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Managing of musculoskeletal infections in children

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Abstract. – OBJECTIVE: Epidemiological features of musculoskeletal infections are in continuous evolution. The incidence of emerging causative pathogen is arising. Nevertheless, up to 50% of osteoarticular infections shows negative cultures. Septic arthritis, with or without concurrent osteomyelitis, are most common in newborn while osteomyelitis frequently affects older patients. We retrospectively analyzed all the children affected by musculoskeletal infections treated at the Children's Hospital Bambino Gesù in ten years, focusing on the results of an early diagnostic and therapeutic management.

MATERIALS AND METHODS: The study population consists of 150 children with acute septic arthritis, osteomyelitis and discitis, treated from 2006 to 2016, excluding patients with less than 12 months of follow-up and previous treatment sustained in others hospitals. A wide spectrum of data has been extracted from clinical charts, laboratory studies and imaging. Patients were categorized into 3 groups on the base of their age. The diagnostic and therapeutic protocol consisted of intravenous empirical treatment while diagnosis was ongoing then switched to oral treatment, according to the pathogen and the systemic symptoms.

RESULTS: Only 31% of pathogens were identified. The most common was *Staphylococcus aureus methicillin-sensible (MSSA)* but an increase of cases caused by *Kingella Kingae and Staphylococcus aureus methicillin-resistant (MRSA)* was observed. The mean antibiotic treatment was 6.8 weeks. It's important to underline a significant correlation between age and C-reactive protein serum levels.

CONCLUSIONS: Among others frequent pathogens, *MRSA* shows a high rate of physis involvement.

Musculoskeletal infections represent a challenge in skeletally immature patients because of their potential severe complications. Timing of diagnosis and consequent targeted treatment is fundamental to avoid complications and functional sequelae.

Key Words
Osteomyelitis, septic arthritis, children, pediatrics, musculoskeletal infections

Introduction

Musculoskeletal infections in childhood are an ongoing condition because of continuous epidemiological changes. The incidence in developed countries is about 2-13 per 100.000 children per year but this rate is higher in other countries[1-4]. A wide spectrum of infections may involve the different musculoskeletal districts of the child. Among all skeletal infections, septic arthritis and osteomyelitis are the most frequent but usually affect bone and joint as separate pathologies[5]. However, in some cases these conditions may arise as concurrent infections[6]. Discitis and pyomyositis occur infrequently, but, because of the seriousness of their sequelae, they should be kept in mind by the physician. The most common pathogenesis of acute osteomyelitis is hematogenous, with a consequent bacterial localization into the long bones metaphyseal portion. Bone involvement by infection contiguity from soft tissues or traumatic contamination is less common[7,8]. Concomitant osteomyelitis and acute septic arthritis occur most often in newborn and young child. In these cases germs contaminates the joint passing through the transphyseal vessels, as a consequence of a transient bacteremia[9,10]. Compared to septic arthritis, osteomyelitis is more common in older children. Its diagnosis is frequently delayed, especially in neonates, because of their reduced immune response[11,12]. Historically *Staphylococcus aureus methicillin*

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susceptible (*MSSA*) has been the most frequent cause of bone and joint infections. Nevertheless, in the last few decades, it has been observed a significant change in osteoarticular infections pathogenesis, due to emerging pathogens[13,14]. A recent study shows that *Kingella kingae* is responsible of up to 80% of osteoarticular infections in children younger than 4 years[15]. In these cases, clinical presentation and inflammatory markers result mild-to-moderate. Infections caused by *Hemophilus influentiae B* (*HiB*) are very rare in developed countries. Anyway *HiB* has to be considered as a possible cause of musculoskeletal infections in unvaccinated children[14]. *Staphylococcus aureus methicillin resistant* (*MRSA*) the responsible pathogen in the 30-40% of cases observed in the USA[13]. *Streptococcus pneumoniae* is responsible for the 67% of osteomuscular infections in immune compromised children affected by *HIV*[16].

