Diagnosis and management of osteoarticular infections in children.

An overview of the literature and retrospective cohort study in a single tertiary care centre

Tine Alliet [a], Liesbeth Cappaert [a], Jasmine Rooryck [a], Marijke Proesmans [b], François Vermeulen [b], Sandra Prinsen [c], Lieven Vermuyten [c], Mieke Boon [b]

[a] Department of Paediatrics, University Hospitals Leuven, Leuven, Belgium
[b] Department of Paediatric Infectious and Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium
[c] Department of Orthopaedics, University Hospitals Leuven, Leuven, Belgium

Tine.alliet@uzleuven.be

Keywords

Osteoarticular infections, osteomyelitis, septic arthritis, spondylodiscitis

Abstract

Objective: To perform a systematic review on the diagnosis and management of osteoarticular infections and to describe the cohort of patients with osteoarticular infections in a Belgian tertiary care centre over a 5-year period.

Methods: A systematic literature search was conducted in MEDLINE. Secondly, we did a retrospective cohort study in a single tertiary care centre.

Results: We included 69 patients with a median age of 1,25 years (interquartile range: 0,9-6,0). They were diagnosed with osteomyelitis in 32/69 (46,4%), septic arthritis in 25/69 (36,2%), spondylodiscitis in 8/69 (11,6%) and a combined osteomyelitis and septic arthritis in 4/69 (5,8%). Delay in presentation was longer in the spondylodiscitis group (p=0,003). C-reactive protein and white blood cell count were significantly higher in the septic arthritis group (p=0,014 and p<0,001).

Blood cultures identified the causative organism in 18/66 (27,3%). Samples from infectious site were positive in 18/34 (52,9%) of whom 10 had negative blood cultures. Polymerase chain reaction identified the organism in 3/6 (50%). In total, 30/69 (43,5%) had a microbiological diagnosis. Total antibiotic course varied from 20 to 64 days. Treatment duration was significantly longer for the Staphylococcus aureus group.

Conclusion: An increase in cultures from the infectious site and the use of polymerase chain reaction techniques could greatly improve microbiological diagnosis and enable targeted antimicrobial therapy. Magnetic resonance imaging remains the most sensitive and specific investigation and should be more easily available to avoid a delay in diagnosis. These findings should be taken into consideration when setting up local and national guidelines/protocols, currently still lacking for the management of paediatric osteoarticular infections.

Introduction

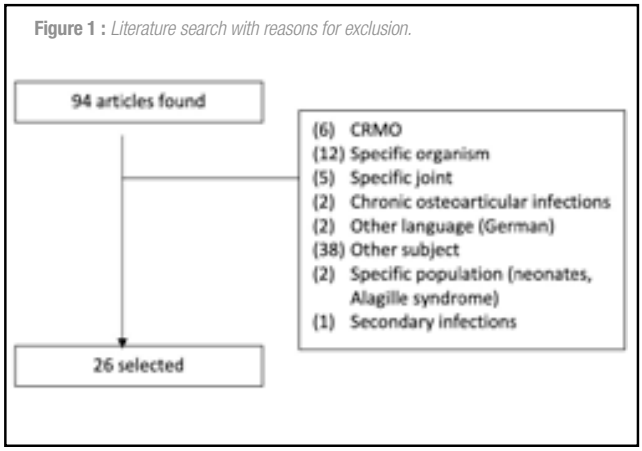
Osteoarticular infections (OAI) are not uncommon in children. Three main types are described: osteomyelitis (OM), septic arthritis (SA) and spondylodiscitis (SD). Delayed diagnosis and treatment can result in severe complications and morbidities (1,2). Until today, there is ongoing discussion regarding the optimal management of these infections and clear algorithms to guide diagnosis and treatment are lacking. The aim of this study was to perform a systematic review on the diagnosis and management of OAI and to describe the cohort of patients with OAI in a Belgian tertiary care centre over a 5-year period.

Materials and Methods

A systematic literature search was conducted in MEDLINE. The following terms were used: "osteomyelitis", "osteoarticular infections", "spondylodiscitis" and "septic arthritis" with one or more of the terms "children" and "paediatric". Results were limited to the past five years and the paediatric population (<18 years). All clinical trials, randomised controlled trials, meta-analyses and (systematic) reviews were selected. Articles in other languages than English, Dutch, French or Spanish were excluded as re publications that focused on one pathogen or neonates only. We found 26 relevant articles which were used to compare our findings with and to provide an update on current knowledge about OAI (Figure 1). Belgian (BVIKM) and European (ESPID) guidelines were also included.

Secondly, all paediatric files within a 5-year period (13.11.2012 - 13.11.2017) were searched through the hospital computer system KWS (Clinical Working Station) for one or more of the following hits: "osteoarticular infections", "septic arthritis", "osteomyelitis" and "spondylodiscitis". Ethics committee approval was obtained. Inclusion criteria were age < 18 years and a formal diagnosis of OAI, with or without a confirmed pathogen. Exclusion criteria were: age <3 months (more often multifocal and complicated infections), confirmed Lyme disease, congenital or acquired immunodeficiency, secondary infections (recent history of important skin wounds, open fracture, surgery at the site of infection or in contiguous areas), sickle cell disease, relapse of AOI, presence of prosthetic materials and insufficient data.

Figure 1 : *Literature search with reasons for exclusion.*



Information was retrieved and entered into an electronic, anonymised database: demographic and clinical details at presentation, final diagnosis and site of infection, laboratory results, imaging results, clinical management (type, route and duration of antibiotics, surgery), clinical and radiographic recovery at follow-up and sequelae. Polymerase chain reaction (PCR) technique used in the lab is 16S rRNA gene sequencing. Imaging results were defined as diagnostic if OAI was the only diagnosis mentioned, as suspicious if mentioned as part of a differential diagnosis, as other signs if there were signs related to OAI but the term itself was not used (eg. intra-articular fluid, periosteal reaction, Brodie Abscess,...) or as normal.

