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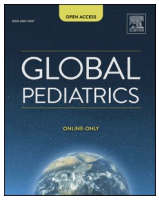

Musculoskeletal infections in childhood: Recognize early to quickly and properly treat

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ABSTRACT

In this review, we aimed to update the recent guidelines on clinical approach, diagnosis, and treatment of common musculoskeletal infections in pediatric age. Their pathophysiology and the microorganisms involved have been focused on. The clinical manifestations of septic arthritis, osteomyelitis, discitis, and pyomyositis have been underlined. Therefore, the appropriate clinical approach to early hypothesized such diseases has been delineated. The first diagnostic steps include a focused patient history and a thorough physical examination, which may offer helpful hints in suggesting a likely diagnosis. Afterwards, a simple laboratory work-up aided by prompt and appropriate imaging could lead to the correct diagnosis; sometimes, arthrocentesis or biopsy (bone, synovial, or muscle) should be performed. Updates regarding the management, including pharmacological and surgical treatments, and complications, have been reported.

1. Introduction

This review aims to update the recent guidelines and literature regarding the clinical approach, diagnosis, and treatment of common pediatric musculoskeletal (MSK) infections. This term includes several diseases, such as septic arthritis (SA), acute osteomyelitis, discitis, and pyomyositis, that may have different clinical manifestations. For this reason, MSK infections in children are challenging to diagnose due to their frequently vague and nonspecific clinical presentation. Delays to diagnosis and management and under-treatment can be life-threatening and may result in chronic disability or even fatal outcomes.[1] The changed epidemiology of these infections over the past two decades has resulted in increased disease incidence and severity in childhood. Recently, a better understanding of the pathogens of such bacterial infections, including *Kingella*, has led to prompt targeted antimicrobial coverage in all MSK infections. A quick diagnosis and treatment continue to be the mainstay in the treatment of children with MSK infections. Efforts to obtain early detection have led to improving rapid lab diagnostic testing; however, more advanced diagnostics, such as arthrocentesis for SA and MRI for osteomyelitis and pyomyositis, remain the gold standard. Shorter and narrowed antibiotic courses, with an appropriate transition to outpatient oral treatment, provide an infection clearance and reduction in complications of the disease.

2. Pathophysiology and micro-organisms

Bacteria typically enter the joint space, bone, or muscle through hematogenous spread from a distant site of infection or direct inoculation resulting from trauma or injections; sometimes, the origin is from an adjacent focus of infection. Once inside the joint or bone, bacteria replicate after adhering to extracellular matrix proteins. This triggers the activation of the host immune response, leading to the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. In SA, the mechanism is well-described: a significant recall of neutrophils further causes inflammation with synovial hypertrophy and pain; the inflammatory mediators act on proteolysis, contributing to the degradation of cartilage matrix proteins, such as collagen and proteoglycans. This process can determine the loss of joint cartilage and permanent damage, especially when not promptly treated. Furthermore, the bone around the joint is also affected. Inflammatory cytokines stimulate osteoclastogenesis, leading to bone resorption and juxta-articular osteopenia. Severe and prolonged infection can cause osteonecrosis and avascular necrosis due to impaired blood supply.[2]

Most cases of acute osteomyelitis in children with transient bacteriemia result from hematogenous seeding, which shows a preference to invade the metaphysis of immature bone. The metaphyseal spongiosa adjacent to the physis is full of blood vessels, where cartilage is

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transformed into bone through endochondral ossification. This spongiosa contains many small terminal arterioles with leaky endothelium. The combination of micro-thrombosis of such arterioles in response to inflammation or infection and drowsy regional blood flow makes a favorable environment for bacterial growth and spread.[3]

Staphylococcus aureus is the most common cause of pediatric MSK infections, followed by streptococci. Recently, *Kingella kingae* is increasingly becoming an important organism in etiology of osteoarticular infections under 3 years of age.[4] MSK infections due to *Haemophilus influenzae* have become rare in countries where immunization coverage is high; when present, children frequently present with multifocal disease with other suppurative foci of infection besides bone or joint.[5] *Salmonella* is a less common aetiologic factor for MSK infections, particularly in not immunocompetent children; among gram-negative bacteria, *Escherichia Coli* should be mentioned, mostly in neonates.

