late sequelae) were retrieved from radiological reports. In terms of laboratory results, it should be noted that PCR was not systematically performed. When it was, the following pathogens were investigated: *Kingella kingae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and oxacillin-sensible *Staphylococcus aureus* (OSSA). The MecA (methicillin resistance in *S. aureus*) gene was also investigated in some patients with PCR. In the presence of aggressive staphylococcal infections, a sample was sent to a specialized laboratory to identify Panton-Valentine leucocidin toxins. Blood culture and bacterial culture results were retrieved. The presence of a sequestrum on imaging studies was also noted.

2.3. Outcome definition

In this study, an orthopedic sequela was defined as either: an osteal deformation that led to a new LLD greater than 5 mm, a new abnormal articular angulation of more than 5°, or a symptomatic chondropathy visible on imaging studies after a 1-year follow-up. Chondropathy is a general term that refers to a disease of the joint cartilage,[27] with or without underlying bone defects. In this study, patients with imaging that showed obvious chondral damage to the affected joint, concurrently with osteoarthritis-like symptoms at more than 1-year of follow-up, were diagnosed with chondropathy. The 5 mm threshold was based on a biomechanical study conducted by Khamis and Carmeli.[28] The 5° threshold was established to account for the presumptive margin of error between radiographs and normal tibiofemoral alignment, believed to be optimal within 3° of the mechanical axis according to Choong et al.[29]

2.4. Statistical analysis

There was no sample size calculation since this is a retrospective, observational study. All missing data is reported in Table 1.

Pursuant to the primary aim of the study, the rate of orthopedic sequelae patients after 1 year of follow-up was calculated.

For the secondary objective, the study population was separated into 2 subgroups (subjects with and without orthopedic sequelae). We also accounted for various patient variables (age, sex, and CRP, and ESR results): the median value and interquartile range (IQR) were calculated for each variable in each subgroup, as well as for the whole study group. Chi-squared tests were then performed for categorical variables (i.e., presence of a radiological sequestrum and sex). Mann–Whitney *U* tests were performed for continuous data (age, initial, and hospital discharge CPR and ESR values, duration of hospital stay, delay between symptom onset and beginning of treatment, total duration of antibiotics therapy, and follow-up time). The purpose of these tests was to discern significant differences between the 2 subgroups, and to identify factors associated with orthopedic sequelae. It should be noted that a longer follow-up time was expected in the sequela subgroup, because of the less favorable clinical condition. The statistical analyses were conducted using SPSS software (IBM SPSS Statistics for Macintosh, Version 25, Armonk, NY: IBM Corp), and two-tailed exact significance *P* values were calculated. The level of significance was set at $P < .05$.

3. Results

The initial patient group included 401 patients diagnosed and treated for OAI. The medical charts of the 325 patients aged 10 or younger were reviewed, and inclusion and exclusion criteria were applied (see Fig. 1). Of the 275 patients excluded, 236 (73%) did not have radiographic results available at 1 year of follow-up.

Of the 50 patients included in the final group (24 (48%) females and 26 (52%) males), 36 (72%) had osteomyelitis, 8

Table 1

Description of study population with comparison between subgroups of osteoarticular infection patients with and without orthopedic sequelae.

