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Acute osteomyelitis and septic arthritis in children: a systematic review of systematic reviews

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Abstract. – OBJECTIVE: Septic arthritis and osteomyelitis are rare in children, but they are difficult to treat and are associated with a high rate of sequelae. This paper addresses the main clinical issues related to septic arthritis and osteomyelitis by means of a systematic review of systematic reviews.

MATERIALS AND METHODS: The major electronic databases were searched for systematic reviews/meta-analyses septic arthritis and osteomyelitis. The papers that fulfilled the inclusion/exclusion criteria were selected.

RESULTS: There were four systematic reviews on septic arthritis and four on osteomyelitis. Independent assessment of their methodological quality by two reviewers using AMSTAR 2 indicated that its criteria were not consistently followed.

CONCLUSIONS: Collectively, these works provide strong evidence regarding a large number of issues including classification, epidemiology and risk factors, causative organisms, clinical presentation, laboratory markers, imaging, diagnostic needle aspiration, antibiotic therapy, surgical therapy, and prognosis. A clinical summary based on the best evidence is supplied.

Key Words:
Osteomyelitis, Septic arthritis, Children.

Introduction

Osteoarticular infections are complex conditions, especially in paediatric patients, which unless treated promptly and correctly can result in limb impairment or in life-threatening conditions[1].

Osteomyelitis (OM) is an inflammation of bone, usually due to infection with bacteria or other micro-organisms (e.g., fungi), that is associated with bone destruction. Septic arthritis (SA) is an infection of the synovial space that involves the synovial membrane, the joint space, and joint structures[2].

SA and OM are commonly divided into three types based on aetiology: haematogenous, secondary to contiguous infection, and secondary to direct inoculation. The distinctive anatomical characteristics of younger children, especially the presence of vessels between metaphysis and epiphysis and of intracapsular metaphyses, involve that a bone infection may lead to SA secondary to OM and vice versa[2]. Unless an effective treatment is promptly initiated, the intense inflammatory reaction that is often associated with SA or OM has the potential to destroy structures such as the articular cartilage[3] and the epiphyseal growth plate, resulting in long-term disability due to functional impairment of the joint or to limb asymmetry[2]. Since timely diagnosis is vital for a satisfactory outcome, SA and OM must be ruled out in any child presenting with a painful limb or joint or with a fever of unknown origin[4].

The main issues related to SA and OM are classification, epidemiology and risk factors, causative organisms, clinical presentation, laboratory markers, imaging, diagnostic needle aspiration, antibiotic therapy, surgical therapy, and prognosis[1,3,5,6].

The aim of this systematic review of systematic reviews is to identify the best available evidence regarding the management of paediatric SA and OM.

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Materials and Methods

Literature Search Strategy

A search of the Medline (via Pubmed), Embase, Amed, and CISCOM electronic databases was performed for works published from 1 January 2000 to 31 October 2017. The search terms used were: septic arthritis, osteomyelitis, children, clinical trial, meta-analysis, and systematic review. The reference lists of all the papers thus identified were examined for further relevant references. No language restrictions were applied.

Study Selection

Only systematic reviews and meta-analyses of studies involving paediatric patients were included. Non-systematic reviews, overviews, clinical trials, and reviews of non-clinical investigations were excluded. The most common reasons for exclusion were the facts that a review was not systematic or that it did not include paediatric populations. Study selection was performed separately by each author. The following clinical information on SA and OM was extracted from the papers: classification, epidemiology and risk factors, causative organisms, clinical presentation, laboratory markers, imaging, diagnostic needle aspiration, antibiotic therapy, surgical therapy, and prognosis.

The methodological quality of the systematic reviews that were included in the study was assessed independently by two reviewers using the AMSTAR 2 tool[7].

Evidence Synthesis

A meta-analysis of systematic reviews is complex, especially due to overlaps, since some of the primary studies may be included in more than one review. To address the problem, a qualitative evidence synthesis was provided for each of the key topics listed above.

Results

The search identified a total number of 97 papers on SA and 224 on OM. After evaluation of the abstracts, the full text of 37 publications on SA and 53 on OM were examined; of these, 9 systematic reviews (SRs), 5 on SA and 4 on OM, were included. Only one SR from each set discussed all the topics addressed in this work, whereas the others focused on specific issues.

The methodological quality of most SRs was low to moderate (Tables I and II).

Septic Arthritis (Table III)

Classification

None of the SRs included in the study examined SA classification.

Epidemiology and Risk Factors

Two of the SRs addressed SA epidemiology and risk factors.

Kang et al[5] reported an incidence of 1 in 100,000 in industrialized countries and a higher incidence in developing countries (1 in 20,000 in Africa and 1 in 5000 in Malawi). These data were confirmed by Rutz et al[3]. The two SRs agreed on the fact that SA affects more frequently young male children (infants and toddlers being involved most frequently) and children with respiratory distress syndrome, an umbilical artery catheter, and conditions associated with heightened susceptibility to infection (e.g., prematurity, low birthweight, sickle-cell haemoglobinopathy, and small size for age).