The rate of negative cultures results fluctuates from 33% to 55% and it's connected to an inability to identify the germ responsible for the infection[17,18].

The typical onset of musculoskeletal infections is characterized by pain, swelling, fever and reduced range of motion. However, in presence of less virulent germs the onset of clinical signs and symptoms may be subacute. Instrumental diagnosis starts with standard plain radiographs. Generally, bone infection detection on X-rays is not possible before 2 weeks from the disease beginning, when a significant mineral density of the bone is lost. MRI is the most complete imaging instrument to detect osteomyelitis, evaluating both bone and adjacent soft tissues involvement. Among others imaging procedures, it's the technique with greater sensitivity (82-100%) and specificity (75-96%). When MRI STIR sequences show normal bone marrow signal the negative predictive value for osteomyelitis is near to 100% [19]. Ultrasound is generally useful to assess the hip joint involvement or to evaluate sub-periosteal abscesses.

Despite a relatively low incidence, musculoskeletal infections may produce dramatic complications. Acute osteomyelitis and septic arthritis could determine osteochondral joint disruption, growth disturbance with leg discrepancy or axial deviation, toxic shock or, rarely, death[20,21]. Since the introduction of systematic antibiotic treatment the mortality rate decreases near to zero. Nevertheless, secondary multi-organ involvement with septic shock is a rare but serious condition generally associated with *Group A*β*–haemolytic Streptococcus pyogenes* (*GABA*) or *Staphylococcus aureus methicillin-resistant* (*MRSA*)[11,21,22]. Commonly, in those cases the blood level of procalcitonin arises, in response to the inflammatory cytokines and endotoxins environment developed [23]. The clinical presentation and response to medical treatment correlate with patient's age, site of infection, type of pathogen and comorbidities[14]. A timely diagnosis is mandatory in order to minimize complications, decrease treatment duration and improve the outcomes. This retrospective study focuses on the results of early management of acute musculoskeletal infections occurred in 150 consecutive children recruited and treated in our Hospital from January 2006 to January 2016.

Patients and methods

A retrospective study including patients affected by musculoskeletal infections was carried out. Children with acute septic arthritis, acute osteomyelitis and discitis, treated in our Hospital from January 2006 to January 2016, were screened for inclusion. Ninety-nine males and 51 females were enlisted. The Hospital's institutional review board (Institutional Ethics Committee) approved all the procedures described in this investigation. The research was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki as revised in year 2000. All the patients and their parents gave written informed consent prior to medical and surgical procedures and agreed to be included in this study. Inclusion criteria were a complete follow-up in our hospital (more than 1 year) and the absence of previous treatment in other medical structures. Patients with an unclear medical history or incomplete follow-up data were excluded as well as patients with chronic infectious processes. Moreover, no patients with less than 12 months follow-up were included in this study. Data were extracted from medical records used during the diagnostic process. Sex, age, site and side of infection, fever and duration of symptoms were examined, like also history of previous traumas, duration of hospitalization and clinical evaluation (refusal to weight-bear, pain scale, swelling, range of motion). Informations about local and general infection related complications like leg discrepancy, growth disturbance, avascular necrosis, chronic osteomyelitis, deep vein thrombosis and pulmonary embolus were also collected. In addition were analyzed data regarding pathogens, laboratory studies (white and red cells count, erythrocyte sedimentation

rate [ESR], C-reactive protein [CRP], aerobic and anaerobic cultures, procalcitonin blood level) and types of imaging (obtained from Carestream digital system). Patients were categorized into three groups based on age. The A group included patients from birth to 1 year old. The B group population was aged from 1 year to 4 years old. The C group patients were between 4 and 17 years old. In our hospital, we developed a diagnostic and therapeutic protocol for the management of osteomyelitis in the pediatric age.