Patients were divided into four groups: OM, SA, SD or mixed type (combination of OM and SA). Statistics were performed through SPSS using Mann-Whitney and Fisher's Exact test. A p-value <0,05 was considered significant.

State of the art literature update

Definition and epidemiology

OM causes inflammation of the bone and marrow following infection. Its incidence varies widely between 1,94 to 13 children per 100.000 in developed countries and up to 80 per 100.000 children in developing countries (2,3). An increase in incidence over the past 2 decades has been noticed (4,5). The lower limb is most often the locus of infection with estimated prevalence of 27-36% in the femur and 22-33% in the tibia (4,6,7). Multifocal disease is more common in neonates (22%) but only occurs in 5-7% of paediatric cases (5).

SA develops after bacterial invasion of a joint and occurs in about 5 to 12 children per 100.000 per year, with similar geographical variability with a higher incidence in developing countries (8,9). Peak incidence is around the age of 3 years and up to 80% of the cases involve the hip or knee (10,11). Both OM and SA have a male predominance (4,6).

SD, infection of the vertebral disc and subsequently the adjacent vertebral bodies, is much less common with an estimated incidence of 1 per 250.000. Three peak age groups have been described: a few weeks to several months old, 6 months to end of preschool age and school-aged children (1,12). The lumbar spine is most often affected, in 75% of the cases (12). In discitis, the infection is limited to the vertebral disc. This entity is much less common in young children because of the rich vascularisation in the metaphysis of the vertebral body below the age of 8 years (1,12). We will focus on SD in this paper.

More than half of all children with OAI are younger than 5 years old and a third of the children with SA is less than 2 years old (4,5,9).

Pathogenesis

The most common origin of childhood OAI is haematogenous dissemination following transient bacteraemia from a previously existing site of infection or from the respiratory tract (1,4). Hence, the most vascularised areas are more often affected. The intervertebral disc for example is extremely vascularised in children compared to adults, particularly below the age of 8 years (12). OM typically occurs in the metaphyseal region of long bones where bacteria presumably aggregate due to the tortuous blood flow. Subsequently, infection can spread and form intraosseous, subperiostal and extraperiostal abscesses (4,7). In young children < 18 months with OM, transphyseal blood vessels predispose to the development of secondary SA, which is much less common in older children when the physis becomes relatively avascular (6,7). Especially the shoulder, elbow, hip and ankle are prone to develop this type of secondary infection (10,13). Other pathogenic mechanisms are spreading of infection from an adjacent area (e.g. cellulitis) or direct inoculation (e.g. trauma, surgery) (8,13). The greater exposure to microtraumata is possibly the explanation for male predominance in SA and OM (3,4).

Microbiologic aetiology

Staphylococcus aureus (S. aureus) is the most frequent cause of all paediatric OAI; up to 70-90% of positive cultures in OM, 25-60% in SA and 80% in SD (1,5,13). Group B streptococcus and gram-negative rods are potential pathogens in newborns whereas Streptococcus pyogenes and Streptococcus pneumoniae should also be considered in older children (7,8). Another important pathogen is Kingella kingae, increasingly detected as aetiology in children and a major pathogen between 6 months and 4 years (1,4). On the other hand, Haemophilus influenzae type B (HiB) has become exceptional since the introduction of successful vaccines (5,13).

Methicillin resistant S. aureus (MRSA), is an emerging problem, especially in southern European countries and the USA. MRSA prevalence is low in northern European countries and Canada (14). Infections with MRSA tend to cause a more severe disease course, with longer need for IV treatment and more systemic complications (7,15). S. aureus carrying the Panton-Valentine leukocidin (PVL) gene, predominantly present in the US, produce a destructive cytotoxin that is responsible for a more severe SA and OM (5,8).

Salmonella is uncommon in Western countries but is a known pathogen in developing countries and in patients with sickle cell disease (9,16). Infections with non-bacterial organisms, e.g. fungi and parasites, are very rare in immunocompetent children (5,9).

In a substantial part of patients with OAI, no aetiological organism is found (17).

Diagnosis

The diagnosis is based on clinical signs, supported by biochemical tests, positive tissue or blood cultures and radiological signs (13). Typical signs and symptoms at presentation in OM and/or SA are fever, malaise, local erythema, swelling and/or pain, limitation of function such as painful and limited range of motion, refusal to weight-bear or to sit and antalgic gait. In neonates, symptoms can be more nonspecific and fever can be absent (5-7). Clinical presentation can also vary depending on the causative organism (2). Mostly, children present within 3-4 days after onset of symptoms (4). Unfortunately, this is not the case in SD where delay in presentation is frequent and diagnosis can take up to 4 months because of mild and nonspecific symptoms such as general malaise, irritability, fever, torticollis, back pain, stiffness, etc. Significant neurological signs on admission are rather infrequent. Therefore, a high index of suspicion is warranted to allow early diagnosis (1,12).

Laboratory findings show increased inflammatory markers in most patients. C-reactive protein (CRP) peaks early (within 48h) after symptom onset and can be helpful in disease monitoring as well (normalisation within 7 days after initiation of appropriate treatment). Erythrocyte sedimentation rate (ESR) rises more slowly (3-5 days to reach its peak) and takes several weeks to normalize (4,6). The combination of CRP and ESR is probably best to estimate disease likelihood, especially when both are within normal limits in which case OAI is highly unlikely though not impossible (7). Moreover, the peak level of CRP is indicative for disease severity and risk of complicated infection (15). White blood cell count can be normal or only slightly elevated, especially in newborns and younger children (2,9). In SD, laboratory findings can be unremarkable (1). Procalcitonin may be more specific than white blood cell count (WBC), CRP and ESR in adult studies (95%). Its sensitivity on the other hand is suboptimal (54%), thus, it is not suitable to exclude the diagnosis. Compared to CRP it increases earlier, has a shorter half-life and it does not rise significantly in response to viral or non-infectious diseases. However, little data is available in children and therefore more research is required before implementing procalcitonin in daily practice (1,15,18).