Causative Organisms

According to both SRs[3,5] *Staphylococcus aureus* is the most frequent causative pathogen of SA, followed by group A Streptococci (GAS) and *Enterobacter* spp. An emerging problem according to both SRs is the increasing incidence of infections caused by methicillin-resistant *S. aureus* (MRSA), also in patients who are not at significant risk of MRSA. These community-associated (CA) MRSA strains exhibit lower antibiotic resistance than hospital-acquired (HA) strains.

The incidence of arthritis due to *Haemophilus influenzae*, a highly common paediatric pathogen in the past, is declining due to vaccination programmes, whereas *Kingella kingae* is increasingly being isolated, probably due to the greater accuracy of current diagnostic tools.

According to Taj-Aldeen et al[8], the most common fungal osteoarticular infections are due to *Aspergillus* and *Candida* spp, whereas hyalohyphomycetes, dematiaceous moulds, and Mucorales are the non-*Aspergillus* filamentous fungi isolated most frequently. The main aetiology of fungal arthritis is direct inoculation, followed by haematogenous dissemination and contiguous spread. In immunocompetent patients, the most common mechanism of infection is road accidents involving knee puncture or penetrating wounds.

Table I. AMSTAR synopsis (modified from Cargnelli et al 2017).

	Study	A prior design	Two reviewers	Literature search	Status of publication	List of studies	Study characteristics	Scientific quality	Conclusions	Combining findings	Publications bias	Conflict of interest
Septic	Kang et al. 2009	NO	CANNOT ANSWER	YES	YES	NO	NO	YES	YES	YES	NOT APPLICABLE	YES
Arthritis	Rutz et al. 2013	NO	CANNOT ANSWER	NO	YES	NO	NO	NO	CANNOT ANSWER	CANNOT ANSWER	NO	YES
	Farrow et al. 2015	NO	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES
	Taj-Aldeen et al. 2015	NO	CANNOT ANSWER	YES	YES	NO	NO	NO	YES	YES	YES	YES
	Table I.	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
	Zhao et al. 2017	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES
Osteomyelitis	Hotchen et al. 2017	YES	CANNOT ANSWER	YES	YES	YES	YES	NO	YES	YES	NO	YES
	Dartnell et al. 2012	NO	YES	YES	YES	NO	NO	NO	YES	YES	NO	YES
	Howard-Jones et al. 2013	NO	CANNOT ANSWER	YES	YES	YES	YES	YES	YES	YES	NO	YES
	Taj-Aldeen et al. 2015	NO	CANNOT ANSWER	YES	YES	NO	NO	NO	YES	YES	YES	YES
	Gill et al. 2017	NO	CANNOT ANSWER	NO	YES	NO	NO	NO	YES	YES	NO	YES
	Mooney et al. 2016	NO	CANNOT ANSWER	YES	YES	YES	YES	NO	YES	YES	NO	

yes; no; cannot answer; not applicable

Table I. AMSTAR synopsis (modified from Cargnelli et al 2017).

	Study	A prior PICO	Selection design	Literature criteria	Selection in search	Extraction duplicate	Excluded in duplicate	studies
Septic arthritis	Kang et al. 2009	Yes No	No	No	Partial yes	No	No	No
	Rutz et al. 2013	No	No	No	No	No	No	No
	Farrow 2015	Yes	No	Yes	Partial yes	No	No	No
	Taj-Aldeen et al. 2015	No	No	No	Partial yes	No	No	No
	De Sa et al. 2015	No	Partial yes	No	Partial yes	Yes	Yes	No
	Zhao et al. 2017	Yes	Partial yes	Yes	P	Yes	Yes	No
Osteomyelitis	Hotchen et al. 2017	No	Yes	No	Partial yes Yes	No	No	No
	Dartnell et al. 2012	No	No	No	Partial yes Yes	Yes	No	No
	Howard-Jones et al. 2013	No	No	No	Partial yes Yes	No	No	No
	Taj-Aldeen et al 2015	No	No	No	Partial yes Yes	No	No	No
	Gill et al 2017	No	No	No	Partial yes Yes	No	No	No
	Mooney et al. 2016	No	No	No	Partial yes Yes	No	No	No

	Study detail	Risk of bias	Sourches of funding	Statistical combination method	ROB in meta-analysis	ROB in results	Heterogeneity expl	Publications bias	Conflict of interest
Septic arthritis	No	Partial yes no	No	No meta-analysis Conducted	No meta-analysis Conducted	Yes	Yes	No meta-analysis conducted	Yes
	No	No	No	No meta-analysis Conducted	No meta-analysis Conducted	No	No	No meta-analysis conducted	Yes
	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
	No	No	No	No meta-analysis Conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Yes
	Yes	No	No	No meta-analysis Conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Yes
	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Osteomyelitis	Yes	No	No	No meta-analysis Conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Yes
	No	No	No	No meta-analysis Conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Yes
	Yes	No	No	No meta-analysis Conducted	No meta-analysis conducted	Yes	Yes	No meta-analysis conducted	Yes
	No	No	No	No meta-analysis Conducted	No meta-analysis conducted	Yes	yes	No meta-analysis conducted	Yes
	No	No	No	No meta-analysis Conducted	No meta-analysis conducted	No	yes	No meta-analysis conducted	Yes
	No	No	No	No meta-analysis Conducted	No meta-analysis conducted	Yes	yes	No meta-analysis conducted	No

yes; no; cannot answer; not applicable

Table III.

