Osteoarticular infections

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Abstract

The aim of this article is to provide a global vision of the presentation, diagnosis and management of osteoarticular infections (OAI) in children. OAI are those infectious diseases that involve bones (Osteomyelitis) and joints (Septic arthritis). Children's bones and joints have a greater vascularization. Therefore, OAI are more common in pediatric patients than in adults. Their etiology is mainly bacterial. The most frequent etiological agent is Staphylococcus aureus, *although* Kingella kingae *also plays an important role in preschooler patients. The typical clinical presentation of OAI is fever, functional impotence together with localized pain in the cases of osteomyelitis and signs of joint inflammation in those patients with arthritis. However, the clinical signs of OAI may be nonspecific in younger patients. Their diagnosis is based on a thorough physical examination, an early collection of biological cultures, as well as the performance of imaging techniques, such as articular ultrasound for septic arthritis, or magnetic resonance imaging in the cases of osteomyelitis. Antibiotic treatment should be started early, and associated with arthrocentesis or arthrotomy in cases of septic arthritis. If the patients' clinical progress is correct, an early switch to oral antibiotic therapy is safe.*

Resumen

El objetivo de este artículo es dar una visión global sobre la presentación, diagnóstico y manejo de las infecciones osteoarticulares (IOA) en Pediatría. Las IOA son enfermedades infecciosas que afectan a los huesos (osteomielitis) y a las articulaciones (artritis sépticas). Dada su mayor vascularización en niños, su incidencia es mayor que en pacientes adultos. La etiología es bacteriana en la mayoría de los casos, siendo el *Staphylococcus aureus* el principal responsable de las mismas y destacando el papel de la *Kingella kingae* en preescolares. La presentación típica consiste en fiebre, impotencia funcional, acompañados de dolor en punta de dedo en el caso de las osteomielitis, y de signos de inflamación articular en el caso de las artritis; aunque la presentación de las IOA puede ser inespecífica en los pacientes de menor edad. El diagnóstico se basa en una exploración física minuciosa, la recogida precoz de cultivos, así como en técnicas de imagen, tales como la ecografía articular para las artritis, o la resonancia magnética en el caso de las osteomielitis. La antibioterapia debe iniciarse precozmente y acompañarse de la realización de artrocentesis o artrotomías en los casos de artritis. Si la evolución es correcta, es seguro el paso temprano a antibioterapia por vía oral.

Key words: *Osteomyelitis; Arthritis;* Kingella kingae; Staphylococcus aureus.

Palabras clave: Osteomielitis; Artritis; *Kingella kingae; Staphylococcus aureus.*

OBJECTIVES

- To understand the pathogenesis of osteomyelitis and septic arthritis and their idiosyncratic behavior in pediatric patients.
- To recognize the main etiological agents involved in osteoarticular infections, both in overall patients and in specific risk groups.
- To describe the usual clinical presentation of osteoarticular infections, as well as identifying the entities with which a differential diagnosis must be made.
- To list the complementary tests, both imaging and laboratory, indicated when an osteoarticular infection is suspected.
- To specify the indications for both medical and surgical treatment.
- To define the duration and choice of antibiotic treatment based on the clinical and epidemiological characteristics of the patients.

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Introduction

Joint infections are those in which bones (osteomyelitis) and joints (septic arthritis) are affected, and can extend to adjacent tissues.

Osteoarticular infections (OAI) are a set of infectious diseases located in the bones and joints, that can also affect adjacent soft tissues. Osteomyelitis (OM) refers to OAI limited to the bone; and septic arthritis (SA) to those located in the joints[1]. It is important to keep in mind that

both entities can coexist in up to 30% of pediatric patients with OAI[2].

OAIs are essentially caused by bacteria, although they can also be of viral or fungal etiology. In most cases, the bacteria reach the bone via hematogenous means, although in cases, such as open fractures or surgeries, it is also possible that the infection occurs through direct inoculation of the microorganisms[3].

Epidemiology

The incidence of osteoarticular infections is higher in pediatric patients, especially in those under 2 years of age, the majority of whom are previously healthy.

It is estimated that the annual incidence of pediatric OAI in developed countries is 4 cases per 100,000 inhabitants for OM and 2-13 for SA[2]. The incidence is higher in pediatric patients compared to the adult population, especially in younger patients. Thus, 50% of pediatric OAIs occur in patients under 5 years of age and 25% in those under two[2]. This fact is explained by the greater vascularization of the growing bones and joints of children. Despite the above, it is rare for OAIs to affect neonates, and these often present risk factors, such as late neonatal sepsis or being carriers of central venous devices[4].