Ideally, a pathogen is found, allowing directed rather than empirical antimicrobial therapy. Nevertheless, finding the causative pathogen is not easy (17). Blood cultures only require venepuncture but are negative in 16-42% of patients with acute OM, 18%-70% in SA, and almost always negative in SD (1,4,13). Repeated blood cultures don't increase the likelihood of a positive culture (7). Joint fluid and tissue cultures yield better results than blood cultures, with 60-90% positive cultures in OM and 45-77% in SA, at the expense of invasive procedures which often require general anaesthesia. For SD, bacteriological sampling through percutaneous or surgical procedures should be reserved for children with unclear diagnosis, who fail to improve with antibiotic therapy, or if atypical organisms are suspected (6,9,12). Panbacterial or species-specific polymerase chain reaction (PCR) improves detection of pathogens but does not allow susceptibility testing (19). Identification of Kingella kingae is challenging as the organism is difficult to grow. Inoculation on blood culture systems or chocolate agar plates improve recovery rates. Use of PCR in samples from the infected site or on throat swabs increases the chance of identifying this organism (12,17,20).

Several imaging modalities are available to explore OAI.

In OM, x-ray is recommended as a first step to exclude other diseases such as malignancies or trauma (3,4,7). Non-specific soft tissue swelling is the most frequent x-ray abnormality and can be detected within 48 hours (7). Lytic changes in the bone, seen in OM, only become visible when 50-75% of the bone mineral density is depleted, mostly after 1-2 weeks (4). Ultrasound is reserved to assess soft tissue changes or subperiosteal collections, and can also be used for guided needle aspiration (3,4,6). Bone scintigraphy can be useful in young children where OM is suspected but the site of infection is clinically unclear. Its diagnostic yield is limited in neonates because of lower mineralization of bone (16,21,22). Computed tomography is excellent to assess bone and articular pathology, such as pathologic fractures, bone destruction, sequestration, subluxation, etc. It is also helpful to guide biopsies (12). Its diagnostic role however is limited with sensitivities and specificities of 66-97% (4).

In SA, indirect signs of joint effusion such as soft tissue swelling and increased joint space can be present on x-ray (10). Ultrasound is most useful as it can detect effusions as small as 1-2 ml. However, distinction between sterile, purulent and haemorrhagic fluid accumulations is impossible and ultrasound can be falsely negative within 24 hours after onset of symptoms (2,10,13).

Narrowing of the intervertebral disc space and destruction of adjacent vertebral endplates only become visible after 2-3 weeks on spine x-ray in SD. However, it remains a good test for initial evaluation (1). As in OM, ultrasound is an easy and non-invasive method to assess abscesses but is not useful for diagnosis (3,4,6). Bone scintigraphy can highlight inflammatory changes within 1-2 days of disease onset with a sensitivity of >90% but lacks spatial resolution. Positron emission tomography with 18 fluorodeoxyglucose (FDG-PET) has good sensitivity (85,1%) and specificity (92,8%) but the current role in paediatric OAI is limited because of radiation exposure and better alternatives. In the adult population, it can be useful to distinguish between inflammatory and degenerative changes which is impossible with bone scintigraphy (1,12,16,22,23).

The most sensitive imaging method remains magnetic resonance imaging (MRI) with high sensitivity and specificity for all types of OAI: respectively 95,6% and 80,7% for OM and 96% and 93% for SD (1,3,23). Moreover, MRI is very sensitive even in the initial stage of the infection when there is only minimal bone oedema (7). MRI also allows the diagnosis of local complications such as abscesses and guides surgical interventions (7,12). Despite this excellent performances, quick access to MRI is often compromised by the need for anaesthesia in young children.

Differential diagnosis should include traumatic, rheumatologic/inflammatory and neoplastic causes (5). Differentiation between SA and other types of arthritis like Lyme disease, transient synovitis, juvenile idiopathic arthritis and reactive arthritis can be difficult (10). Clinical examination, lab tests, cultures and imaging allow differential diagnosis in most children.

Treatment

Prompt treatment is needed to avoid sequelae (joint destruction, growth disturbances). In SA, the combination of bacterial invasion and host inflammation causes joint damage. In joints like the hip, ischemia can play a role as well due to impaired blood and nutrient supply caused by compression of blood vessels (13).

Although antibiotic treatment is evidently the appropriate treatment for OAI, no consensus has been reached regarding the optimal regimen, the mode of administration and the duration of treatment. In general, it is advised to cover Staphylococcal and Streptococcal species for all age groups, gram-negative organisms in neonates and Kingella kingae in children < 4 years (1,8).

Suggested antibiotic management is an anti-staphylococcal penicillin (ASP) (e.g. flucloxacillin) or a third generation cephalosporin (e.g. cefotaxime) combined with gentamicin for neonates <3 months. An alternative for this age group is a combination of ASP with third generation cephalosporin. First generation cephalosporin (e.g. cefazolin) should be used in the group between 6 months and 4 years (Kingella kingae) and ASP or first generation cephalosporin in older patients (6,9,10,24). In areas where the prevalence of MRSA is >10%, clindamycin or vancomycin (if clindamycin resistance rate >10%) is a better choice for empirical treatment (9,10). Neither of these antibiotics cover Kingella kingae so at least a first generation cephalosporin should be added if K. kingae is suspected (6,10). Preferential treatment according to the Belgian guidelines are a combination of cefotaxime with ASP for neonates <3 months, cefazolin or ASP for children between 3 months and 5 years of age and ASP for older children (25).