Classification	Not mentioned in the SRs included in the study
Epidemiology	1/100,000 in industrialized countries; 1/20,000 to 1/5000 in developing countries
Risk factors	Young age (neonates and toddlers); invasive catheterization; host status (all immunodeficiency-associated conditions)
Causative organisms	*S. aureus* is the most common agent. The incidence of MSSA, MRSA, GAS, group B streptococci, and Enterobacter spp is rising. *H. influenzae* in non-vaccinated children, *K. kingae* in younger children
Clinical presentation	Age-related. *Neonates:* pseudoparalysis, paradoxical irritability. *Infants and toddlers:* refusal to bear weight. *Older children:* pain, ROM loss, antalgic position
Laboratory markers	*WBCs:* age-related (higher values in older children); their threshold in association with other parameters is > 12 x 109/L. CRP: high predictive value, threshold > 20 mg/L. ESR: useful when SA is suspected (threshold, 40 mm/h). PCT: high diagnostic value (threshold, 0.5 ng/mL)
Imaging	*US*: useful to detect and monitor joint effusion. X-rays: mandatory to exclude other conditions. *MRI:* highly sensitive and specific
Microbiological investigations	*Joint aspiration:* Mandatory when SA is suspected. A Gram stain and a WBC count (threshold > 50,000 with > 75% of polymorphonuclear leukocytes) should be performed to confirm the diagnosis. Synovial culture is required to confirm diagnosis and target therapy, but is positive in 34 to 82% cases. If no is fluid obtained, injection of 3-5 mL sterile saline solution and reaspiration is recommended. *Blood culture*: should always obtained
Antibiotic therapy	Empirical antibiotic should be started immediately and targeted treatment should be administered as soon as the causative micro-organism is isolated; short IV course (2-4 days) followed by oral antibiotic (6 weeks) in case of non-complicated SA
Surgical therapy	Should be adopted in case of frankly purulent fluid on diagnostic aspiration, absence of response to antibiotics, late presentation (> 5 days from symptom onset)

Clinical Presentation

According to the three SRs mentioned above[3,5,8], clinical presentation varies depending on patient age and causative organism.

In neonates and infants, the clinical presentation may be barely appreciable or completely absent. In the early stage, symptoms are non-specific and may include irritability, refusal to walk, absent or limited spontaneous movement of the limb (pseudoparalysis), and/or paradoxical irritability. In older children, the most common findings are local signs and symptoms, especially at the onset. Clinical findings typically include a swollen and painful joint associated with the typical signs of inflammation (pain, effusion, functional impairment, tenderness, and local warmth). In SA involving the hip, the limb is often held in an antalgic position (slightly flexed, externally rotated, and abducted) to reduce intracapsular pressure. Loss of passive ROM is often an early symptom, at least in hip SA[3].

As regards fever, Kang et al[5] stressed that other clinical signs, imaging studies, and inflammatory markers besides hyperpyrexia are required to rule out SA.

Late presentation is associated with systemic manifestations and oedema involving the entire lower limb, cellulitis, or abscess formation.

As regards joint infections related to fungi, Taj-Aldeen[8] reported that fever alone is not sufficient to exclude SA and that the most characteristic findings are local pain and inflammation.

Laboratory Markers

White blood cell count. According to Kang et al[5], the white blood cell (WBC) response is age-related: leukocytes are rarely elevated in newborns with SA, they may be raised in younger children, and are commonly elevated in older children, although the authors do not report a threshold value. Rutz et al[3] described 6 studies where the WBC threshold, associated with other parameters suspicious for SA, was > 12 x 10^3/L.

Erythrocyte sedimentation rate. According to Kang et al[5], the erythrocyte sedimentation rate

Table IV.

Summary	Key Points
Classification	Several classifications have been described. Those for clinical use should include bone involvement, antimicrobial resistance patterns of the causative micro-organisms, host status, and soft-tissue coverage
Epidemiology	From 1.94 to 13 new cases in 100,000 in developed countries rising to 43 in 100,000 in Polynesia and to 200 in 100,000 among Aboriginal populations
Risk factors	Systemic infection; penetrating trauma; SCD. Risk factor are not found in nearly 50% of cases
Causative organisms	*S. aureus* is the most common pathogen, but the incidence of MRSA is rising. *H. influenzae* must be suspected in non-immunized children. *K. kingae* is becoming one of the most common Gram-negative causative pathogens and must be suspected in younger children
Clinical presentation	Local signs and symptoms are the most common clinical elements; 40% of children can be afebrile
Laboratory markers	WBCs: elevated values may indicate a severe form of OM. ESR: > 55 mm/h is highly suspicious for abscess formation, whereas a value < 22 mm/h seems to rule out SA. CRP: > 100 mg/L values seem to be indicative of associated arthritis and of the need for longer IV antibiotic therapy. ESR and CRP combined are the most sensitive diagnostic markers
Imaging	US: poor sensitivity and specificity. Useful to depict and monitor complications (e.g. periosteal thickening, soft-tissue / periosteal abscess, joint effusion); X-rays: mandatory to exclude other conditions: the typical findings do not appear in the early stage; MRI: gold standard with high sensitivity and specificity, especially in early-stage disease; CT: the best approach to assess bone status (e.g. cortical destruction, sequestrum): it should be reserved for selected cases; bone scan: discordant sensitivity and specificity data; useful to exclude multifocal OM
Microbiological investigation	Biopsy: usually unnecessary to diagnose OM; early biopsy, recommended in the past, is now rarely performed
Antibiotic therapy	A short course of IV antibiotics followed by 3 weeks oral antibiotics for uncomplicated OM. The clinical condition (persistent fever and elevated CRP) is the best indicator of the need for continuing IV antibiotics

(ESR) alone has a sensitivity of 79%, but combined with other measures (e.g., high temperature, increased WBC count, very painful weight-bearing) it is an important exclusion parameter whose sensitivity exceeds 98%. Rutz et al[3] reported the results of 5 studies where ESR (threshold, 40 mm/h) was considered as a key diagnostic parameter for SA.

