Review article

Sequelae of pediatric osteoarticular infection

B. Ilharreborde*

Service de chirurgie orthopédique pédiatrique, CHU Robert-Debré, université Paris Diderot, 48, boulevard Séruer, 75019 Paris, France

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ABSTRACT

The epidemiology and diagnosis of osteoarticular infections (OAI) have changed considerably in recent years, partly due to the development of molecular biology. *Kingella kingae* is now recognized as the most frequent pathogen in children under 4 years of age, while methicillin-resistant *Staphylococcus aureus* (SA) has been increasingly reported. Although the clinical course of OAI is mostly benign, with shorter antibiotic regimens and simplified treatments, serious functional impairments and life-threatening complications can still occur, especially in case of delayed diagnosis or infection caused by Panton-Valentine leukocidin-producing strains of SA. Newborns and patients with sickle cell disease have greater risk of orthopaedic sequelae, which need to be detected and managed early. The main sequelae of osteomyelitis are angular limb deformity, due to partial growth arrest, and lower limb discrepancy. Therapeutic options are guided by the patient’s age and predictions at maturity. The main complications of septic arthritis are joint stiffness and osteonecrosis. The procedures to consider are arthrodesis, joint reconstruction in immature children, and arthroplasty at the end of growth.

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1. Introduction

Osteoarticular infections (OAI) are frequent in pediatrics, with an annual incidence in developed countries between 10 and 25 per 100,000 children [1]. The physiopathology, clinical examination, and initial management have been thoroughly described in three previous teaching conferences [2–4], but the epidemiology and certain therapeutic protocols have evolved in recent times, notably based on contributions from molecular biology. The objective of this study was therefore to relate the data recently reported in the literature so as to optimize the initial treatment and thus reduce the risk of complications, and then to describe the situations at risk of sequelae and detail the different treatment options.

2. Epidemiology

Studies have found an increase in the incidence of OAI in the past 20 years, but this rise can be explained by the improvement of diagnostic methods. Early MRI investigations are now widespread, and the use of molecular biology techniques has considerably reduced (by more than 50%) the number of suspected cases of OAI without the bacterium being identified [5]. Broad-spectrum PCR 16S as well as PCR specific to *Kingella kingae* (Kk) have become highly useful tools and have demonstrated that this Gram-negative bacillus, commensal of the upper airways, had become the most frequent pathogen in children under 4 years of age (nearly 80%) [5,6]. The clinical picture is often poor and progression benign, but cases of intraosseous abscess have recently been reported [7].

The second important notion is the significant worldwide increase in the number of community-acquired infections related to community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) already reported in 2008 by Ben Ghachem, responsible for unusually severe clinical cases [8]. Depending on the region in the United States, the percentage of CA-MRSA varies between 9 and 76% (for the most part clone USA300), thus influencing the probabilistic antibiotic therapy protocols. In Europe, there is great clonal diversity and the frequency in France is currently evaluated at 5–10% [9].

3. Physiopathology

The physiopathology of OAI, resulting from the interaction between the pathogen and the host’s immune reaction, has previously been described in detail [2]. However, certain aspects should be reviewed to understand the genesis of the sequelae. In osteomyelitis, the initial bacterial fixation is metaphyseal, encouraged by the local vascular anatomy and the rarity of macrophages. If it goes untreated, the infection will lead to the creation of a purulent intraosseous collection that needs to be evacuated. Since the
mechanical properties of the adjacent tissues vary with age, it can be diffused along three trajectories:

- toward the epiphysis in children under 18 months of age (risk of osteoarthritis);
- toward the periosteum (subperiosteal abscess, aggravating cortical vascularization);
- toward the diaphysis, especially in older children (pandiaphyseal osteomyelitis).

The newborn presents particular features: greater permeability of the growth plate and the existence of communication between metaphyseal and epiphyseal vascularization (with no transphyseal communication), making spread of infection toward the epiphysis and then toward the adjacent joint cavity easier [10]. Moreover, the cortical bone of infants is thin and more permeable, thus favoring the development of subperiosteal abscesses as well as the risk of osteoarthritis by diffusion within the joints whose metaphysis is intracapsular (hip, shoulder, elbow).

In cases of osteoarthritis, synovial involvement is the most often hematogenic, and joint destruction is stimulated by the release of proteolytic enzymes from both bacteria and the patient’s immune reaction. There is joint effusion, a source of hyperpressure that is harmful to vascularization and that can result in cases of capsular distension to subluxation and even to dislocation, notably in the infant’s hip.