Characteristics	Total (50 patients)	No orthopedic sequelae (45 patients)	Significant orthopedic sequelae (5 patients)
Age in years, median (IQR)	2.0 (1.0–6.0)	2.0 (1.0–5.5)	7.0 (2.5–9.0)
Sex			
Male	26	22	4
Female	24	23	1
Laterality			
Left	22	21	1
Right	28	24	4
Site of infection			
Isolated osteomyelitis			
Proximal humerus	1	1	0
Proximal radius	2	2	0
Distal radius	2	1	1
Distal ulna	2	2	0
Proximal femur	5	5	0
Distal femur	12	11	1
Proximal tibia	3	3	0
Tibial diaphysis	1	1	0
Distal tibia	4	3	1
Proximal fibula	1	1	0
Distal fibula	3	3	0
Isolated joint infection			
Hip	5	5	0
Knee	2	1	1
Ankle	1	1	0
Combined infection			
Proximal femur and hip joint	2	2	0
Distal femur and knee joint	1	0	1
Proximal humerus and glenohumeral joint	1	1	0
Distal humerus and elbow joint	2	2	0
Presence of a bony sequestrum*	4	2	2
Causal pathogen			
Staphylococcus aureus sensible to oxacillin	14	11	3
Kingella kingae	5	5	0
Pseudomonas aeruginosa + Escherichia coli	1	1	0
SGA	3	3	0
Streptococcus pneumoniae	1	1	0
Bartonella henselea	1	1	0
Staphylococcus warnerii	1	1	0
Fusobacterium sp.	1	0	1
No etiological agent identified	23	22	1
Duration of hospital stay in days, median (IQR)	6.0 (4.8–9.3)	6.0 (4.0–9.0)	6.0 (5.5–21.5)
Inflammatory markers, median (IQR)			
Initial CRP (mg/L)*	29.2 (5.0–57.4)	27.3 (5.0–55.7)	43.0 (22.5–151.5)
Hospital discharge CRP (mg/L)**	2.8 (0.7–17.8)	2.7 (0.8–16.9)	21.1 (0.4–71.4)
Initial ESR (mm/h)#	35.0 (22.0–48.0)	35.0 (22.0–48.0)	34.0 (8.2–54.0)
Hospital discharge ESR (mm/h)†	25.0 (17.0–45.8)	25.0 (17.0–45.8)	26.5 (5.6–52.8)
Delay, median (IQR)			
Between onset of symptoms and beginning of treatment in days*	9.0 (3.0–23.5)	8.0 (3.0–17.0)	27.0 (10.0–52.0)
Between onset of symptoms and first consultation	2.0 (1.0–7.0)	2.0 (1.0–7.0)	6.0 (3.0–31.5)
Between first consultation and beginning of treatment	3.5 (1.0–10.3)	3.0 (1.0–9.5)	8.0 (4.5–29.5
Duration of antibiotic treatment, median (IQR)	66.5 (42.0–88.3)	51.0 (41.5–84.5)	114.0 (89.5–175.5)
Follow-up time, median (IQR)			
Delay between hospital admission and last follow-up radiographic image in days	693.5 (464.0–1336.8)	694.0 (463.0–1255.5)	586.0 (417.5–2243.5)
FU in orthopedics in days	590.0 (429.3–831.5)	598.0 (403.0–784.5)	539.0 (499.0–2249.0)
FU in infectiology in days	66.5 (42.0–118.3)	59.0 (41.5–102.0)	294.0 (97.5–433.5)

* Population size of 49/50 patients due to lack of available data.
** Population size of 48/50 patients due to lack of available data.
# Population size of 43/50 patients due to lack of available data.
† Population size of 42/50 patients due to lack of available data.
CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FU = follow-up, IQR = interquartile range.