Historically, routine treatment consisted of six weeks of IV antibiotics. Nowadays, shorter parenteral treatment of 3-4 days with subsequent oral antibiotics for another 1-4 weeks can be advised for uncomplicated OAI and has been shown to be equally effective compared to longer treatment (1,2,4,26). This not only reduces cost (shorter hospitalisation) but also the risk for complications related to IV access and prolonged IV administration (4,7,27). Also, shorter antibiotic treatment than the classic 4-6 weeks can be successful in OM with the exception of vertebral OM (26). This is also shown in a prospective study in Finland which compares 20 to 30 days of treatment for hematogenous osteomyelitis (28). However, individualised decision making is advised to guide treatment and overall, transition to oral antibiotics is only advised in previously healthy children with clinical improvement, normalising CRP, settling of temperature and ability to take oral medications. Close follow-up, within 1-2 weeks after discharge is recommended to monitor further improvement (6,24,29). An average duration of therapy of 2-3 weeks for SA and 3-4 weeks of OM should be respected (24).

In SD, relative rest can be useful to allow optimal healing, normal position of the spine and to prevent progressive deformities. In cases without resolution in the first weeks of treatment short immobilisation and bracing/casting should be considered (1).

Surgical or percutaneous drainage is recommended in all patients with SA and removing all purulent material from the joint to avoid destruction is urgent (2,9,24). In OM, surgical or percutaneous drainage of subperiosteal collections and large abscesses is warranted (4). In SD surgery is only applied for children with neurological deficit, spinal instability, progressive deformity or unmanageable pain (12). When surgery is performed, appropriate cultures and biopsies should be taken (4).

A meta-analysis with 4 RCT's compared the use of dexamethasone (0,15-0,2 mg/kg, 4 times daily for 4 consecutive days) to placebo as adjuvant therapy with antibiotics for children with SA and strongly advocated for the use of corticosteroids (30). However, a Cochrane review which included 2 of these 4 RCT's, didn't draw the same conclusion and warranted that the current evidence for corticosteroids is of low quality needing further research (31).

Outcome and prognosis

Complications occur in approximately 6% of children with OM and 10-25% of children with SA. Early complications are related to persistent bacteraemia. Deep venous thrombosis for example occurs in 0,4-6%, especially in MRSA related infections (4,13). Late complications include chronic infection (1,7% in OM), avascular necrosis, growth disturbance due to involvement of the growth plate (1,8% in OM), stiffness and/or pain and pathologic fractures (1,7% in OM) (4,32). Long-term follow-up is indicated, especially in patients with infections near the growth plate (10). In SD, severe spinal deformities like scoliosis and kyphosis are possible and radiologically, the disc space can remain reduced in size and progress to a block vertebra (fusion of the adjacent vertebra) (1,12).

Described risk factors for poor outcome in OM and SA are delay in diagnosis, contiguous infection of bone and joint, neonatal infections and infections with more aggressive organisms like MRSA (13,33).

Outcome and prognosis might benefit from a consensus on classification and an algorithmic treatment approach. However, up until today, these are not available for children and long-term studies are needed to prove whether these initiatives could positively influence outcome and prognosis of OAI (4).

Retrospective cohort study

The retrospective search yielded 196 different contact files of 168 different patients. Based on the in- and exclusion criteria, 69 patients were included.

Reasons for exclusion were: other diagnosis (68), Lyme disease (4), age <3 months (6), prosthetic materials (3), chronic recurrent multifocal OM (4), relapse (3), secondary infections (6), immunodeficiency (3), insufficient data due to (partial) treatment in a district hospital (2).

Median age was 1,25 years (interquartile range (IQR): 0,9-6,0) with 42/69 (60,9%) males. Previous trauma was reported in 6/69 (8,7%) and 19/69 (27,5%) had a recent viral illness. Final diagnosis was OM in 32/69 (46,4%), SA in 25/69 (36,2%), SD in 8/69 (11,6%) and a combined OM and SA in 4/69 (5,8%). We had no cases of discitis only. The most common site of infection was the femur (10/32; 31,3%) followed by the tibia (8/32; 25%) in OM, the knee (9/25; 36%) followed by the hip and sacroiliac joint (both 5/25; 20%) in SA and the lumbar spine in SD (7/8; 87,5%).

Median interval between onset of symptoms and presentation was 2 days (IQR: 1-6). Delay in presentation was significantly longer in the SD group (median 12,5 days; IQR 2,5-19,3; p=0,003). Patients came on their own initiative in 30/69 (43,5%) and were referred by the general practitioner or the paediatrician/district hospital in 13/69 (18,8%) and 26/69 (37,7%) of the cases respectively. Swelling, pain and local warmth were significantly less present in the SD group (p=0,006, p=0,012, p=0,019 respectively) (Table 1a). Other symptoms did not differ. Median temperature at diagnosis was 38,5°C (IQR 37,1-39,5). Twenty-three patients (33,3%) were afebrile: 12/32 in the OM group, 5/25 in the SA group, 5/8 in the SD group and 1/4 in the combined OM and SA group. Six patients received antibiotics before diagnosis for other indications: ear infection (2), upper airway infection (1), suspected cellulitis (2) and fever of unknown origin(1).