All children hospitalized for osteomyelitis underwent intravenous empirical antibiotic treatment. It is known that it's highly recommended to obtain diagnostic specimens prior antibiotic treatment to start. This approach is mainly useful in regions with a high rate of *MRSA* or *Panton-Valentine leucocidin-positive* (*PVL-positive*) *Staphylococcus aureus*.

Children were intravenously treated until they got a clinical improvement (no pain or no fever and decreased inflammation indexes, such as CRP). After that we usually switched the antibiotic treatment to oral administration after 5-7 days, unless risk factors were present. The most common oral therapies were ciprofloxacin, linezolid, rifampicin (never alone) or amoxicillin/clavulanate. In uncomplicated osteomyelitis the most frequently empiric therapies used were 3rd generation cephalosporin, first generation cephalosporin, or anti-staphylococcal penicillin. In case with *MRSA* as pathogen (either confirmed or suspected), osteomyelitis and osteoarthritis were treated with vancomycin, linezolid, daptomycin or clindamycin, alone or associated with rifampicin or gentamicin. In children under 5 years of age we always associated a specific antibiotic therapy against *Kingella kingae*. In young infants up to 3 months old cefotaxime with gentamicin may be a good choice. The global time of therapy was of 3-4 weeks in uncomplicated forms and up to 4-6 weeks in *MRSA* infections, newborns, slow-resolution forms and spine or pelvis localization.

Even if this protocol is in line with the osteomyelitis international guidelines, we adapted it to our local microbiological situation and according to local resistance patterns.

Statistical Analysis

Standard statistical methods have been used for descriptive statistics. Correlations between data were determined via the Spearman test. All analyses were performed according to the intention-to-treat principle. All tests were two-sided, with significance set at a p value less than 0.05. Results are presented as mean ± standard deviation (SD).

Results

One hundred and fifty patients met the inclusion criteria of the study. The mean age was 6.48 SD 5.097 years. Fifty percent of the musculoskeletal infections occurred in children under 4 years of age. Fever (59%) and swelling (59%) resulted as the most common clinical symptoms at onset. Septic bacteremia was observed in 20% of cases. Table I shows clinical signs and diagnostic procedures related to age. Osteomyelitis was diagnosed in 78 cases (52%) and septic arthritis in 72 children (48%). In 33% of patients an abscess was detected.

Musculoskeletal infections localizations in newborns were 46 (group A), in toddler were 40 (group B) and in older children and teen-agers (group C) were 88. Fifteen children had multifocal osteomyelitis (10%).

Table II reported the site of infection related to age. Overall, the most frequent localization was

Table I. Baseline characteristics of Patients pertaining to age.

	0-1 years of age (yrs)	2-4 yrs	5-17 yrs	Total
Swelling	64%	43%	63%	59%
Fever	44%	53%	67%	59%
Sepsis	12%	13%	26%	20%
Arthritis	66%	50%	44%	50%
Abscess	36%	25%	35%	33%
Positive Microbial Culture	21%	19%	33%	27%
Pain	97%	97%	97%	97%
Biopsy	12%	15%	23%	18%
Curettage	0.6%	0.9%	14%	12%
Time of treatment (weeks)	5.6 SD 2.4	5.1 SD 1.6	7.9 SD 8.6	6.8 SD 6.9

Table II. Location of the infection related to the age.

	0-1 years of age (yrs)	2-4 yrs	5-17 yrs	Total
Mandible	0	0	1	1
Humerus	9	0	2	11
Clavicle	0	0	2	2
Femur	10	10	26	46
Fibula	2	1	6	9
Tibia	5	5	17	27
Talus	6	3	6	15
Ulna	0	0	2	2
Radius	2	0	3	5
Hip	0	1	5	6
Spine	7 (1C, 2D, 3L, 1S)	11 (0C, 0D, 7L, 4S)	11 (0C, 2D, 6L, 3S)	29 (1C, 4D, 16L, 8S)
Calcaneus	5	9	7	21
	46	40	88	174