C-reactive protein. According to Kang et al[5], the values of C-reactive protein (CRP) have the highest predictive significance for SA; in contrast, Rutz et al[3] reported that CRP levels > 20 mg/L 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.

Procalcitonin. Zhao et al[9] conducted a meta-analysis on the ability of procalcitonin (PCT) to distinguish SA from non-septic arthritis and concluded that it has a greater diagnostic value than CRP. However, as in the case of the other blood indices, PCT alone cannot diagnose or exclude SA, whereas combined with other factors it may help diagnose an infected joint (threshold value, 0.5 ng/mL).

Imaging

Ultrasound. Rutz et al[3] and Kang et al[5] reported that ultrasound (US) is very useful to detect joint effusion, especially at the level of the hip joint. However, given that the rate of false negatives is 5%, Rutz et al[3] suggest that a negative US scan should be interpreted with caution, particularly in patients where symptoms have arisen less than 24 h earlier. They also stated that US is not sufficient to discriminate SA from transient synovitis.

X-rays. Kang et al[5] noted that plain radiographs are required to differentiate SA from other conditions (e.g., OM, fracture, neoplasms), and that an increase in joint space is an indirect sign of effusion. In contrast, Rutz et al[3] stressed that

plain radiographs, though essential, are not sufficiently sensitive to diagnose or exclude SA.

Magnetic resonance imaging. As regards magnetic resonance imaging (MRI), Kang et al[5] and Rutz et al[3] both reported that SA is associated with a signal change in bone marrow and with a signal alteration of surrounding soft tissues on contrast-enhanced scans. In patients with transient synovitis of the hip, the relevant MRI findings are effusion in the contralateral, asymptomatic hip joint and absence of bone marrow changes. In addition, MRI is extremely sensitive and specific in diagnosing SA, particularly of the hip, and in differentiating it from other conditions (such as OM or non-infectious arthritis)[5].

Diagnostic Aspiration

According to Rutz et al[3], there is an agreement in the literature that diagnostic needle aspiration is required to confirm a diagnosis of SA, to isolate the pathogen and initiate an appropriate antibiotic treatment. They also stressed that the procedure is mandatory in the presence of four clinical factors that are highly suggestive for SA – a CRP value > 20 mg/L; pain on weight-bearing; fever ≥ 38.5°C; and a serum WBC count > 12×10^9/L – and in unclear situations. If no fluid is drawn, the aspiration should be repeated after injection of 3-5 mL sterile saline solution.

A positive Gram stain (found in < 40% of patients according to Kang et al[5]), a positive culture, purulent aspirate, and > 50,000 WBCs/mm^3 with a predominance of polymorphonuclear cells in synovial fluid are all suggestive of SA. The threshold of 50,000 WBCs ,however, should be correlated with the clinical picture, to diagnose or exclude juvenile idiopathic arthritis.

According to Kang et al[5] and Rutz et al[3,5], a blood culture has an important diagnostic role, and in some cases, it may show the causative micro-organism even in the presence of a negative synovial fluid culture. The authors thus suggest performing both examinations.

Kang et al[5] noted that since SA diagnosis based on blood and synovial fluid culture is obtained in 34 to 82% of cases, a negative culture should be correlated with other parameters such as laboratory, clinical, and imaging findings, to exclude SA.

Treatment

Antibiotic therapy. Kang et al[5] and Rutz et al[3,5] agreed that empirical antibiotic treatment should be initiated immediately, and later modified once the causative micro-organism has been isolated. The empirical treatment should consider patient age and condition (disease severity, risk factors, and immune status), local epidemiological patterns, the antibiotic susceptibility of local isolates, and Gram stain results. The two SRs state that the initial antibiotic therapy should cover Gram-positives (particularly *S. aureus* and GAS) and that clindamycin is effective to treat infections due to clindamycin-sensitive MRSA. Hib (*H. influenzae* type B) coverage is also mandatory in non-vaccinated patients and in young children with *K. kingae* infection. The authors of the two SRs also agree that the initial antibiotic treatment should be intravenous (IV), although the ideal time of the switch to oral therapy and total treatment duration are debated. There is mounting evidence for short-course (2-4 days) IV antibiotic treatment in case of a positive response and clinical improvement, and agreement on the fact that prolonged IV antibiotics should be reserved for patients who do not respond or have clear clinical or microbiological contraindications. Rutz et al[3] reported that treatment duration (IV + oral) used to range from 10 days to 24 weeks, whereas in the more recent studies it ranges from 20 to 31 days. Kang et al[5] stressed that a shortened treatment (< 6 weeks) does not involve adverse effects.