3. History and physical examinations

A focused review of the patient history and a thorough physical examination may offer helpful hints in suggesting a likely diagnosis. In the history, the pediatrician should especially investigate recent trauma, skin wounds, surgical interventions, previous respiratory or cutaneous infections (e.g., chickenpox and impetigo), animal or insect bites, recent use of antibiotics, vaccinations, or intramuscular injections. Obviously, any pre-existing pathology, such as chronic lung disease, liver disease, immunodeficiency, sickle cell anemia, rheumatological disease, and diabetes should be considered. For newborns, special conditions (prematurity, perinatal asphyxia, umbilical catheterization femoral venipuncture, pre-existing pathologies such as sepsis, urinary tract infection, and admission to the neonatal intensive care unit) should be investigated.[4]

On physical examination, peripheral and axial joints, bone, and muscle should be carefully checked. Children with suspected SA, have arthritis with pain or restricted range of motion of the affected joint, clinical signs of effusion as feel warm to touch and overlying erythema. When a joint or muscle of the lower extremity is affected, children may be unable to bear weight or walk or at least have a limp. The hip represents a challenge to evaluate for effusion because the joint cannot be visualized and appreciated by physical examination. Beyond osteoarticular examination, the physician should evaluate the child with a special attention to the general condition (quick look), skin, mucous membranes (lesions, wounds, rashes, and aphthae), eyes (redness), and abdomen looking for hepato-splenomegaly. Fever should be measured, as well as vital parameters.

4. Clinical manifestations

The diagnosis of childhood SA and acute osteomyelitis is fundamentally a clinical one. Presenting symptoms in pediatric patients may be non-specific and vary by age. Children with SA commonly complain of a single swollen, painful joint but they may also present with nonspecific symptoms, such as fever or limp, whereas neonates and infants present acutely with septicemia, cellulitis, or fever with no origin.[1] Although a history of trauma is usually absent, families may attribute symptoms to a known trauma.

Children with acute osteomyelitis have symptoms that progress over several days to a week; they most commonly present with low or no fever, pain in the affected limb without evident signs of inflammation. Focal findings (warmth, swelling, and tenderness) with limited mobility may develop in the following days.

The challenge is the wide spectrum of presentation modalities, ranging from fever, alone or associated with a limp, to fulminant septic shock; this variability is also related to the different ages. In infants, it often manifests with difficulty or refusal to weight bear or use an extremity (pseudo paralysis).[6] A further challenge is represented by the common association between SA and acute osteomyelitis, the latter often complicated by the first (possible, although rarely, vice versa). Childhood pyomyositis, occurring either in isolation or in association with SA and/or osteomyelitis, can further complicate the diagnostic process because of its nearly identical clinical and biochemical presentation; pain and non-weight-bearing with pseudo-paralysis are the chief cornerstone of the diagnosis in neonates and young children. The thigh and pelvis seem to be the most affected by pyomyositis.[1]

5. Laboratory diagnostic tests

There is no single test that can confirm or rule out MSK infections. A combination of careful history, physical exam, few laboratory tests, imaging, and aspiration/biopsy is typically required to make a definitive diagnosis. White blood cell (WBC) count is generally, but not always, elevated; WBC $>$ 12,000 is considered indicative of MSK infection. The value of C-reactive protein (CRP) according to Bisht et al., has the highest predictive significance for SA;[7] Rutz et al reported that CRP levels $>$ 2 mg/dL in patients with intense pain on weight-bearing are highly suggestive for SA and should be further explored, whereas a negative CRP and the ability to bear weight are consistent with transient synovitis of the hip.[8] CRP is higher when osteomyelitis and SA are associated; values $>$ 10 mg/dL seem to be indicative of associated arthritis and the need for longer IV antibiotic therapy. CRP is also useful for monitoring the course and therapeutic response: it peaks 36–50 h after the infection onset and normalizes after a week of therapy. Erythrocyte sedimentation rate (ESR) $>$ 40 mm/h is suspicious for MSK infection and $>$55 mm/h for abscess formation, whereas a value $<$ 22 mm/h seems to rule out SA. ESR and CRP combined, although not specific, are the most sensitive diagnostic markers for MSK infections, and they have high value as negative predictors.[9] Procalcitonin (PCT) is a potentially useful biomarker during the initial assessment of children suspected to have a MSK infection; however, it seems to be outperformed by CRP.[1,10]

In a recent prospective study on 258 children with MSK infections, the authors concluded that a systematic evaluation using a combination of parameters improves the accuracy of assessment and assists predictive judgment under uncertainty: PCT $<$0.1 ng/mL, ESR $<$18 mm/h, CRP $<$3.3 mg/dL, and temperature $<$37.8 °C should reasonably exclude the MSK infection, given the high negative predictive value and collective accuracy of these parameters[11] .