CRP and WBC count were significantly higher in the SA group compared to the other groups (p=0,014 and p<0,001) (Table 1b). Blood cultures were taken in all but 3 patients. Samples from the infectious site were obtained in 24/69 (34,8%) before and in 10/69 (14,5%) after start of antibiotics of which 7/32 (21,9%) in OM (bone biopsy in 4, drainage of collection in 3), 22/25 (88%) in SA, 1/8 (12,5%) in SD and 4/4 (100%) in the combined group. In 25/34 patients additional irrigation was required (4/32 with OM, 16/25 with SA, 1/8 with SD and 4/4 with combined OM and SA). Three patients with SA underwent needle aspiration twice.

Blood cultures identified the causative organism in 18/66 (27,3%). Samples from the infectious site were positive in 18/34 (52,9%) of whom 10 had negative blood cultures. PCR identified the causative organism in 3/6 (50%, 2/3 Kingella kingae, 1/3 Streptococcus dysgalactiae) of which 2 were not detected by other methods. In total, 30/69 (43,5%) had a microbiological diagnosis (Figure 2a). In half of the cases (3/6) receiving antibiotics before diagnosis, the organism was not found. Patients with Kingella kingae infection (5/30) were significantly younger with a median age of 0,86 years (IQR 0,60-1,44) compared to other organisms (median age 3,71 years; IQR 1,03-11,73; p=0,031) and had a lower maximum temperature (38,4°C, IQR 37,4-38,6 vs. 39,3°C; IQR: 38,3-39,7; p=0,04). S. aureus infections (13/30) on the other hand were associated with significantly older age (median 11,7 years; IQR 8,75-12,95 vs. 0,98 years; IQR 0,80-1,87; p<0,001), lower WBC count (9.490/µL, IQR 7.370-11.175 vs. 14.050/µL, IQR 12.100-17.375; p<0,001), longer oral (median 35 days, IQR 23,5-38,5 vs. 22 days, IQR 14-28; p=0,008) and total (median 44 days, IQR 41,5-54 vs. 32 days, IQR 23-40; p<0,001) antibiotic treatment . No cases of MRSA were detected.

Figure 2a : *Final microbiological identification.*

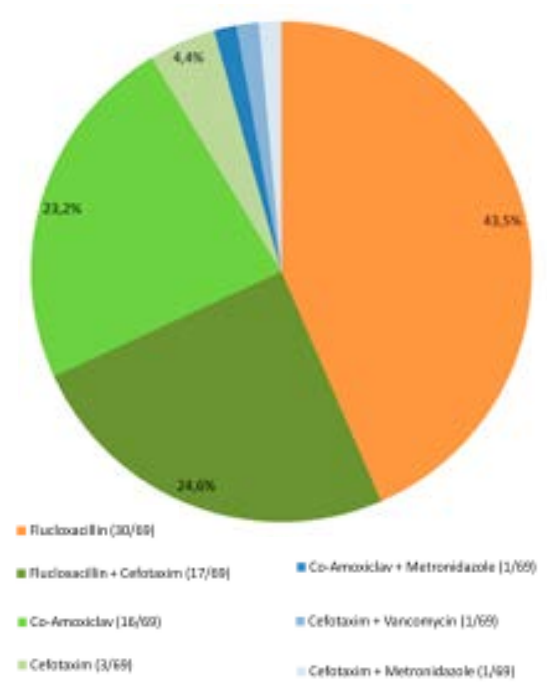


Table 1a: *Clinical signs at presentation. Groups compared using Fisher Exact.*

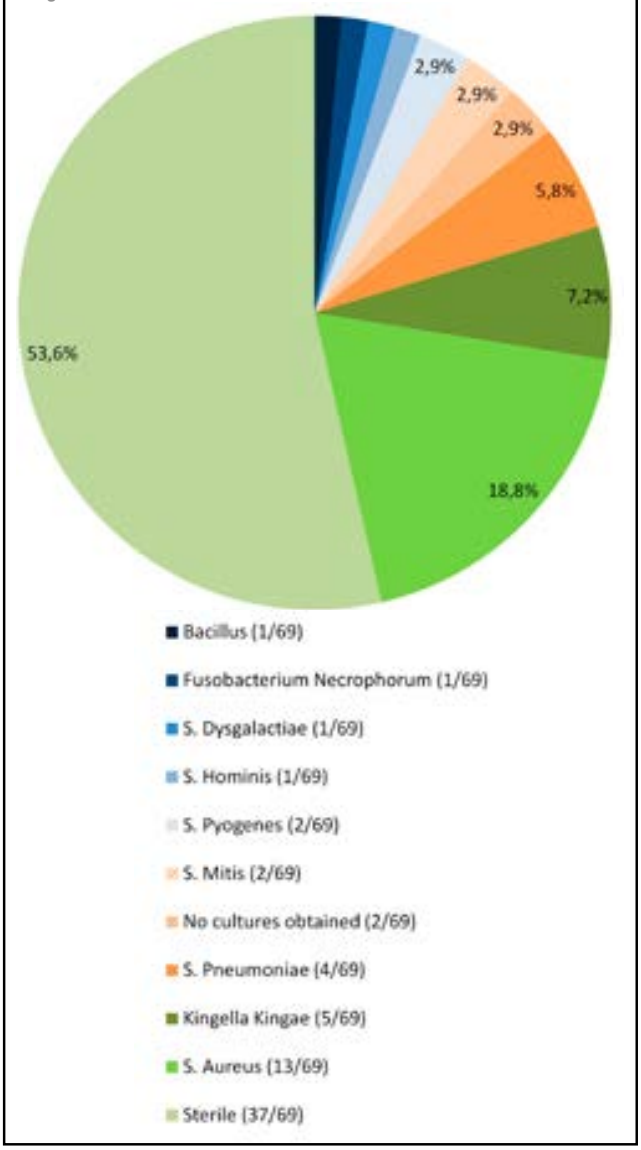
	Osteomyelitis	Septic arthritis	Spondylodiscitis	Mixed	P-value
Rubor	13/32 (40,6%)	6/25 (24%)	0/8 (0%)	0/4 (0%)	0,058
Calor	13/32 (40,6%)	11/25 (44%)	0/8 (0%)	3/4 (75%)	0,055
Dolor	32/32 (100%)	25/25 (100%)	6/8 (75%)	4/4 (100%)	0,001
Tumor	18/32 (56,3%)	11/25 (44%)	0/8 (0%)	3/4 (75%)	0,023
Functio laesa	30/32 (93,8%)	25/25 (100%)	8/8 (100%)	4/4 (100%)	0,497
Fever	20/32 (62,5%)	20/25 (80%)	3/8 (37.5%)	3/4 (75%)	0,142
Tenderness on palpation	27/32 (84,4%)	20/25 (80%)	5/8 (62,5%)	4/4 (100%)	0,393