Farrow's SR on corticosteroid use in SA[10] reported that their addition to antibiotic therapy is held to reduce symptom duration and the levels of the inflammatory indices, with a possible protective effect exerted on the articular cartilage, without side effects. The author concluded that "*...There is however insufficient evidence to make treatment recommendations at present ... Long-term safety data and the determinations of the optimum route, dose, and timing of corticosteroids are also required*".

Surgical therapy. Although paediatric SA is considered as an emergency, neither Kang et al[5] nor Rutz et al[3] found a consensus in the literature on the timing and type of surgery to be performed, although both SRs reported that arthrotomy is accepted in patients with hip arthritis. However, the SR on hip arthritis by Rutz et al[3] suggests that recent disease (symptoms onset < 5 days) without complications could initially be treated without surgery; however, *"at all times a septic joint condition should be treated as an emergency and after finding pus by the diagnostic needle aspiration, arthrotomy or arthroscopic irrigation should be performed immediately"*. The authors also stated that surgery becomes necessary if the clinical picture does not improve and

CRP does not decline within 24 h of antibiotic initiation.

Neither SR found studies showing the superiority of one surgical treatment over another. The procedures described were i) arthrotomy and joint lavage and ii) daily US-guided aspiration and irrigation with arthroscopic drainage.

The SR on hip arthroscopy by de Sa et al[11] stated that the procedure is a "*safe and effective treatment option for selected patients (e.g., no deformity, no bacterial infections, and not immunocompromised)*"; they reported no complications, particularly in paediatric or adolescent patients suffering from conditions such as acute slipped capital femoral epiphysis, avascular necrosis, premature physeal closure, or proximal femoral growth arrest.

Prognosis

Kang et al[5] described a reduction in SA mortality from 50% in 1874 to < 1% in 1973, due to diagnostic and therapeutic advances. They listed five negative prognostic factors: young age, since diagnostic problems involve delay in treatment initiation; transepiphyseal vessels in newborns, which are also associated with immune system immaturity; therapeutic delay (excellent results are obtained in 75% of patients treated promptly and in only 15% of those treated ≥ 4 days from symptom onset); causative bacteria (*S. aureus*, particularly MRSA, is associated with a more severe course); and site (the hip has the worst outcome). The three SRs[3,5,11] concurred that prompt diagnosis and treatment are the most critical prognostic factors.

Osteomyelitis

Classification

Hotchen et al[12] reported that several variables for OM classification are described in the literature. However, only bone involvement, antimicrobial resistance pattern of the causative micro-organism, host status, and soft-tissue coverage correlate therapeutic response and prognosis. Parameters such as aetiopathogenesis and onset (acute/chronic) do not show a close correlation.

Epidemiology and Risk Factors

Dartnell et al[6] reported that the incidence of OM varies widely, from 1.94 to 13 new cases in 100,000 in developed countries, to 43 in 100,000 in Polynesia and to 200 in 100,000 in Aboriginal populations.

Analysis of its skeletal distribution showed that the metaphyses are the sites affected most commonly, due to the characteristic circulation and the presence of sinusoids, especially in the femur and tibia.

The same paper[6] stressed that in more than 50% of cases it is impossible to find underlying risk factors or causes, and that a history of systemic infection or penetrating trauma accounts for the majority of the remaining cases. Sickle-cell disease (SCD) is an established risk factor for OM. The skeletal distribution of lesions is similar to that found in non-SCD-associated OM, but multifocal forms are more frequent. Aetiopathogenesis is related to the effects of SCD on the microcirculation, including intestinal and bony micro-infarcts that facilitate bacterial penetration and OM development.

The SR by Gill et al[13] has found that non-typhoidal *Salmonella* OM in immunocompetent children without haemoglobinopathy involves a low risk; in particular, only 14% of the cases described in their SR were associated with recent foreign travel or exposure to undercooked food or reptiles.

Causative Organisms

In children less than 4 years old, 60% of cases of infection are related to *Streptococcus* and Gram-negative bacteria; the remaining cases are due to *S. aureus*. In children older than 4 years, the most common bacterium is *S. aureus*. In the past decade, several studies have reported an increase in the frequency of MRSA compared with community-related infections, either CA and HA.

The Hib vaccine has significantly reduced the incidence of OM due to *H. influenzae* type B in paediatric patients. However, in areas where its diffusion is limited or vaccination programmes are poor the bacterium is still a frequent cause of paediatric OM.

The rate of culture-confirmed OM due to *K. kingae* has been increasing and has overcome Hib as the most common Gram-negative cause of OM in young children. This aerobic Gram-negative is usually found in the respiratory tract of children, it is characterized by slow growth, and it is notoriously difficult to isolate in culture.

According to Dartnell et al[6], the most common causative agents of SCD-associated OM are *S. aureus* and *Salmonella*. Gill et al[13] reported that non-typhoidal *Salmonella* OM is an uncommon disease that is however associated with a high rate of complications such as abscess formation,

relapse, and multifocal OM. The most common causative serotypes are *S. enteritidis*, *S. typhimurium*, group B, group C1, *S. oranienburg*, and *S. saint-paul*.