the femur (26,5%) followed by the spine (17%), the tibia (15%) and the heel (12%). In newborns the humerus was the second site of infection. The pathogen responsible of infection was identified in 46 patients (31%) (Table III). The most common pathogen successfully cultured was *MSSA* and it was found in twenty-two cases (48%). *Staphylococcus aureus methicillin-resistant* (*MRSA*) was identified in 5 cases (11%), *Mycobacterium tuberculosis* in 3 cases (7%), *Streptococcus pneumoniae* in 3 cases (7%) and others in the remaining 27%.

The inflammatory markers, in total sample, evidenced a mean erythrocyte sedimentation rate of 41.66 SD 28.18, a mean value of C-reactive protein of 6.616 SD 7.932 and a mean white cell count of 12033 SD 6346 (Table IV). A high value of procalcitonin blood level was seen in children with fever > 39° or with bacteremia (20%). The totality of patients underwent X-Rays study as first step imaging. Early MRI was performed in 137 children of the total. Ultrasound has been used to study all forms of septic arthritis (72 cases). Computed tomography has been helpful in twenty-seven selected patients.

This study evidenced an increasing rate of musculoskeletal infection during the last 6 years. Above all, we observed that, from 2012 to 2016, the rate of infection has doubled year by year.

The mean treatment duration was 6.8 weeks and the mean follow-up was 13 months. Twelve percent of patients required a surgical curettage of the bone infection or a drainage/aspiration of the septic arthritis. Complications were observed in 47 patients (31%). Twelve patients presented joint range of motion limitation, in 8 patients was evidenced a

Table III. Pathogens identified by culture-positive specimen.

Pathogenic Agents	Cases	Percentage
Staphylococcus aureus methicillin-susceptible (MSSA)	22	48%
Staphylococcus aureus methicillin-resistant (MRSA)	5	11%
Mycobacterium tuberculosis	3	7%
Others (group B *Streptococci*, *H. influenzae*, *K. kingae*…)	16	27%

Table IV. Inflammatory markers value at baseline.

	0-1 years of age (yrs)	2-4 yrs	5-17 yrs	Total
ESR	48.31 SD 32.75	34.93 SD 25.10	41.60 SD 27.06	41.66 SD 28.18
CRP	4.82 SD 7.8	3.81 SD 5.2	8.4 SD 8.4	6.616 SD 7932
Leucocyte count	14652 SD 7177	11610 SD 5504	11092 SD 6041	12033 SD 6346

Table V. Correlation analysis between inflammatory markers values and time of treatment and age.

	Time of treatment/ ESR	Time of treatment/ CRP	Time of treatment/ Leucocytes	Age/ESR	Age/CRP	Age/ Leucocytes
Spearman r	0.3314	0.2669	0.06713	-0.03826	0.2591	-0.2168
95% confidence interval	0.1690 to 0.4762	0.1014 to 0.4181	-0.1048 to 0.2352	-0.2006 to 0.1261	0.1026 to 0.4032	-0.3649 to -0.05798
p-value (two-tailed)	<0.0001	0.0014	0.4306	0.6489	0.0014	0.0079
p-value summary	***	**	ns	ns	**	**

joint avascular necrosis, 8 patients suffered from leg discrepancy and 3 from vertebral deformity. In 16 cases a delayed chronic osteomyelitis was still present after treatment. Several correlations between the obtained data were performed and results were reported in Table V. Specifically, it was observed a significant correlation between age and C-reactive protein while ESR blood value related to age was not significant (Figures 1-2).

Conclusions

Our survey evidenced an increased incidence of pediatric musculoskeletal infections over time, starting from 2010. Since 2010, the cases of skeletal and muscle infection have doubled every year compared to the previous one. Boys had a double infection rate than girls. Single-bone infection resulted more common than multifocal.