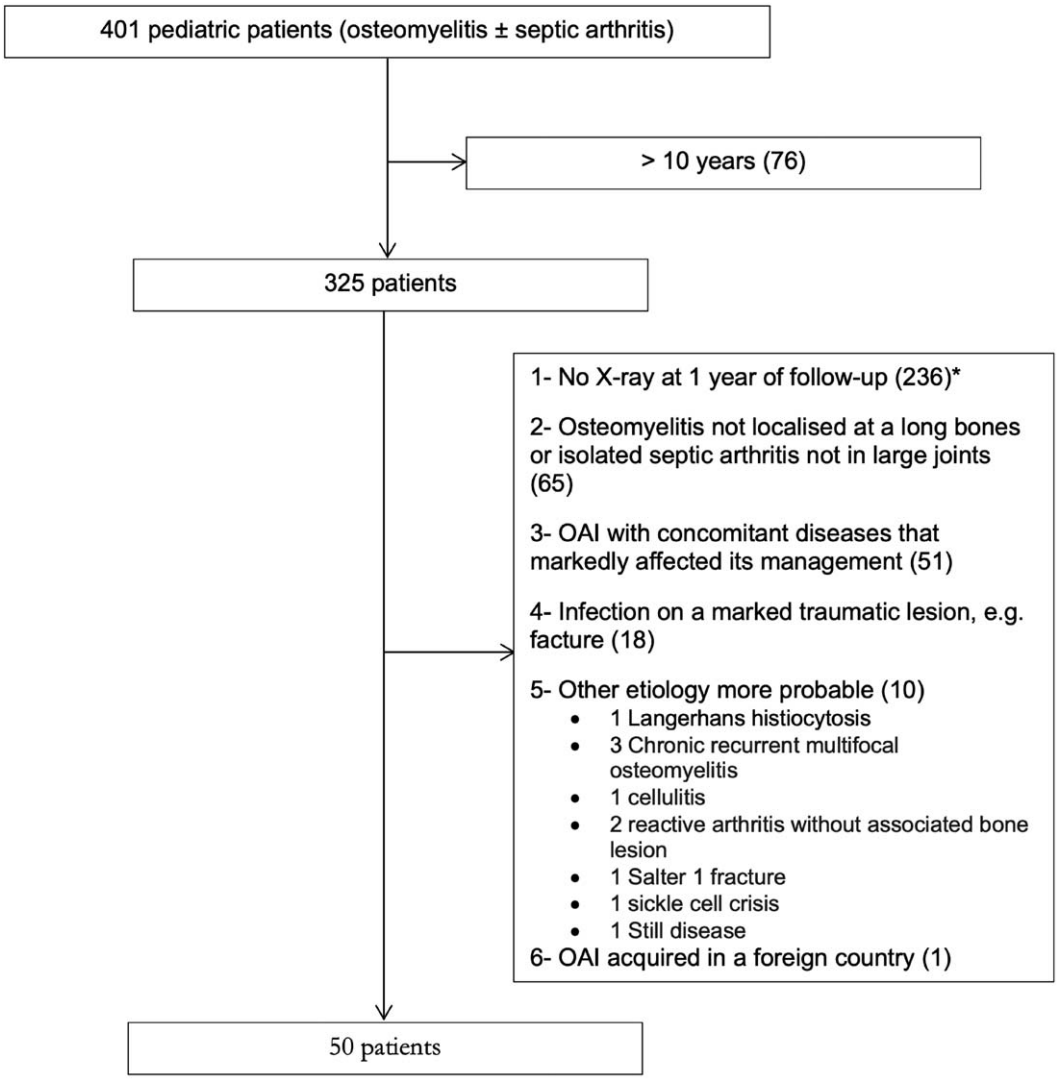

Figure 1. Flow chart of patient inclusion.

(16%) had septic arthritis and 6 (12%) had a combined infection (3 acute/subacute and 3 chronic). At the onset of infection, the median age was 2.0 (IQR: 1.0–6.0, further IQR in parentheses) years with range of 0 to 10. Median length of hospital stay was 6.0 (4.8–9.3) days. The delay between symptom onset and the first consultation was 2.0 (1.0–7.0) days. That between the first consultation, whether at a family physician's office, an emergency room, or a pediatric hospital (in few cases), and the beginning of antibiotic treatment was 3.5 (1.0–10.3) days. The delay between signs of infection (onset of symptoms) and the beginning of antibiotic treatment was 9.0 (3.0–23.5) days, and antibiotic treatment lasted 66.5 (42.0–88.3) days. The orthopedic and infectious disease follow-ups lasted 590.0 (429.3–831.5) and 66.5 (42.0–118.3) days, respectively.

The causal pathogen was identified in 54% of cases. One culture was positive for *Micrococcus luteus,* which is not considered pathogenic in immunocompetent patients. *S. aureus* was the predominant etiological agent (28% of patients), followed by *K. kingae* (10% of patients), and *S. pyogenes* (4% of patients). Neither the MRSA (methicillin-resistant *S. aureus*) nor the MecA gene were found. Blood cultures were performed on 45 patients. Seven were positive, 4 oxacillin-sensible *S. aureus*, 2 *S. pyogenes*, and 1 *S. pneumoniae*. Joint aspiration contributed to pathogen identification in 4 patients, with 4 positive joint liquid cultures for OSSA, 1 for *S. pyogenes*, and 1 for *K. kingae*. Pus samples during surgical drainage or joint lavage were positive for 12 patients. They helped identify 9 OSSA cases, 1 *S. pyogenes* case, 1 *Staphylococcus warneri* case, and 1 *K. kingae* case. Nineteen patients (38%) underwent a PCR analysis, either a multiplex-based PCR assay (which detects *K. kingae*, *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae*) or a PCR for *OSSA* and MRSA, or both. Multiplex PCR was performed on specimens from 13 patients, and *S. aureus* PCR was performed on specimens from 19 patients. This contributed to bacterial identification in 8 patients (18%). PCR identified *K. kingae* in 4 cases (8%) and OSSA in 4 cases (8%). The median CRP