Laboratory Markers

White blood cells. Dartnell et al[6] found no study addressing serum WBCs in relation to the age of OM patients. They reported that abnormal counts at presentation are found in 35.9% of cases, that the parameter has limited sensitivity and specificity, particularly in younger children, and that values vary widely depending on the causative organism and on the presence/absence of SA. Since the highest values are found in patients with particularly virulent bacteria and with concomitant SA, the WBC count is a useful marker that can alert the clinician to a severe course.

Erythrocyte sedimentation rate. Dartnell et al[6] reported that the ESR affords high sensitivity, especially in patients with an abscess or associated SA. In particular, an association has been found between an ESR value > 55 mm/h and abscess formation in a patient with pelvic OM, whereas a value < 22 mm/h was a negative predictive factor in patients with a periosteal abscess or pyomyositis in generalized OM.

C-reactive protein. Dartnell et al[6] stressed that CRP is the most useful blood marker to distinguish OM from the SA-associated disease. In particular, values > 100 mg/L are more frequently associated with a complicated course and are the best predictor of the need for > 6 days of IV antibiotics. According to Taj-Aldeen et al[8], CRP is useful to monitor treatment effectiveness in OM due to non-*Aspergillus* spp, but not in disease due to *Candida*.

Imaging

X-rays. X-rays are critical for differential diagnosis. However, abnormalities are rarely seen before 2 weeks, whereas the characteristics changes may take 2-3 weeks to show in the long bones and up to 4-6 weeks in flat bones.

Ultrasound. Dartnell et al[6] reported that US affords poor sensitivity and specificity in OM diagnosis. However, in developing countries, where second-level imaging may not be available, the US is quite useful, especially in association with X-rays. Deep soft-tissue swelling is an early sign of OM; periosteal elevation > 2 mm on US indicates a periosteal abscess. In patients managed conservatively, the US can be used to monitor treatment efficacy. Finally, US can depict all OM complications, such as periosteal thickening, soft-tissue/periosteal abscess, and joint effusion.

Magnetic resonance imaging. Dartnell et al[6] noted that an emergency MRI scan is the best diagnostic imaging tool for early OM diagnosis and that it also detects complications such as abscesses or joint involvement. Mooney et al[14] shared this view and reported that MRI was consistently accurate in diagnosing calcaneal OM. The latter authors reported that the evidence for the usefulness of MRI is conflicting, due to the high vascularization of the metaphyses which hampers the discrimination of pathological from normal signal. They also noted that contrast-enhanced imaging is useful the when oedema is visible on unenhanced scans.

Tc99 bone scintigraphy. The data on the sensitivity and specificity of this approach in OM patients are contrasting[6]. Recent studies have reported false-negative results in about half of the cases described. Bone scans are useful to identify OM sites, to exclude/diagnose multifocal forms, and to predict prognosis, since cold positive scans are often associated with a more severe course that requires more aggressive treatment.

Treatment

Antibiotic therapy. Howard-Jones et al[15] in their SR concluded: "We suggest that uncomplicated acute osteomyelitis in children > 3 months old should be treated with 3-4 days of IV antibiotics, and if the child is responding clinically, they can transition on oral antibiotics to a total duration of 3 weeks (GRADE 2B). First generation cephalosporins and clindamycin have shown similar efficacy in the treatment of acute osteomyelitis in geographies with low MRSA and *K. kingae* prevalence (GRADE 2B). There are insufficient neonatal data to support 4 weeks of IV antibiotics for neonatal osteomyelitis". An initial short IV course with anti-staphylococcal cover, to be modified after delivery of the culture data and followed by 3-week oral therapy in patients with uncomplicated OM, is also supported by Dartnell et al[6]. Temperature > 38.4°C and a CRP value > 100 mg/L are the best indicators of the need for continuing the IV treatment. Dartnell et al also stated that: "Provided the oral antibiotic is effective and the correct dose is given, the child should be converted as soon as there is a clinical improvement and the haematological markers are normalizing. A total of three weeks of antibiotic treatment is usually sufficient in uncomplicated cases, but the clinician must be guided by the in-

dividual patient". They stressed that benzylpenicillin or a cephalosporin should be added to the regimen of unvaccinated children and that the MRSA cover in the starting antibiotic therapy is still a debated issue. They also noted that clindamycin, due to its excellent bone penetration and oral bioavailability, was effective against OM caused by clindamycin-sensitive MRSA.

In patients with SCD-associated OM, in the absence of data on the local prevalence of *S. aureus* and *Salmonella,* the empirical treatment should include antibiotics effective against both.

Surgical therapy. Dartnell et al[6] reported that surgical management with early biopsy and debridement is now used less frequently than in the past, and that there is a tendency to employ conservative treatment. Several authors recommend surgical treatment if the clinical picture does not improve with antibiotic therapy. In addition to treating OM, the surgical procedure also allows collecting samples of purulent material for isolation of the causative bacterium.

The surgical approach is important in case of complicated OM, for instance, to drain abscesses. According to Dartnell et al[6], surgical drainage should be performed in patients with pelvic OM showing abscesses > 2 cm and periosteal elevation > 2 cm in long bones on US, even though good results have also been reported with periosteal abscesses > 3 mm. The surgical treatment should thus be guided both by lesion size and by the local antibiotic response. Mooney et al[14] reported that in patients with calcaneal OM surgical treatment should be reserved for patients with "*continued pain, localized erythema and swelling despite initial treatment, and the presence of an abscess or osseous destruction with imaging*", although the literature is not univocal on this issue.