In more than 1/3 of patients, the infectious process started after a trauma, more frequently of the lower limbs. This is probably due to a transient silent bacteremia that found in the traumatic hematoma a rich, favorable microenvironment for germs growth. More than 10% of the infections were sustained by *MRSA*. These patients had major early complications and/or delayed sequelae with frequent physis involvement (Figure 3). They also required prolonged medical therapy and surgical drainage of the infection (Figures 4a-b). In absence of germ identification, an empirical antibiotic therapy was adopted in more than half of the patients. Musculoskeletal infections with poor symptoms and signs, low inflammatory indexes and absence of high fever or without signs of systemic involvement, were treated suspecting *Kingella kingae* as pathogen with excellent results. The study evidenced a high correlation between CRP and the age of the patient at the onset. Furthermore a significant correlation was observed between treatment duration and ESR and CRP values. However, in reason of the quicker blood level decrease, CRP better correlates with therapeutic response to antibiotics than ESR and clinical signs.

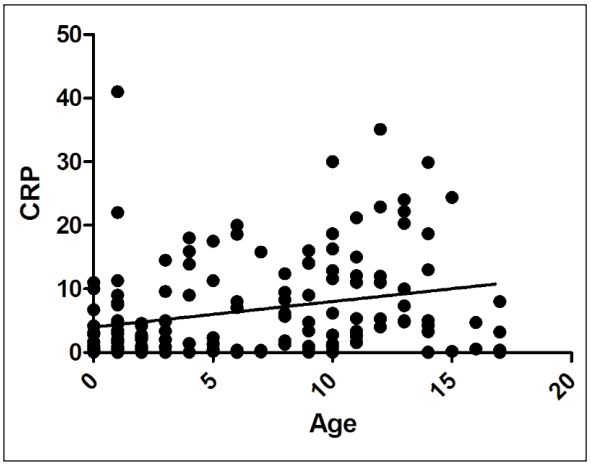

Figure 1. Correlation analysis between age and CRP.

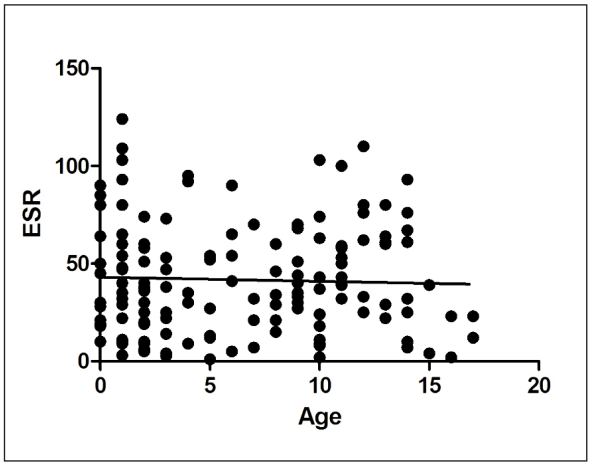

Figure 2. Correlation analysis between age and ESR.