4. Risk factors for sequelae

4.1. Diagnostic delay

Diagnostic and therapeutic delay is considered by the majority of authors as the main risk factor for sequelae. Although a 4-day delay has been suggested as acceptable in treatment of uncomplicated osteomyelitis, septic arthritis of the hip is an extreme emergency and should be treated within the first 6–12 h of its course [11]. When there is doubt between septic arthritis and transitory acute synovitis of the hip, the Kocher criteria, secondarily modified by Caird et al., can be used, with a positive predictive value greater than 97.5% when all five parameters are present (Table 1) [12].

4.2. Poorly adapted treatment

Treatment of uncomplicated osteomyelitis remains medical. In osteoarthritis, the reference treatment is joint lavage through arthroscopy, but the trend is turning toward minimally invasive arthroscopic surgery, and some authors report one or several needle puncture-lavage procedures with satisfactory results [13, 14]. Antibiotic protocols remain variable, but it is recommended to use high doses (called transosseous) and to respect regular 6-h administration intervals to guarantee good efficacy. The duration of treatment, traditionally from 4 to 6 weeks, can now be reduced to 2–4 days intravenously, followed by 20 days per os for osteomyelitis and 10 days only for septic arthritis [15, 16].

4.3. The newborn

The predisposing factors are prematurity, perinatal hypoxia, and catheter placement (venous or umbilical). The specificities of the newborn are the possibility of multifocal involvement and the frequency of osteoarthritis because of the physiopathological particularities described above. The severity also stems from the frequent diagnostic delay given the difficulty of the exam and the limited clinical expression. Indeed, fever and local signs are often absent, the biological markers are initially only slightly disturbed, and the diagnosis must be made based on irritability, refusal to feed, a pseudoparalytic attitude, and any unexplained bacteremia. With no clinically identifiable source, an ultrasound of the hip should be taken given the high risk of necrosis or subluxation favored by hyperpressure. The functional prognosis of these early OAs remains severe, with 47% painful hips at 40 years of follow-up after septic arthritis occurring before the age of 3 months [17].

4.4. Sickle cell patients

Sickle cell patients are particularly at risk, especially if they are homozygote SS. The risk of infection is related to a progressive destruction of the spleen, an organ frequently involved in bacteriological destruction, and a decrease in serum complement, a substance that normally activates phagocytosis of neutrophils. The existence of bone infarct is also a favorable background. The most frequently blamed pathogens are Salmonella species (60–80% of cases), whose passage in the blood stream is facilitated by occlusion of the digestive tract capillary vessels. The main difficulty is making an early distinction between vaso-occlusive crisis (VOC) and OAI. The local clinical signs are often similar, whereas biology and imaging tests have low specificity. The prognosis is related to the rapidity of treatment, and one must therefore multiply the exams to develop a collection of diagnostic arguments and discuss each case in a multidisciplinary fashion [18]. It should be remembered, however, that VOC is much more frequent than OIA and that the latter often occurs on a poorly vascularized bone segment that has already undergone several infections.

4.5. SA-secreting Panton-Valentine toxin

The past decade has experienced a worldwide emergence of infections caused by Panton-Valentine leukocidin (PVL)-producing strains, responsible for multiple and severe bone pathology [9]. Diagnosis is based on identification of the toxin or demonstration of PVL-coding genes. More often produced by MRSA (notably community-acquired) than methicillin-susceptible S. aureus (MSSA), the toxin causes tissue necrosis and destruction of the neutrophils, thus facilitating extension of the infection [19, 20]. Treatment is urgent given the risk of toxic shock and the life-threatening nature of the infection. If in doubt before the microbiological confirmation, probabilistic antibiotic therapy must be associated with an antitoxin such as clindamycin or rifampicin. Bacteremia can persist for several days despite effective antibiotic therapy, and the number of surgical interventions and the length of the hospital stay are often increased. The risk of complications is high, with, notably, subperiosteal abscesses, pyomyositis, necrosis of fasciitis, as well as a high incidence of deep vein thrombosis (Fig. 1). The rate of orthopaedic sequelae varies in the literature from 33 to 85%.
5. Treatment of orthopaedic sequelae

5.1. Osteomyelitis sequelae

5.1.1. Lateral epiphysiodesis

Involvement of a part of the germinal cells can lead to irreversible growth arrest (epiphysiodesis), manifesting as an axial deviation of the limb. Desepiphysiodesis can be proposed in cases with less than 50% bone bridge of the tibial shaft surface (CT or MRI) and if there remains at least 2 years of residual growth. The bridge is resected either through a metaphyseal tunnel (Langenskiöld technique) or after having performed a physyeal progressive distraction (Bollini technique) [21,22]. The principle is based on interposition of a natural or synthetic inert material after resection, which is even more effective if it is attached to the epiphysis [23]. The results reported in the literature remain controversial, influenced by the etiology of the bridge location. The peripheral forms seem more accessible, but failures are frequent in OAI recovery because the cartilage can be damaged beyond the bridge zone. MRI can therefore have a prognostic value preoperatively to assess the thickness of the tibial shaft and estimate its residual growth potential.