Prognosis

Dartnell et al[6] stated that OM mortality had decreased significantly compared to the pre-antibiotic era, when it was > 30% in patients with tibial OM and > 50% of those with femoral OM. They also reported that the main negative prognostic factors include infection due to MRSA, *Streptococcus pneumoniae*, or micro-organisms carrying the Panton-Valentine leukocidin gene (PVL), which are most frequently related to MRSA or methicillin-sensitive staphylococcal (MSSA) infections. The gene encodes a necrotizing cytotoxin that confers extreme virulence. Other negative prognostic factors include concomitant SA, pyomyositis, and abscess; a positive culture (probably because a negative one is found with less virulent bacteria such as *K. kingae*, which have a less severe course); younger age (probably due to diagnostic delay, anatomical and vascular features, and immune system immaturity); and treatment delay (results are worse if treatment has been started > 5 days from symptom onset).

Discussion

Acute osteomyelitis (AO) and acute septic arthritis (ASA) are serious conditions that are viewed as emergencies, since a satisfactory outcome depends on prompt diagnosis and treatment.

Given the scanty number of cases, especially in developed countries, the literature on most diagnostic and therapeutic approaches (like the multidisciplinary approach, which involves the intervention of several specialists) is quite limited. Although several innovations have been introduced, they are not mentioned in any of the SRs included herein.

As regards prognosis, recent studies suggest that infections involving different tissue types behave differently in relation to the primary tissue involved, with a descending hierarchy from bone to joint, muscle, and soft tissue[16,17]. Children with OM only and those with OM and SA have higher rates of bacteraemia at presentation than those with SA alone[17].

Septic Arthritis

The incidence of ASA is age-related and tends to decline with rising age. Special care should be devoted to neonates, who are at high risk of bone, joint, and deep soft-tissue infection with CA and HA pathogens. In particular, neonates with invasive lines and catheters (especially an umbilical artery catheter) are at high risk of developing HA infections – including MRSA and multidrug-resistant Gram-negative rods – as well as *Candida* spp – most often *C. albicans* and *C. parapsilosis* – during hospitalization, but sometimes even weeks after discharge. The immature immune system of neonates may induce an abnormal presentation, for instance with lack of fever, unremarkable levels of the inflammatory markers, and limited pain, and pseudoparalysis may be the only sign on clinical examination.

Streptococcus agalactiae (group B Streptococci) infection is a frequent cause of SA in infants. In older children, the most common cause of musculoskeletal infection is *S. aureus*, although

SA due to *K. kingae* is frequent in children aged from 6 months to 4 years. SA caused by *S. pneumoniae* and *H. influenzae* is most frequent in unimmunized children, but it can also be caused by non-vaccine serotypes in fully immunized children[17-21]. Children with suspected SA showing risk factors for and clinical features of OM in adjacent bones present a clinical challenge.

Joints with intracapsular metaphyses, such as the proximal humerus and proximal femur, are most susceptible to develop adjacent OM[22]. Advanced imaging should be considered to assess young children with SA and possible adjacent OM[23,24].

Supplemental laboratory tests, including chemical and cellular analysis of joint fluid, peripheral WBC count, and serum ESR and CRP, are often employed to diagnose SA in children[25]. According to the widely accepted[3] diagnostic algorithms reported by Kocher et al[26,27] and modified by several authors, patients with joint infection typically have peripheral a WBC count > 12,000/mL, serum CRP levels > 2 mg/dL, and an initial ESR > 40 mm/h.

In patients where a high clinical suspicion is supported by imaging findings, blood culture and joint aspiration are needed to confirm the diagnosis. However, obtaining confirmation of an SA diagnosis is difficult, due to the low rate of microorganism isolation from joint fluid. PCR amplification of DNA sequences of bacteria retrieved in joint fluid increases sensitivity and specificity, but since it is still experimental, it is neither standardized nor widely available[18,21].

Most patients with proved or suspected SA are immediately started on empirical parenteral anti-staphylococcal antibiotics. According to the most recent literature, a short course (3-4 days) of IV antibiotics followed by short-term (< 6 weeks) oral antibiotics targeting the causative micro-organism (when known) provide good results in responders (who show improved inflammatory indices and clinical condition) with non-complicated ASA[28]; in patients with complicated ASA (e.g., concomitant OM) a longer antibiotic course is recommended.

If antibiotic treatment is ineffective (lack of improvement in the clinical picture or the inflammatory markers), surgical treatment should be considered. Several approaches have been described to treat ASA. However, given the lack of evidence regarding the superiority of any one treatment over the others, surgical management should be selected according to the surgeon's level of comfort with the approach[20]. Arthroscopic drainage has proved safe and effective in a variety of joints, including hip, knee, ankle, shoulder, elbow, and wrist. Minimal soft-tissue disruption, a shorter hospital stay, and improved joint space visualization are its key advantages[11,29]. Advanced imaging may be required in patients who do not exhibit clinical or laboratory improvement within the first 3-4 days after joint irrigation and drainage[30]. In children not showing the expected improvement, the possibilities of contiguous OM and abscess should be explored. If repeated imaging does not demonstrate an infectious cause for the failure to improve, conditions mimicking SA, such as leukaemia, should be considered.