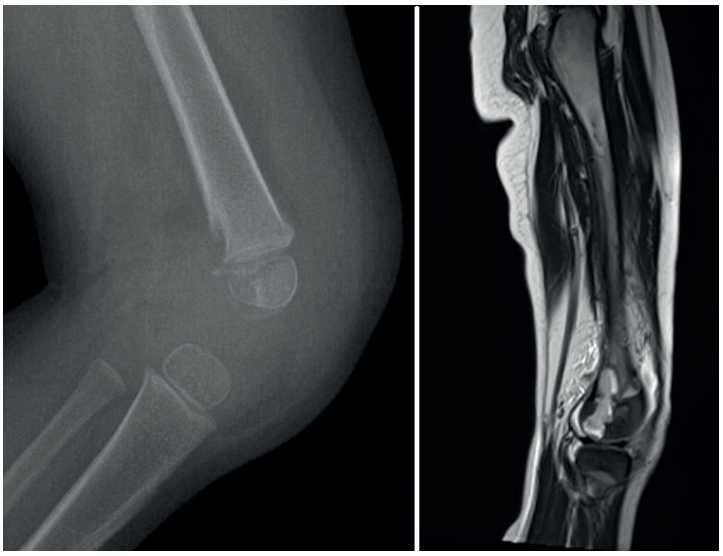

Figure 3. A 2 years and 4 months old boy presented one day fever, weight bearing refusal and reduced articular range of motion from 1 month. After 2 weeks appeared left knee swelling. At the X-rays lateral view we observe a posterior cortex irregularity, periosteal reaction and soft tissues swelling. On MRI, a low density lesion with peripheral contrast enhancement is recognizable on the posterior-lateral side of the distal femur crossing the growth cartilage and invading the physis. The microbial culture of the synovial fluid was negative. The first pharmacological treatment used Linezolid and Ceftriaxone without healing marks. After 6 days the antibiotics were interrupted and a treatment with Meropenem started which led the patient to healing.

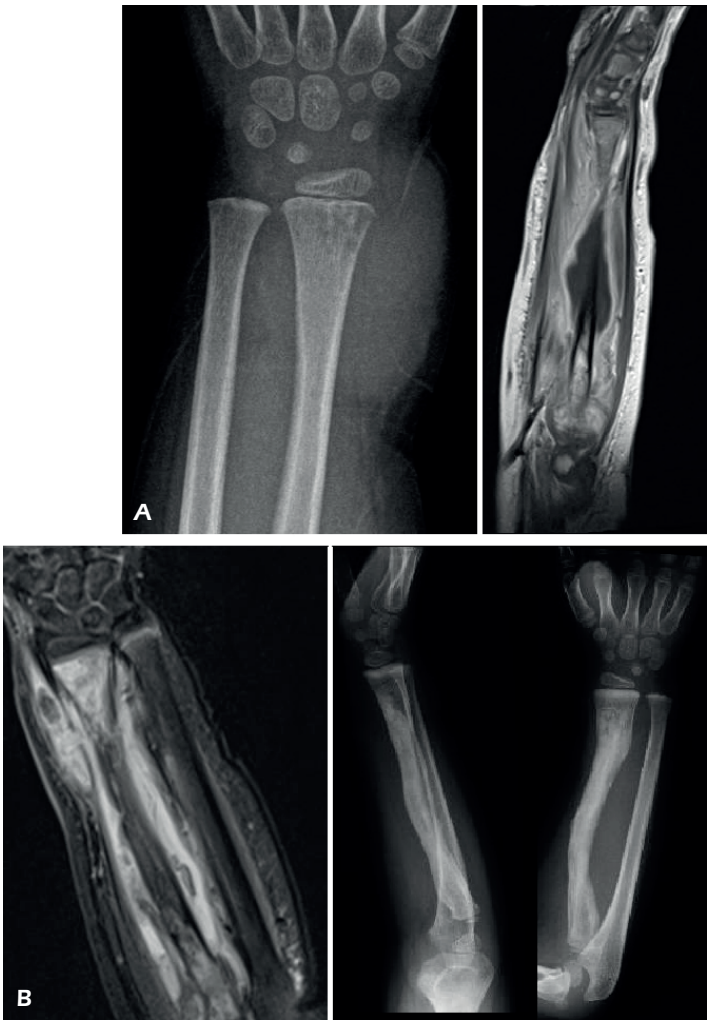

Figure 4. A-B, A 3 and half years old female presented upper right limb swelling, erythema and fever from 3 days, with reduced hand and fingers motility. No significant images were detected on immediate X-rays. MRSA was found on blood culture and antibiotic therapy started with Clarithromycin and Ampicillin. After 9 days radiographs showed osteolysis spots on the distal radius metaphysis. Antibiotic treatment continued but, after an attempt of switching the treatment from intravenous to oral, a soft tissue abscess developed, shows on MRI. So, a new intravenous therapy with Ceftriaxone and Linezolid was prescribed. The 3° month X-ray shows an evident deviation of the radius diaphysis that improved during the patient growth.