The traditional methods of evaluation, including serology, synovial fluid analysis and culture remain other significant management steps. Cultures of blood and synovial fluid may be helpful; nevertheless, it is well known that more than half of the results are negative, although the infection still exists. Emerging technologies, including biomarkers and DNA sequencing techniques, molecular investigations by real-time polymerase chain reaction can improve pathogen detection.[12]

6. Imaging

Imaging evaluation is a crucial component of the diagnostic workup of these entities. Diagnostic workup of pediatric MSK infections involves several imaging modalities. Conventional radiographs, although they have a low sensitivity for the detection of osteomyelitis, continue to be the first-line imaging modality for evaluating pediatric MSK infections, particularly early in the course of the disease. Ultrasound, which is fast, noninvasive, and radiation-free, is ideal for evaluating superficial soft tissue infections and SA. In addition, ultrasound-guided joint aspiration can both facilitate diagnosis and provide symptomatic relief. However, its role in aiding the early detection of pyomyositis and osteomyelitis, is not fully delineated. MR imaging, due to its superior sensitivity and specificity, is the current gold standard to diagnose and localize sites of the infection, in particular acute osteomyelitis and pyomyositis, and to identify associated complications.[13] CT can be useful if rapid MRI acquisition is difficult.

7. Treatments

As *Staphylococcus aureus* is the prevalent agent responsible for MSK infections, first-line empirical therapy should be based on this etiological concern and MRSA prevalence: cephalosporin I or II generation (cefazolin, 150 mg/Kg/day) or anti-staphylococcal penicillin (oxacillin, 150–200 mg/Kg/day in 4 doses) in countries with low prevalence (<10 %) is the best choice; clindamycin (45 mg/Kg/day in 3 doses) should be chosen where MRSA prevalence is over 10 % and clindamycin resistant to S. aureus <10 %; vancomycin (45 mg/Kg/day in 3 doses) should be added if MRSA prevalence >10 % and clindamycin resistant *S. aureus* >10 %. Antibiotic selection is then adjusted based on culture and sensitivity results, and treatment is prolonged for a total of 4–6 weeks depending on age and disease severity. Recent literature suggests an early transition to oral therapy: in uncomplicated MSK infections with localization other than the vertebra, children > 3 months, apyrexia from 48 h, CRP < 3 mg/dL, and good compliance the switch is possible within 7 days; in the complicated forms (such as multiple distribution, immunocompromised child, sepsis, extensive bone destruction, high suspicion of resistant microorganism) the iv antibiotics should be prolonged until 14 days, and even longer (21 days) in children under 3 months of age.[14] The benign form due to the *Kingella kingae*, when ascertained, can be treated with oral amoxicillin-clavulanate or cefixime since the beginning. Additionally, if a child is ill-appearing, is failing antibiotics, or has an abscess greater than 2 cm in diameter, surgical intervention is recommended, either abscess drainage or tissue debridement, as indicated.[15] Up to 90 % of patients with osteomyelitis are treated conservatively successfully, especially if they start antibiotics in the first few days of illness.[15]

8. Conclusions

Musculoskeletal infections are relatively rare but potentially serious conditions in the pediatric age. If detected early, they heal without results. Therefore, the identification of signs and symptoms often blurred at onset is the pillar to approach children with MSK infections for whom the hospitalization is necessary. The appropriate management consists of prompt intravenous antibiotic therapy; subsequently, close clinical and laboratory monitoring is required to early detect complications.

A multidisciplinary approach is optimal in the management of MSK infections in children, given the complexity with which such infections may manifest, particularly among severely ill children. The team approach includes emergency medicine, pediatric intensive care, pediatric hospitalist medicine, infectious disease service, orthopedical surgery, radiology, pharmacology, and hematology.[16]

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Sandra Trapani: Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

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