In addition to age, there are other factors that predispose to suffering from OAIs, such as sickle cell anemia, immunodeficiencies such as chronic granulomatous disease or Wiskott-Aldrich syndrome, or a recent history of osteoarticular surgery or trauma. Although it is not clear whether autoimmune arthropathies, such as juvenile idiopathic arthritis or systemic lupus erythematosus, are risk factors for SA, they are pathologies that can cause a diagnostic delay[5].

The bones most affected in OM are the long bones, especially the femur (30%), tibia (22%) and humerus (12%), with the metaphyses being the most frequent site of infection. The non-long bones most affected are: vertebrae, pelvis and calcaneus. Regarding SA, the most commonly affected joints are: the knee (35-40%), hip (25-30%) and ankle (13-15%)[2].

Pathogenesis

Hematogenous dissemination is the most common route of infection. Marked vascularization of the joints and the growing bone metaphyses favor its spread.

Pathogenesis of osteomyelitis

Hematogenous dissemination of microorganisms to the long bones begins from the metaphysis. Their blood vessels are abundant, with slow and tortuous blood flow and highly permeable endothelial cells. All of this makes it easier for circulating bacteria to locally invade the bone marrow. Consequently, there is an increase in intramedullary pressure that causes the release of purulent material towards the cortex through the Volkmann canals, potentially breaking the periosteum and potentially reaching adjacent tissues[3]. Sometimes, as in chronic osteomyelitis, there is containment of the purulent content at the intraosseous level without being eliminated, which is known as Brodie's abscess[6].

There are age-related aspects that modify the ability to locally control the infection. As the skeleton matures, the cortex and periosteum become progressively thicker and denser. This makes it difficult for the infection to progress to adjacent tissues; but, on the contrary, it makes the formation of subperiosteal and intraosseous abscesses more common (the latter especially in adolescents). Another limiting factor is the ossification of the epiphysis, with the consequent atrophy of the metaphyseal capillaries. This fact, which is parallel to the formation of the epiphyseal plate and which culminates around 18 months of age, limits the spread of the infection to the adjacent joint[4].

On the other hand, regarding vertebral osteomyelitis, it must be taken into account that the marked vascularization of intervertebral discs, in the first ten years of life, favors the development of spondylodiscitis.

Pathogenesis of septic arthritis

Joints generally contain synovial fluid that is scant, clear, viscous, and acellular. This is surrounded by the synovial membrane, which is a highly vascularized tissue that lacks a basement membrane.

The arrival of microorganisms to the joints can essentially be through three routes:

1. Hematogenous dissemination (most common route). This mechanism is favored by the high blood flow that reaches the joints, as well as the absence of basement membrane of the synovial tissue. When the microorganisms reach the joint, they settle on the synovial membrane, from where they easily invade the synovial fluid[3].
2. Direct inoculation, generally in the context of a wound with exposed bone. In these cases, it is common for SA to be of polymicrobial etiology[4].
3. Extension from adjacent tissue, as in the case of osteomyelitis, which is more common in younger children, as explained above.

Be that as it may, when microorganisms invade the joint, a local inflammatory reaction occurs that induces the migration of leukocytes (increasing the inflammatory response) and stimulates the release of proteolytic enzymes, which destroy the synovium and the collagen of the matrix. In the medium term, increased intra-articular pressure can distend the joint and facilitate its dislocation, as well as compromise blood flow to it, which can cause complications, such as avascular necrosis (particularly of the femoral head)[3].

Etiology

***Staphylococcus aureus* is the most frequently involved agent in all age groups. *Kingella kingae* plays an increasingly important role in preschool patients.**

The agent *Staphylococcus aureus* (*S. aureus*) is primarily responsible for OAIs in all age groups. In our environment, the rate of methicillin-resistant *S. aureus* (MRSA) is low in the community[2]. Even so, hospitalized patients have a higher risk of suffering OAI due to MRSA, as do those patients from areas with higher rates of community MRSA, such as the USA, Latin America, North Africa or Eastern Europe[4]. Table I shows the main agents causing OAIs by age groups.