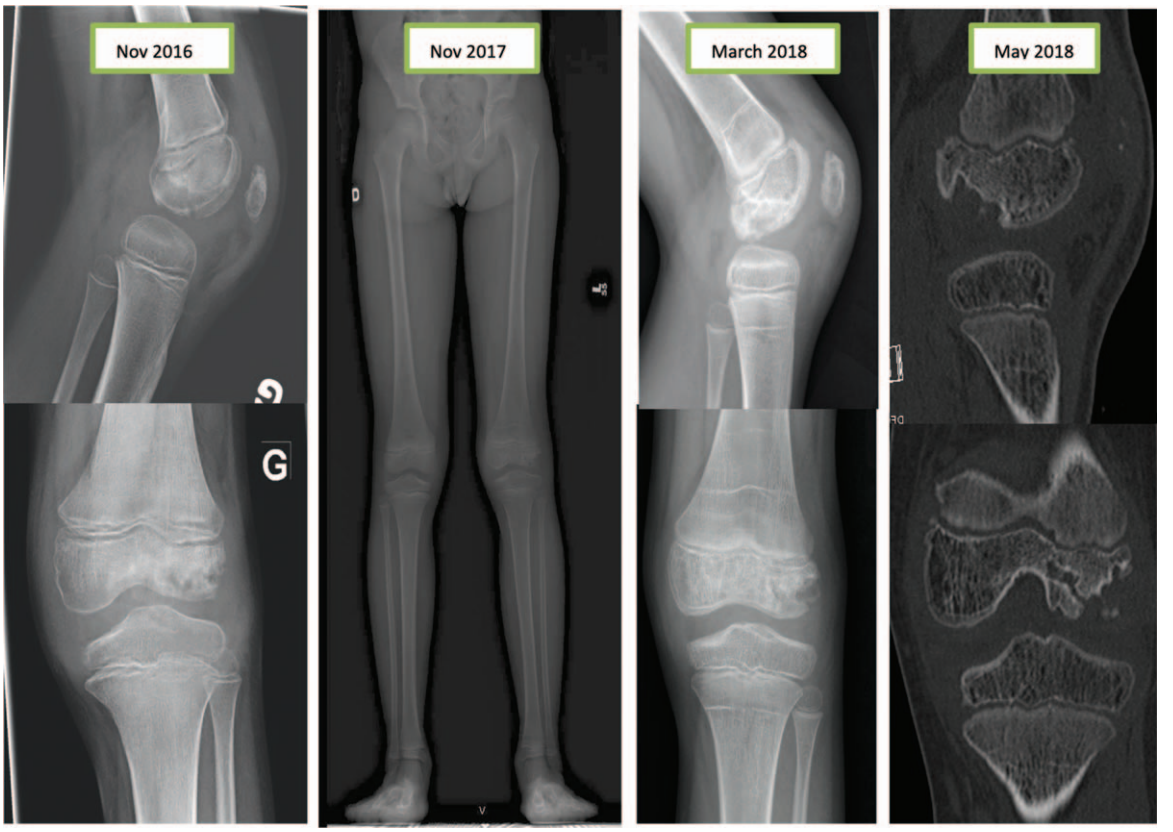

Figure 2. Limb-length discrepancy and chondropathy after a septic arthritis of the knee and chronic osteomyelitis of the distal femur of the left lower limb. (A) Plain radiograph, patient at 7.4 years old. (B) EOS (low X-ray dose) radiograph, patient at 8.4 years old, LLD: 12 mm. (C) Plain radiograph, patient at 8.8 years old. (D) CT-scan, patient at 8.9 years old.

concentrations, initially and at hospital discharge, were 29.2 (5.0–57.4) mg/ and 2.8 (0.7–17.8) mg/L, respectively. The median ESR values at hospital admission and discharge were 35.0 (22.0–48.0) mm/hour and 25.0 (17.0–45.8) mm/hour, respectively. The median time between hospital admission and the last follow-up radiograph, to determine long-term sequelae, was 693.5 (464.0–1336.8) days. All patient characteristics are presented in Table 1.