When the residual growth is less than 2 years (12 bone age years for girls and 14 bone age years for boys), it is preferable to complete the epiphysiodesis and associate corrective osteotomy (Fig. 2).

5.1.2. Limb length discrepancy

5.1.2.1. Lower limb length discrepancy. More extended damage to the tibial shaft can result in lower limb length discrepancy (LLLD). Use of low-dose EOS stereoradiography (EOS imaging, Paris, France) is particularly advantageous here because it can quantify (in 3D) the discrepancy, even in case of fixed sagittal deformities [24]. The younger the child is and the more the damaged tibial shaft participates in overall growth of the limb, the more progressive LLLD will be. Treatment will therefore be guided by the child’s age, the prognosis in terms of final height, and the predicted discrepancy at the end of growth. Treatment will generally be envisaged in cases in which the LLLD is greater than 2 cm.

The first option is extemporaneous shortening, a simple method used at the end of growth and normally reserved for the femur. The current choice method is progressive shortening using epiphysiodesis, when the residual growth of the shortest limb is at least equal to the limb length discrepancy.

The key component of the treatment remains the planning stage, which should be repeated and carried out rigorously. The profile of postinfectious epiphysiodesis is most often linear (Shapiro type I), making the prediction of the final discrepancy relatively reliable, but types IV (linear, then a plateau, and then delayed progression) can also be encountered, notably in the proximal femur (Fig. 3) [25]. The prediction methods, for the most part based on bone age and

Fig. 1. Pyomyositis of glutei and iliopeosao during PVL-secretning SA OAI.

Fig. 2. Postinfectious medial epiphysiodesis of the distal tibia in a 10-year-old girl, treated with supramalleolar osteotomy and epiphysiodesis complement.

Fig. 3. Progressive coxa valga in a 15-year-old boy, following neonatal osteoarthritis of the hip.
the Green and Anderson tables, were thoroughly detailed by Karger in the 1998 GEOP monograph and then by Bronfen in 2009 [26,27].

In cases of greater discrepancy or at the end of growth, progressive lengthening of the limb can be proposed, possibly associated with epiphysiodesis of the opposite side. The principle is based on lengthening of the osseous callus (callotasis), at a speed of 1 mm per day, while maintaining joint range of motion and monitoring the adjacent joints. The reference technique is the external fixator, circular or monoplanar, but the recent trend is the development of intramedullary nails, better accepted by patients and limiting disfigurement. Orthofix intramedullary skeletal kinetic distractor (ISKD) nails have been used for more than 10 years and require external maneuvers to obtain lengthening (Fig. 4). The clinical results are highly encouraging, but lengthening failures and most particularly excessively rapid gains in length have been reported [28]. The current trend is the development of implants allowing passive lengthening, with either motorized (Fitbone nail) or magnetic (Phenix and Precice nails) devices, but these fairly rare and expensive techniques are still in the evaluation phase [29,30]. In the postinfectious context, a prior study of the medullary cavity will always be necessary, because modifications in its diameter can make nailing difficult, as will an assessment of the risk of reactivating infection, given the risk of pandiaphysitis with material that has an uncertain prognosis, and an evaluation of the mobility, quality (chondrolysis?), and stability of the adjacent joints.

5.1.2.2. Upper limb length discrepancy. Damage to the proximal extremity of the humerus in the young child can result in major shortening (8–10 cm) of the upper limb. Lengthening with an external fixator, either monoplanar or circular, can be proposed in cases of discrepancy greater than 5 cm, with a bone union speed slower than what has been observed for the lower limbs. The main complications reported are iterative fractures, elbow stiffness, varus deviations, and paralysis of the radial nerve [31].