Osteomyelitis

The clinical examination of a child with OM often discloses bone tenderness that is most marked over the epicentre of the disease.

In all patients, blood cultures should be obtained and laboratory tests performed (including a complete blood count with differential, ESR, and CRP), and antibiotics should not be administered until the results of the blood culture are available[17].

Plain radiographs should be obtained for possible infections, to establish other causes of the symptoms (e.g., fracture, neoplasm), as well as to depict the radiographic changes that may occur in advanced disease (like lytic lesions, cortical erosion, sequestrum, and involucrum). Since a loss of about one-third of local bone mineral density is required before the change shows on plain radiographs, the key finding is deep soft-tissue swelling.

MRI has been demonstrated to be the most accurate imaging approach to detect early AO, depict the anatomical and spatial extent of bone, joint, and soft-tissue infection, and document the size of any abscesses that may require surgical drainage[17,31-33]. Its disadvantages include cost and the need for sedation or anaesthesia in younger children. Rapid acquisition protocols allow coronal screening from the lumbar spine to the ankles with minimal sedation[31].

Evidence from recent comparative studies indicates that children with MRSA-related OM may have more severe diseases than those with OM due to MSSA. A prediction algorithm has been devised to try to anticipate which patients will be confirmed to have an MRSA infection before the culture results are available[34]. However, the use of such algorithms has not been confirmed in other communities, some of which have a higher incidence of MRSA-related OM[35].

There is consensus on the need for prompt empirical antibiotic treatment when AO is suspected: whereas in stable patients antibiotics can be withheld until the culture results have become available, in unstable patients, such as those with signs of haemodynamic instability or sepsis, early empirical antibiotic therapy should be begun immediately[17]. The starting treatment should be appropriate for patient age, underlying chronic disease (e.g., SCD or primary immunodeficiency), and the local epidemiology and antimicrobial susceptibility of the most likely pathogens[16,34,36-38].

In recent years, CA MRSA has caused a high proportion of culture-positive bone, joint, and soft-tissue infections which have required an increased use of vancomycin and clindamycin in place of cephalosporins, which were the medication of choice when MSSA infections predominated[35,37,39,40]. The standard practice involved administration of IV antibiotics in the hospital for 4-6 weeks. The advent of peripherally-inserted central catheters has led to catheter placement and a short antibiotic course administered in hospital followed by a course of parenteral antibiotics administered at home. Oral treatment after a course of IV antibiotics has also become quite common. Several children received a short course of IV antibiotics followed by oral treatment for 3-5 weeks[41-44]. Antimicrobial therapy is completed when the prescribed course has been administered, there are no physical findings suggesting inflammation, and the levels of the inflammatory indices have reverted to normal. In patients where physical examination or the inflammatory markers remain abnormal, the antibiotic treatment should be continued, and clinical and laboratory reassessments should be performed at intervals of 1-2 weeks until normalization. Lack of improvement should raise the suspicion of a residual focus of infection (e.g., an abscess or sequestrum). Lack of improvement or of resolution of the inflammatory indices should prompt repeat MRI and possible repeat incision and debridement as well as a new culture, to ensure that the previous antibiotic is still appropriate[31].

Although the literature provides no clear guidance, surgical management is generally indicated in children with OM and haemodynamic compromise consistent with septic shock or with imaging findings that are unlikely to resolve with antibiotics alone, like drainable intraosseous, subperiosteal, or extraperiosteal abscesses[36,45]. In children with OM, disease severity at presentation is a predictor of the need for repeat surgery[39,45]. Children with mild illness are unlikely to require surgery, whereas those with severe disease (markedly elevated inflammatory markers; recurring fever on antibiotics; and clear evidence of disseminated diseases, such as deep-vein thrombosis, septic pulmonary emboli, or pneumonia) are more likely to require surgery, and more than one procedure may be needed to resolve the infection[45].

The incidence of abscesses seems to have increased in the MRSA era and may underpin a higher rate of surgical interventions in children with OM[34,38-40]. Data to guide in the selection of the surgical procedure(s) that should be performed in OM patients are not available. Options include drainage of subperiosteal abscesses, bone drilling, and incision of cortical bone with irrigation and debridement of infected cancellous bone. Surgical decompression of infected bone can be effective in reducing intraosseous pressure, which may hamper perfusion and antibiotic delivery to the site of the infection. In all drainage procedures, injury to the growth plate and perichondral ring should carefully be avoided. Surgical planning should include a review of all foci of infection on advanced imaging. Abscesses due to adjacent or contiguous OM should be drained at the time of bone decompression. In children with AO, the involvement of adjacent joints may be more frequent than expected[16,23,33].

Conclusions

In the absence of satisfactory clinical or laboratory improvement within 72 to 96 h from debridement, repeat irrigation and debridement may be considered. Additional imaging is unlikely to be useful, except to document an additional suspected focus of infection. Although the postoperative MRI scans often seem to show a deteriorating condition, they depict the normal progression of the infection and should therefore be interpreted with caution[31].

Conflict of Interest

The Authors declare that they have no conflict of interest.

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