There were 5 patients [10% (5/50)] with significant orthopedic sequelae at their last follow-up.

The first patient was a 7-year-old male who suffered sequelae from aseptic arthritis of the knee that was initially accompanied by staphylococcal bacteremia and multifocal pneumonia. Sequelae also included an osteomyelitis of the distal femur that became chronic and involved a sequestrum. Radiographs showed residual deformity of the lateral femoral condyle and a chondropathy requiring 2 late surgical interventions: an arthroscopic sequestrectomy with synovectomy and lysis of adhesions, followed by arthrolysis and manipulation of the joint under anesthesia. The same patient had a LLD of 12 mm, with an overgrowth of the affected limb, but his imaging showed reassuring Harris lines at latest follow-up (Fig. 2).

The second patient, a 10-year-old male, had an asymptomatic 15 mm distal radius overgrowth secondary to staphylococcal chronic osteomyelitis with a sequestrum at the injured site that required sequestrectomy.

The third patient, a 5-year-old male, experienced severe symptomatic chondrolysis following septic arthritis of the knee. It was refractory to initial empiric treatment because of its atypical etiology (*Fusobacterium* sp.), required joint lavage twice, and is still being followed. The persistence of osteal modifications at the posterior face of the epiphyseal cartilage and the ossification center of the lateral femoral condyle were observed on the latest radiograph.

The fourth case involved a staphylococcal osteomyelitis of the distal femur in a newborn male with metaphyseal osteolysis that required debridement early on. It caused asymmetrical epiphysiodesis, a 16 mm LLD, and a progressive knee valgum (Fig. 3).

The last case was chronic osteomyelitis of the distal tibia in an 8-year-old female, where the causal pathogen was not identified. It had an osteolytic presentation and resulted in a 6 mm LLD, with an overgrowth of the affected limb. However, surgical management was not required in this patient.

Mann–Whitney *U* tests were conducted to assess the significance of the differences in continuous parameters between the subgroups (with or without sequelae). The tests showed statistical significance for the total duration of antibiotic therapy (5.0 (41.5–84.5) days for the "without" subgroup and 114.0 (89.5–175.5) days for "with" subgroup, with $P = .002$) and follow-up duration by an infectious disease specialist (59.0 (41.5–102.0) days for the "without" subgroup and 294.0 (97.5–433.5) days for the "with" subgroup, with $P = .002$).