5.1.3. Pandiaphyseal osteomyelitis

Pandiaphyseal osteomyelitis is a complication of chronic osteomyelitis manifesting as radiological signs covering more than 75% of the diaphysis or as involvement of the opposite metaphysis. Its long and complex treatment often requires repeated interventions to drain the abscess and excise any sequestra. The main complications are chronic fistulization, joint stiffness, and pathological fractures, immobilized with a cast or external fixation [32]. There is a risk of evolving toward septic pseudarthrosis: the treatment principles are excision (which should not be overly extensive), stabilization, and then reconstruction. Monoplanar fixation is the most widely used for osteosynthesis, with or without a cement spacer (induced membranes according to the Masquelet technique), and the reconstruction takes place after 4–8 weeks using a cancellous bone graft, if possible applied on the fibula in cases of tibial damage. The alternative methods are the Papineau technique, the Ilizarov bone transfer technique, and vascularized bone grafting, without any of these methods having been demonstrated as superior.

5.2. Sequelae of osteoarthritis

5.2.1. Septic dislocation of the hip

If treatment has been delayed, in infants the abundance of the joint effusion can result in capsular distension responsible for subluxation or even dislocation of the coxofemoral joint. Emergency treatment is the same as for osteoarthritis, but instability must also be treated with a hip spica cast more or less frequently relayed by an abduction orthosis for at least 3 months.
5.2.3. Arthrodesis treatment. Arthrodesis was long the reference treatment, because of the insufficient survival rate for prostheses in young patients (Fig. 6). This procedure still deserves consideration because the long-term results are relatively favorable. The vital component to guarantee patient satisfaction is complete information on the objective of the intervention and the postoperative period. It is indispensable to prevent future LLD and the persistence of asymmetry, but also to explain that the joint will no longer be painful if bone fusion is acquired. Although the bone nonunion rates in the early descriptions sometimes reached 50%, the improvements in osteosynthesis have made it possible to obtain bone union in more than 80% of cases. Two studies with more than 35 years of follow-up, with nearly half of the cases involving postinfectious situations, reported excellent quality of life and underscored the subjects’ satisfaction, the majority of whom had resumed a professional activity. The main problems reported were spinal column pain (45–60%), pain in the homolateral knee (55–60%) or in the ipsilateral hip (15–30%), and an underlying increased risk of femur fracture [33,34]. The technical considerations to take into account are keeping the abductor muscles intact, with a potential future conversion to arthroplasty in view, as well as the optimal position of the fixation (20–30° flexion, 5° adduction, and 5–10° lateral rotation), thus limiting adjacent pain [35].

5.2.3.2. Conservative reconstruction surgery. Severe proximal femur damage can result in residual cervical and/or cephalic deformities. The Choi classification, based on the extension of the initial damage as well as on the radiological aspect at maturity, is currently the most widely used to analyze these sequelae [36] (Fig. 7). It is also the basis of a treatment algorithm (Fig. 8). Types III and IV are considered severe sequelae, warranting reconstruction surgery in the immature child to improve the functional prognosis and delay any definitive procedure to the end of growth. The goal of these interventions is to reduce acetabular dysplasia and length discrepancy as well as to improve mobility. The functional objective set out by Hunka et al. is to obtain a hip that is stable, mobile (range of motion >50° and <20° flessum) and painless, allowing the child to participate in daily activities with no major limping [38].

The choice procedure in types III is a proximal corrective femoral osteotomy, associating valgus osteotomy and flexion or extension, with satisfactory 10-year results in more than 70% of stage IIIA

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cases. Preoperative arthrography is very useful because it tests the position of the femur with the best congruence, thus orienting toward the best adapted osteotomy procedure. Acetabuloplasty can also be associated in the same operative time or secondarily in cases of insufficient cotyloid coverage. The results of stages III B (pseudarthrosis of the femur neck) and IV (destruction of the femoral head and neck) cases are more irregular, especially since the majority of the series report a short follow-up period and few patients. In these cases, surgery should be systematically compared to therapeutic abstention while waiting for a future prosthesis.

In stage IVA cases, therapy should be guided by the child's age and preoperative MRI, which assesses the cartilage stock remaining above the femoral neck residue. If this is sufficient and if the child is under 6 years of age, modified Albee arthroplasty or a modified Harmon intervention can be proposed (Fig. 9) [37,39]. The latter procedure consists in an incomplete osteotomy of the remainder of the femur, adjoining the greater trochanter to obtain an opening effect filled with iliac graft with varus derotation and neck lengthening. Other interventions should generally be planned during follow-up such as a distal transfer of the greater trochanter, acetabuloplasty, or a procedure to treat length discrepancy. Cheng et al. also described vascularized iliac graft reconstruction, but the results remain unpredictable [40].