In general, musculoskeletal infections remain a relatively rare event. Nevertheless, osteomyelitis and septic arthritis represent a challenge in skeletally immature patients because of their potential severe complications or sequelae. To avoid delay in diagnosis, a timely multidisciplinary approach is required. Timing in diagnosis makes the difference. A particular attention should be given to children suffering from chronic diseases, sickle-cell condition, premature newborns and immune-compromised patients due to their greater vulnerability to atypical organism and high-risk for related complications[3,24]. According to recent Literature, short intravenous antibiotic therapy (3-7 days) followed by a shift to oral treatment for 20-30 days shows good results in both uncomplicated osteomyelitis and septic arthritis[25,26]. Some authors have evaluated the efficacy of short therapy in two groups of patients with and without bacteremia[27]. This study suggest that, even in case of bacteremia associated with uncomplicated bone and joint infections, short antibiotic therapy give good results. It reduces the time of hospitalization and related costs with better compliance of children and parents. Prolonged intravenous treatment should be reserved to complicated musculoskeletal infections. The inflammatory markers are the best indexes to decide to stop the therapy. Commonly, CRP normalizes in 10 days while ESR needs about 25-30 days. However, complete remission of signs and symptoms remains a good guide for monitoring the progress of therapeutic response.

Pathogens should be identified before starting treatment. However, in more than 50% of cases, it doesn't happen and an empiric treatment is required. In those patients, the antibiotic choice should be taken regarding to patient age, infection localization (osteomyelitis vs septic arthritis) and the illness severity. In children less than 4 years old, in presence of mild-to-moderate inflammatory markers (WBC <14.000/mm; CRP <55 mg/l; bands <150/mm), fever <38° and poor clinical signs, the suspect of infection sustained by *Kingella kingae* should be taken[28]. It represents an emergent cause of infection in children under 4 years old[17].

The suspect of a creeping osteomuscular infection is primary based on clinical evaluation, especially in presence of an unclear history that explains a reduced range of motion or weight bearing refusal.

Identifying the germ causing the infectious process may be difficult. Osteomyelitis with unidentified etiology (culture-negative) represent a significant rate[17,18]. This aspect must be considered for the potential complications related to treatment delay. In osteomyelitis and septic arthritis sustained by *MRSA* and *Group A beta-haemolytic streptococcus pyogenes* (*GABA*), if systemic symptoms are present, an aggressive treatment with surgical decreasing of bacterial load is strongly recommended in order to reduce the level of cartilage-degrading enzymes and germs toxins and minimize or prevent rapid joint involvement.

A proper therapy for musculoskeletal infections results from a methodological approach in the diagnostic process. Complications could be reduced if joint fluid or bone specimen acquisition is rigorous and antibiotic therapy started in a timely manner. First-line empirical therapy may be adjusted considering the geographical incidence of pathogens, state of immunization, age of child, and site of infection. Once germs identification is obtained, treatment must be confirmed or revised. If, despite antibiotic treatment, inflammatory markers remain elevated, the patient should be reevaluated. This because high levels of serum markers of infection is generally related to poor outcomes and delayed complications. In reason of a more rapid blood level decrease, CRP better correlates with therapeutic response to antibiotic treatment than ESR and clinical signs.

The retrospective nature of the study partially limited the results. In the future, the systematic use of polymerase chain reaction for detection of DNA/RNA of different pathogens will help to promptly identify these forms and to start specific therapy. These efforts will be directed to reduce prolonged, often empirical and poorly specific antibiotic treatments and effectively treat more virulent infections that, in a considerable percentage of cases, still hesitate in significant sequelae.

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Conflict of Interests

The authors have no conflict of interest to declare.

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