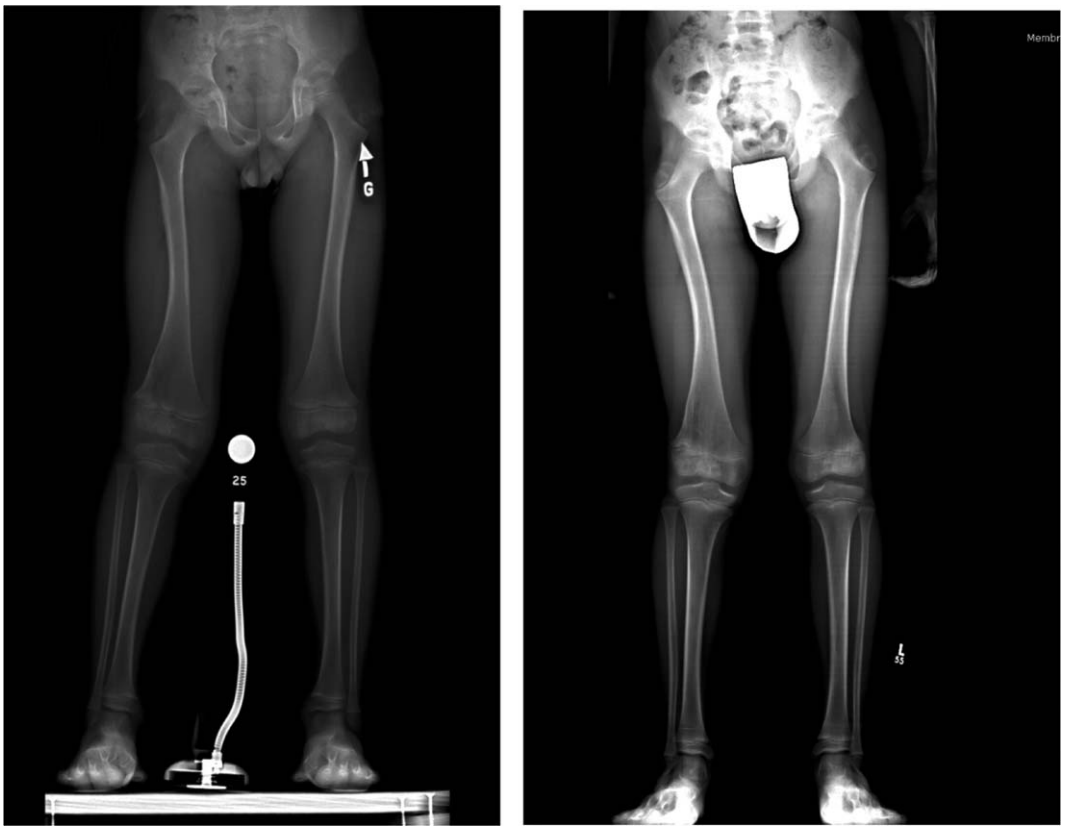

Figure 3. Evolution of hemiepiphysiodesis with limb-length discrepancy and genu valgum following metaphyseal osteomyelitis of the right distal femur. (A) Patient at 5 years old, with a 13 mm LLD and 4 degrees of genu valgum. (B) Patient at 8 years old with 16 mm LLD and 6 degrees of genu valgum.

There were no significant differences between the 2 subgroups for the other variables, but some presumptive trends were noted. Needless to say, these should be interpreted with caution. Only 4 patients out of 50 developed a sequestrum, 2 of which were in the orthopedic sequelae subgroup. Furthermore, initial CRP values were higher in the sequelae subgroup (43.0 (22.5–151.5) mg/L as opposed to 27.3 (5.0–55.7) mg/L), as were CRP values at hospital discharge (21.1 (0.4–71.4) mm/hour as opposed to 2.7 (0.8–16.9) mm/hour). The orthopedic follow-up was also longer in the sequelae subgroup (539.0 (499.0–2249.0) days vs 598.0 (403.0–784.5) days in the "without sequelae" subgroup). Finally, the delay between the onset of symptoms and the beginning of antibiotic treatment was longer in the sequelae subgroup (114.0 (89.5–175.5) days as opposed to 51.0 (41.5–84.5) days).

4. Discussion

Four hundred and 1 patients were screened, but only 27% were followed for at least 1 year. Of these, 12.5% met all the inclusion criteria. Of the 50 remaining pediatric patients without long-term comorbidities meeting the exclusion criteria, 36 had osteomyelitis, 8 had septic arthritis, 6 had a combined infection and only 5 had orthopedic sequelae.

The median time from infection onset and the beginning of antibiotic therapy was 8 days in the subgroup without sequelae, and 27 days in the one with sequelae. This period exceeds the recommended 4 days with an acute presentation.[12] However, many of the patients included in the study had a subacute or chronic infection with subtle symptoms at onset that might explain this delay. In this group of patients, we observed a notable difference between the first consultation delay (median of 2 days) and the treatment delay (9 days). This gap could be caused by the inclusion of initial consultations, which are usually at an emergency room or family physician office. At that time, patients often only exhibit mild or atypical symptoms and receive negative laboratory (e.g., CRP or complete blood count) and radiographic results. These results are consistent with a diagnosis of reactive arthritis or transient synovitis, both of which are managed without antibiotics. As half of our patients had chronic OAI, and exhibited vague rather than acute symptoms, this diagnostic delay (and thus treatment delay) is justifiable. Total duration of antibiotic therapy was longer in the sequelae subgroup. This should probably not be construed as a risk factor to the sequelae, but rather as a reflection of the refractory and more complicated infections in these patients, which require prolonged treatment. This difference is likely due to our decision not to exclude chronic infection cases from the study. The same holds true for follow-up duration by an infectious disease specialist. Indeed, the treatment for chronic osteomyelitis is typically much longer than for acute infections.[30] Similarly, the duration of orthopedic follow-up was also longer in the sequelae subgroup even if it did not reach statistical significance.