In stage IVB cases with totally destroyed joint cartilage, the options are therapeutic abstention until the end of growth, particularly if the hip is mobile and without pain, or reconstruction surgery, with more unpredictable results that may lead to painful stiffness that is less well tolerated than the initial condition. Before 6 years of age, trochanteroplasty can be proposed, with the essential goal of preventing progressive dislocation of the femur in the buttocks. Without a femoral head and neck, pelvic weight bearing is returned to the femur on its trochanteric extremity, using its remodeling potential [41]. The child should first be placed in traction so as to lower the femur. The first procedure consists in releasing the muscle attachments of the proximal femur (the glute, lateral vastus, iliopsoas, and lateral abductors and rotators of the hip) and in positioning the greater trochanter in the bottom of the acetabulum, which has been cleaned, and then to reattach the muscle insertions. After 5–6 weeks with a stabilization cast, a varus derotational osteotomy combined with an acetabuloplasty is performed. The results of the trochanteroplasty remain controversial.
in the literature, with the main problems being uncertain vascularization of the proximal femur, progressive return of femoral valgus, abductor stiffness and weakness, as well as difficult conversion to a prosthesis.

For these different reasons, the rescue treatment if the above procedures fail or in first-line treatment in children over 6 years of age is Ilizarov hip reconstruction, combining a proximal pelvic support osteotomy and more a distal femoral osteotomy to lengthen the limb and realign the knee [42]. Proximal osteotomy creates valgus and corrects flessum and makes it possible to obtain pelvic weight bearing by interposition of soft tissues between the proximal femur fragment and the ischiatic tuberosity (Fig. 10). The greater trochanter is lateralized and lowered, tightening the glutei and thus increasing the lever arm of the abductors. The number of cases reported in the literature currently remains very limited, but the results seem excellent according to the authors in terms of limping and LLLD. However, a risk of varus remodeling of the proximal femur exists during follow-up, and pelvic support osteotomy is therefore reserved for adolescents and young adults.

5.2.3.3. Arthroplasty. Arthroplasty in the young subject has long suffered from a poor reputation, but this can be partially attributed to the fact that the main indication was chronic juvenile arthritis. The 2007 SOFCOT symposium series reported a 50% survival rate for an overall total hip arthroplasty (THA) prosthesis, implanted before 30 years of age, at 15 years of follow-up and 40% at 20 years [43]. A recent meta-analysis on 736 THAs also demonstrated that aseptic arthritis complications accounted for only 2.2% of the indications in young subjects, demonstrating the reluctance of surgeons to propose arthroplasty in a postinfectious context [44]. Recent progress has moved toward the use of cementless implants and the choice of highly reticulated or metal–polyethylene or ceramic–ceramic friction bearing components (hard–hard bearing), which have considerably reduced the number of cases of loosening, notably at the femoral level (Fig. 11) [43,44]. The 10-year survival rate of hard–hard bearing components is now greater than 85%, with satisfactory functional results.

The problems specific to the postinfectious context, detailed in the review of the 74 cases presented at the 2007 SOFCOT symposium, are limb length discrepancy, frequent preoperatively, with a mean 3-cm shortening that increases the risk of neurological injury, and resulting proximal femur and acetabulum deformity. The survival rate of prostheses in this indication does not differ from those found in the overall series, but the risk of infection (8%) is multiplied by 3, despite delaying the procedure more than 10 years after the initial infectious episode. The therapeutic approach recommended to limit this risk is therefore taking intraoperative microbiological samples covered by a standard antibiotic therapy (when the bacterium is not known) or targeted to the initial bacterium and interrupting antibiotic therapy after 48 h when the samples are negative or adapting it to the bacterium found when the samples are positive.
Fig. 10. Ilizarov hip reconstruction principle, with proximal osteotomy correcting adduction and flessum, and secondary, more distal osteotomy to realign and lengthen the limb [42].

Fig. 11. Hip arthroplasty at 3 years of follow-up in a 17-year-old girl, following delayed postinfectious osteonecrosis.
6. Conclusion

Early diagnosis and adapted treatment are therefore the essential prognostic components to prevent orthopaedic sequelae. Intervention of infectious disease specialists and multidisciplinary meetings is therefore strongly recommended to optimize the management of OAI patients. Recent progress in surgery tends to increasingly abandon conservative, disappointing treatments for early arthroplasty at the end of adolescence, taking into account, however, the risk of reactivating infection.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

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