Table 1b: *Inflammatory signs at presentation, median shown with interquartile range (IQR).*

	Osteomyelitis	Septic arthritis	Spondylodiscitis	Mixed
CRP (mg/L)	24,3 (4,4-53,8)	48,8 (24,6-82,4)	12,6 (3,1-28,7)	45,5 (22,8-166,4)
Sedimentation (mm/h)	30 (16,5-42,5)	46 (22,5-61,5)	45 (37-70)	34 (28-65)
WBC (/µL)	10.380 (8,3-12,7)	14.020 (11,8-17,1)	10.665 (9,0-13,8)	13.440 (7,0-19,9)

In our population, CT, MRI and scintigraphy were all equally diagnostically helpful (Table 2). The median waiting time for MRI was 3 days (IQR: 0-7). This was not related to a longer delay in diagnosis. If we take all diagnostic, suggestive and other signs related to OAI into account, MRI was most useful with 24/26 (92,3%) positive cases followed by CT (9/10 ; 90%) and scintigraphy (22/26 ; 84,6%). We noticed that MRI was executed more often in the second half of the study period (8/28 ; 28.6% in the first half (13.11.2012 - 13.05.2015) vs. 18/41 ; 43.9% in the second half (14.05.2015 - 13.11.2017)). We also found that MRI was executed after all other investigations in most cases (20/26 ; 76,9%), suggesting that MRI was necessary to confirm the diagnosis.

Figure 2b : *Choice of initial antibiotic treatment.*



IV antibiotic treatment was started in all patients for a median period of 8 days (IQR 6-11). Subsequently, oral therapy was given for a median of 28 days (IQR 21-36,5). Total antibiotic course varied from 20 to 64 days (median 41 days, IQR 29,5-44). Intravenous treatment duration was comparable in all groups (p=0,49). Length of oral and total treatment on the other hand was significantly shorter in the SA group compared to the other groups (21 days, IQR 17-28 vs. 35 days, IQR 26,3-39 and 28 days, IQR 23,5-40 vs. 42 days, IQR 35-46,8 respectively; both p<0,001). As stated above, treatment duration was significantly longer for the S. aureus group. Choice of antibiotics differed greatly (Figure 2b). In the group of 5 years and older, most children received flucloxacillin (15/20; 75%). In the group of 3 months to 4 years (49), none received first generation cephalosporin. Instead they received ASP (15/49), amoxicillin-clavulanate (16/49), ASP combined with a third generation cephalosporin (17/49) or a third generation cephalosporin only (1/49).

Complications during admission were abscess formation in 11/69 (15,9%) and venous thrombosis in 1/69 (1,4%). The frequency of abscess formation did not differ between the four groups (p=0,851).

All but 3 patients had a clinical follow-up after a median of 31 days (IQR 22-41) and a mean of 42,6 days (SD 52,8). Clinical resolution was achieved in 52/66 (78,8%) whereas complete resolution on conventional x-ray was present in only 26/60 (43,3%) but 7 of the abnormal 34 x-rays showed great improvement. Remaining abnormalities on x-ray were (7 cases with great improvement not included): Brodie's abscess (6/27), sclerotic changes (4/27), periostal reaction (2/27) and avascular necrosis (1/27) for the OM group, scoliosis (2/27), kyphosis (1/27), narrowing of the intervertebral space (5/27) and chronic infection (1/27) in the SD group, avascular necrosis (1/27) and sclerotic changes (4/27) in the SA group and chronic infection (1/27) and sclerotic changes (1/27) for the combined OM and SA group.

In 14/66 (21,2%) patients, clinically relevant sequelae were documented: avascular necrosis (2/14), chronic infection (3/14), limb length differences (1/14), lytic changes near the growth plate (3/14), proprioceptive difficulties (1/14), impaired range of motion (2/14), kyphosis (1/14), hyperlordosis (1/14) and scoliosis (2/14). These patients were diagnosed with OM (4/14), SA (4/14), combined infection (1/14) and SD (5/14). Two patients had a possible relapse.

Discussion

We described a large cohort of paediatric OAI, recruited at a tertiary care hospital. Epidemiological data from our study were consistent with the literature with a male predominance and the majority of patients (49/69, 71%) below the age of 5 years (4,5,9). Symptoms at diagnosis are vague in the SD group which explains the well known delay in diagnosis. CRP was significantly higher in the SA group, in line with what has been described by others (13). In our population, 6/69 (8,7%) had both negative CRP (<5mg/L) and ESR (<20mm/h) and 22/69 (31,9%) had normal WBC count (<10.000/µL) so a high index of suspicion is warranted despite negative inflammatory markers in suspicious cases.