Sequestrum incidence was also significantly different between the 2 subgroups (with $P = .005$). Among the 4 patients who developed a sequestrum,[31] 2 were in the orthopedic sequelae subgroup. This is consistent with the well-documented physio-

pathology of chronic osteomyelitis, where the avascular necrotic bone does not heal by itself, requires debridement, and can impair growth if it alters the physes.[32] Indeed, sequestra are formed when the periosteum detaches from the cortical bone, and the resulting lack of blood supply to the bone causes necrosis.[33]

Based on reports from previous studies, we expected higher initial and hospital discharge CRP and ESR values in the sequelae subgroup. However, there was no statistical correlation, although median CRP values were higher in the sequelae subgroup. The correlations described in previous studies were for pediatric patients with acute osteomyelitis, whereas this case series study also included the subacute and chronic presentations, where inflammatory markers are less elevated, which could explain this difference.[20] Missing data might also have played a role.

Although recent literature reports that some causal pathogens, particularly Panton-Valentine toxin-producing staphylococci, are more virulent and are associated with poorer outcomes,[18,19] there were no causal pathogens associated with a higher risk of orthopedic sequelae in this patient group. A larger subgroup with late sequelae would be needed to identify a trend in noncontinuous data (such as our data set).

Finally, there was no difference in age at the onset of infection between the 2 subgroups. The exclusion of infants with important comorbidities, including those resulting from congenital diseases or severe prematurity requiring high doses of corticosteroids or other immunocompromising medication, could help explain this. A larger study population might have helped indicate a correlation with age, as even healthy children, and especially newborns, are more vulnerable to the sequelae associated with OAIs.[9,15]

This study provides an up-to-date, exhaustive review of the outcomes of OAIs in pediatric patients with no comorbidities and a median long-term follow-up of 694 days. Recent studies on this topic are uncommon considering how quickly patient management is evolving.

The limitations include the inherent selection bias of a minimum 1-year follow-up which excluded 73% of patients. However, this was important to detect sequelae which would have ostensibly been undetected with a shorter follow-up period. Nonetheless, some studies suggest that orthopedic follow-up is not recommended for longer than the duration of the antibiotic therapy, unless the OAI affects the growth plates or surrounding areas, or presents with early sequelae.[24] In this regard, all patients included in the study had metaphyseal osteomyelitis, initial osteolysis or initial chondrolysis, making them more sequelae-prone. Finally, some laboratory results (less than 20% of all data) were missing, which could have impacted the results.

This study raises questions about the optimal follow-up duration for OAI in a pediatric setting: should it extend beyond the duration of antibiotic therapy, especially considering that osteomyelitis cases are generally metaphyseal? Although the exclusion criteria were quite restrictive, the patient cohort was still heterogeneous, as infection sites and treatments varied. Other studies have focused on a single joint or bone, and could detail the sequelae in a homogenous manner.[4,7,8,10,15] We, in contrast, sought to provide a more global portrait of pediatric OAIs. Furthermore, the retrospective nature of the study made it difficult to categorize treatment, as it was adapted to each patient's condition, often with several changes along the way. Treatment could have been suboptimal and prompted the development of sequelae, but this impact was difficult to assess retrospectively

A small proportion (12.5%) of the 401 patients diagnosed with an OAI were eligible for this study because most of them did not require 1-year follow-up. There was a 10% rate of orthopedic sequelae amongst the 50 skeletally immature patients included. This study suggests that patients with orthopedic sequelae require longer antibiotic treatment and infectious disease follow-up as a result of suboptimal evolution, and are more likely to have initially presented with a sequestrum.

Author contributions

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