Table I. Main causative agents of osteoarticular infections by age groups and special situations

Age	*Agent*	*Comment*
Children under 3 months	*Staphylococcus aureus*	– Main agent in all age groups – Strains resistant to methicillin (MRSA) are associated with greater severity
	Streptococcus agalactiae	
	Gram-negative bacilli	
	Neisseria gonorrhoeae	– It can cause septic polyarthritis
3 months-5 years	*Staphylococcus aureus*	
	Kingella kingae	– It frequently affects flat bones – It usually presents with milder and subacute symptoms – Lower yield of biological sample cultures – It can be associated with the presence of oral thrush
	Streptococcus pyogenes	– Increased risk in the context of varicella-zoster virus infection
	Haemophilus influenzae	– Especially in incorrectly vaccinated patients
	Streptococcus pneumoniae	– Especially in patients under 2 years of age – It usually occurs without extra-osteoarticular involvement
Over 5 years	*Staphylococcus aureus*	
	Bartonella henselae	– Typically causes vertebral osteomyelitis
	Neisseria gonorrhoeae	– Rare, but typically affects sexually active adolescents as septic arthritis in the setting of disseminated disease
Special situations	*Pseudomonas aeruginosa*	– Puncture wounds in the foot – Intravenous drug users
	Salmonella spp	– Typically in patients with sickle cell anemia – Also exposed to reptiles and amphibians
	Brucella spp	– Intake of unpasteurized milk – Typically affects the spine – May be accompanied by hepatomegaly
	Neisseria meningitidis	– Increased risk of complement deficiency

Clinical presentation

Typically, they present with: fever, functional impotence, localized pain and joint swelling, although young patients may present non-specific signs.

Overview of clinical presentation

Neonates and small infants usually present with non-specific symptoms, such as irritability, vomiting, fever without focus or even sepsis of no apparent origin. Furthermore, in this patient profile, it is usually difficult to elucidate the location of the pain, and pseudoparalysis of an extremity may occur, as well as refusal to crawl or sit. Local inflammatory symptoms (edema, erythema, pain) are more evident in SA than in OM, although they are usually more subtle than in older patients. Furthermore, although OAIs are usually unifocal, patients in this age group with severe infections may present several foci of infection[7]. Thus, neonates with SA due to *Neisseria meningitidis* and *Neisseria gonorrhoeae* typically present with polyarticular involvement, while OM caused by MRSA, *Bartonella* or in the context of sickle cell anemia are usually multifocal.

In older patients, the classic presentation is more common, in the form of localized pain in a bone or joint, and local inflammatory symptoms in the form of edema, erythema and heat. Generally, it is accompanied by fever or low-grade fever. The limitation of mobility of a limb in this context is a sign highly suggestive of SA[8]. In any case, it must be taken into account that preschool patients often present referred pain (e.g., gonalgia in the context of SA of the hip or sacroiliitis). The joint pain of SA classically lasts during the night, unlike what occurs in inflammatory diseases[4].

Specific clinical presentations

SA of the hip most commonly affects neonates and small infants. It may be accompanied by edema in the thigh and buttock, and is classically accompanied by a fixed position of flexion, abduction and external rotation of the lower extremity, as well as irritability to passive mobility. In case of prolonged evolution, the purulent content of the capsule can drain into the obturator internus muscle, presenting as an infraabdominal mass in the inguinal canal. It must be taken into account that pelvic osteomyelitis, unlike hip arthritis, is not usually accompanied by limitation of passive joint movement, although active movement is usually limited by pain.

Infectious sacroiliitis is typical of older patients (mean age of 10 years). It occurs in the form of pain in the buttocks and pain with sitting, but it can also present in the form of symp-

toms suggestive of acute appendicitis or urinary tract infection. Typically, sacroiliac maneuvers are positive (Fabere maneuver: flexion, abduction and external rotation)[9].

Spinal infections can affect both the vertebral body and the intervertebral disc, affecting, above all, patients over 8 years of age. They present in the form of back pain, often lasting weeks or even months, which may be associated with pain on palpation of the transverse process of the affected vertebral body, pain on flexion-extension of the spine, and contracture of the paraspinal muscles[4].

On the contrary, involvement of the intervertebral discs occurs more often in young patients, and is located especially in the lumbar area. It usually presents as irritability accompanied by progressive refusal to crawl or walk. Furthermore, it may be accompanied by neurological symptoms, such as loss of strength or reflexes in the lower extremities and even paralytic ileus (in T8-L1 lesions)[10].