Microbiological diagnosis was confirmed in 43,5%, with blood cultures taken in almost all patients and sampling from the disease location in 34/69 (49,2%; positive in 18/34). As expected, tissue cultures and PCR were an important asset on top of standard blood culture. Samples from the infectious

Table 2: *Imaging tests performed. The test was defined as diagnostic if it was the only diagnosis in the protocol and as suspicious if it was mentioned as part of a differential diagnosis. Other abnormalities were any other abnormalities mentioned without the use of the terms OAI, osteomyelitis, septic arthritis or spondylodiscitis. Other abnormalities assumed to be related to OAI were presence of intra-articular fluid, effusion, abscess, avascular necrosis or lytic changes.*

	Performed	Diagnostic	Suspicious	Other abnormalities	Related to OAI	Normal
X-Ray	63/69 (91,3%)	5/63 (7,9%)	13/63 (20,6%)	7/63 (11,1%)	4/7 (57,1%)	38/63 (60,3%)
Ultrasound	49/69 (71%)	3/49 (6,1%)	6/49 (12,2%)	18/49 (36,7%)	15/18 (83,3%)	22/49 (44,9%)
CT	10/69 (14,5%)	6/10 (60%)	2/10 (20%)	2/10 (20%)	1/2 (50%)	0/10
MRI	26/69 (37,7%)	17/26 (65,4%)	4/26 (15,4%)	5/26 (19,2%)	3/5 (60%)	0/26
Scintigraphy	26/69 (37,7%)	17/26 (65,4%)	4/26 (15,4%)	2/26 (7,7%)	1/2 (50%)	3/26 (11,5%)

site yielded 10 additional microbiological diagnoses and PCR identified 2 organisms that weren't detected by any other method. However, they were only performed in 34 and 6 patients respectively. A clinical study from France with 2308 patients with OAI showed that PCR detected an organism in 9% of the culture-negative joint and bone samples. Systematic use of PCR in culture-negative cases is an important consideration to aim for higher numbers of pathogen identification. Nevertheless, the impossibility of determining the antibiotic susceptibility, the high cost and the detection of contamination with irrelevant germs must be kept in mind (19).

S. aureus was the most commonly identified pathogen, but no MRSA strain nor other multidrug-resistant organisms were isolated. This is in keeping with previous publications on MRSA prevalence and is an important confirmation to set up local algorithms for empiric antibiotic treatment (14). Kingella kingae was identified in only 5 cases, all within the age group 6 months - 4 years. This age group included 48 patients of which 30 had negative cultures. Possibly, some Kingella kingae infections were missed due to its difficulty to grow on regular cultures.

Similar to other studies, MRI was shown to be most useful for definitive diagnosis of OAI. The median waiting time for MRI was rather long with 3 days (IQR 0-7). Even though this was not related to a difference in diagnostic delay, we strongly feel that dedicated slots for paediatric OAI infections would be beneficial. MRI should be feasible within 24-48h, with anaesthesia if necessary, potentially followed by guided biopsies or punctures for microbiological samples before start of antibiotics, if clinically affordable.

There was no clear consistency in antibiotic choice for our population, especially in the group below 5 years of age, partially explained by referred cases who were already started on treatment. Another explanation is the lack of local clear guidelines as all choices except for the combination of ASP with a third generation cephalosporin are valid alternatives according to the guidelines (24,25). In the group > 5 years, most did receive antibiotic treatment according to current guidelines. Duration of IV treatment was longer than suggested in most studies but the retrospective nature of our study makes it difficult to explain this difference. Reason for longer duration of treatment in the S. aureus can be explained by local complications (5/13) and delay in presentation (3/13). We believe that both clinical and biochemical evolution are crucial before stepping down to oral antibiotics.

Follow-up was extended to a maximum of 398 days and was longer than the recommended 1-2 weeks after discharge in most cases (6,29). Most cases had complete resolution of symptoms, but we documented a high incidence of clinically important sequelae (21,2%) which highlights the importance of strict and long-term follow-up. This high number of sequelae could partially be explained by the fact that this cohort-study was performed in a tertiary care centre with more complex cases and therefore more sequelae. More than 1/3 of the cases were referred from other hospitals.

This study has several limitations, the retrospective nature being the most important one. Nevertheless, our cohort distribution seems to be a fair representation of the total population when comparing our findings to the literature. Therefore, we feel that our findings in combination with the literature update is a good starting point for both local and national guidelines and protocols.

Conclusion

Paediatric OAI is an important entity that can cause significant morbidity if not treated promptly and adequately. An increase in tissue culture collection and the use of PCR techniques could greatly improve the microbiological identification of the responsible pathogen and enable directed antimicrobial therapy. Besides, dedicated MRI slots for paediatric OAI could be useful to avoid a delay in diagnosis and plan early bacteriological sample collection before start of antibiotics.

These are important findings to take into consideration when setting up local guidelines and protocols, currently still insufficiently applied for the management of paediatric OAI.

REFERENCES:

1. Principi N, Esposito S. Infectious Discitis and Spondylodiscitis in Children. Int J Mol Sci. 2016;17(4):539.
2. Gigante A, Coppa V, Marinelli M, Giampaolini N, Falcioni D, Specchia N. Acute osteomyelitis and septic arthritis in children: a systematic review of systematic reviews. Eur Rev Med Pharmacol Sci. 2019;23(2):145–58.
3. Jaramillo D, Dormans JP, Delgado J, Laor T, St Geme JW. Hematogenous osteomyelitis in infants and Children: Imaging of a Changing Disease. Radiology. 2017;283(3):629–43.
4. Funk SS, Copley LAB. Acute Hematogenous Osteomyelitis in Children: Pathogenesis, Diagnosis, and Treatment. Orthop Clin North Am. 2017;48(2):199–208.
5. Chiappini E, Mastrangelo G, Lazzeri S. A case of acute osteomyelitis: An update on diagnosis and treatment. Int J Env Res Public Heal. 2016;13(6):539.
6. Agarwal A, Aggarwal AN. Bone and Joint Infections in Children: Acute Hematogenous Osteomyelitis. Indian J Pediatr. 2016;83(8):817–24.
7. Whyte NSB, Bielski RJ. Acute hematogenous osteomyelitis in children. Pediatr Ann. 2016;45(6):e204–8.
8. Castellazzi L, Mantero M, Esposito S. Update on the Management of Pediatric Acute Osteomyelitis and Septic Arthritis. Int J Mol Sci. 2016;17(6):855.
9. Chiappini E, Mastrolia MV, Galli L, De Martino M, Lazzeri S. Septic arthritis in children in resource limited and non-resource limited countries: an update on diagnosis and treatment. Expert Rev Anti Infect Ther. 2016;14(11):1087–96.
10. Brown DW, Sheffer BW. Pediatric Septic Arthritis: An Update. Orthop Clin North Am. 2019;50(4):461–70.
11. Holmen JE, Yi J. Pyogenic arthritis. Pediatr Ann. 2019;48(9):e354–9.
12. Mohanty CB, Fieggen G, Deopujari CE. Pediatric spinal infections — a review of non-tuberculous infections. Childs Nerv Syst. 2018;34(10):1947–56.
13. Agarwal A, Aggarwal AN. Bone and Joint Infections in Children: Septic Arthritis. Indian J Pediatr. 2016;83(8):825–33.
14. Hassoun A, Linden PK, Friedman B. Incidence, prevalence, and management of MRSA bacteremia across patient populations-a review of recent developments in MRSA management and treatment. Crit Care. 2017;21(1):211.
15. Benvenuti M, An T, Amaro E, Lovejoy S, Mencio G, Martus J, et al. Double-Edged Sword: Musculoskeletal Infection Provoked Acute Phase Response in Children. Orthop Clin North Am. 2017;48(2):181–97.
16. Signore A, Glaudemans AWJM, Gheysens O, Lauri C, Catalano OA. Nuclear Medicine Imaging in Pediatric Infection or Chronic Inflammatory Diseases. Semin Nucl Med. 2017;47(3):286–303.
17. Yagupsky P. Microbiological Diagnosis of Skeletal System Infections in Children. Curr Pediatr Rev. 2019;15(3):154–63.
18. Zhao J, Zhang S, Zhang L, Dong X, Li J, Wang Y, et al. Serum procalcitonin levels as a diagnostic marker for septic arthritis: A meta-analysis. Am J Emerg Med. 2017;35(8):1166–71.
19. Levy PY, Fournier PE, Fenollar F, Raoult D. Systematic PCR detection in culture-negative osteoarticular infections. Am J Med. 2013;126(12):1143.e25-1143.e33.
20. Zhorne D, Bradford KK, Jhaveri R. Review of Pediatric Osteoarticular Infections. Rev Recent Clin Trials. 2017;12(4):260–8.
21. Drubach LA. Nuclear Medicine Techniques in Pediatric Bone Imaging. Semin Nucl Med. 2017;47(3):190–203.
22. Parisi MT, Otjen JP, Stanescu AL, Shulkin BL. Radionuclide Imaging of Infection and Inflammation in Children: a Review. Semin Nucl Med. 2018;48(2):148–65.
23. Llewellyno A, Jones-Dietteo J, Krafto J, Holton C, Harden M, Simmondso M. Imaging tests for the detection of osteomyelitis: A systematic review. Heal Technol Assess. 2019;23(61):1–127.
24. Saavedra-Lozano J, Falup-Pecurariu O, Faust SN, Girschick H, Hartwig N, Kaplan S, et al. Bone and Joint Infections. Pediatr Infect Dis J. 2017;36(8):788–99.
25. BVIKM (Belgische Vereniging voor Infectiologie en Klinische Microbiologie) - werkgroep: infecties van het osteo-articulair stelsel. IGGI guidelines DocID 1139-1142. Belgium: BVIKM, 2019, 10, 1139-1142.
26. Huang CY, Hsieh RW, Yen HT, Hsu TC, Chen CY, Chen YC, et al. Short- versus long-course antibiotics in osteomyelitis: A systematic review and meta-analysis. Int J Antimicrob Agents. 2019;53(3):246–60.
27. Alcobendas R, Remesal A, Murias S, Nuñez E, Calvo C. Outpatients with acute osteoarticular infections had favourable outcomes when they received just oral antibiotics without intravenous antibiotics. Acta Paediatr. 2018;107(10):1792–7.
28. Peltola H, Pääkkönen M, Kallio P, Kallio MJT. Short-versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: Prospective, randomized trial on 131 culture-positive cases. Pediatr Infect Dis J. 2010;29(12):1123–8.
29. Wood JB, Johnson DP. Prolonged intravenous instead of oral antibiotics for acute hematogenous osteomyelitis in children. J Hosp Med. 2016;11(7):505–8.
30. Press D. Corticosteroids as adjunctive therapy with antibiotics in the treatment of children with septic arthritis : a meta-analysis. Drug Des Devel Ther. 2018;12:2277–84.
31. Delgado-noguera M, Forero Delgadillo J, Franco A, Vazquez J, Calvache J. Corticosteroids for septic arthritis in children. Cochrane Database Syst Rev. 2018;11(11):CD012125.
32. Alvares PA, Mimica MJ. Osteoarticular infections in pediatrics. J Pediatr. 2020;96(S1):58–64.
33. Mue DD, Salihu MN, Yongu WT, Ochoga M, Kortor JN, Elachi IC. Paediatric Septic Arthritis in a Nigerian Tertiary Hospital: A 5-Year Clinical Review. West Afr J Med. 2018;35(2):70–4.