Diagnosis

Physical examination must be thorough. Cultures must be obtained early. Ultrasound and magnetic resonance imaging are the main imaging tests indicated.

History and physical examination

The diagnosis of OAIs is essentially clinical, although the signs and symptoms may initially be nonspecific, especially in young children. This is why it is important that, when a diagnosis of OAI is suspected, both pediatricians and child traumatologists jointly participate in the diagnostic process. The physical examination must be carried out in detail, palpating the bony prominences and mobilizing all the joints. Patients with SA usually present pain, even with low degrees of joint mobilization, increasing with intra-articular pressure maneuvers. On the contrary, those with traumatic or other pain usually present pain-free ranges of mobilization. The examination of the joints can be performed following the pGALS (Pediatric Gait, Arms, Legs, Spine) methodology, a validated instrument that allows homogenizing the examination of the musculoskeletal system of pediatric patients[2].

Laboratory investigations

In case of clinical suspicion of OAI, it is recommended to obtain blood tests with: complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and blood culture. Leukocytosis may be absent in up to two-thirds of patients, making it far from being a sensitive marker of OAI. Elevated ESR, on the other hand, is found in 90% of them, although it usually remains elevated, even after 3-4 weeks of having treated the infection, so it is not a good marker of response to treatment. On the contrary, C-reactive protein also has a high sensitivity (around 80%), but shows rapid normalization after the start of targeted treatment[7].

In children under 1 month of age with a diagnosis of OAI, it is mandatory to perform a complete extension study, which includes blood culture, urine culture, and cerebrospinal fluid study, preferably before starting antibiotics.

It is recommended to collect at least one blood culture prior to or at the start of antibiotic therapy. Although only about a third of patients with OAI have a positive blood culture, in many cases (especially in OM) this represents the only opportunity to define the etiology of the infection and the consequent antibiotic adjustment. In those OM that require surgical intervention, direct collection of tissues is recommended (such as bone biopsy in the case of open surgery or collection of purulent fluid in the drainage of abscesses)[2].

On the contrary, in the case of AS, obtaining synovial fluid is easier, so that microbiological confirmation is achieved in up to 50-70% of cases. Thus, it is always desirable to obtain a sample of joint fluid (which can be done using ultrasound guidance). Gram stain, cell count, culture and PCR (*S. aureus, Streptococcus pneumoniae* and, in patients under 5 years of age, *Kingella kingae*) should be performed on the synovial fluid. A cell count with more than 50,000 leukocytes and a predominance of neutrophils is highly suggestive of SA (Table II), although in SA caused by certain bacteria such as *Brucella*, lower counts may be present. Finally, it must be taken into account that, in patients under 5 years of age, the synovial fluid sample should be inoculated in a blood culture bottle to increase the chances of isolating *Kingella kingae* colonies[4].

Imaging tests

If OAI is suspected, a simple x-ray of the affected extremity is always recommended, especially to rule out other non-infectious causes that justify the clinical presentation, such as fractures or tumors. Although plain radiographs may show findings such as periosteal reaction (bone formation), periosteal elevation (suggestive of subperiosteal abscess), or lytic sclerosis (indicative of subacute/chronic injury), these are not usually seen until 10-21 days of progress (even more in non-long bones). Hence, the normality of the simple x-ray does not allow to rule out an OAI. In the specific case of vertebral OM, the typical findings are alteration of the vertebral plateau and subsequent involvement of the vertebral body itself. Regarding SA, radiographs can show indirect signs of joint inflammation, such as soft tissue edema, increased joint space or joint subluxation[7].

Magnetic resonance imaging (MRI) is the imaging test of choice when there is clinical suspicion of OM with normal radiographs, given that radiological changes appear early. As advantages,

Table II. Main characteristics of joint fluid[2,19]

	Normal	*Septic*	*Inflammatory*	*Mechanic*
Aspect	Clear	Purulent	Opaque, cloudy	Clear or hematic
Leukocytes/ml	<200	>50,000	2,000-50,000	<2,000
Neutrophils	<25%	>90%	50-80%	0-30%
Glucose, mg/dl	80-100	<20	20-50	>50

it is especially useful for detecting signs of concomitant SA (although ultrasound is also sensitive, but cheaper and more accessible), discitis or pelvic OM (which is particularly difficult to detect by radiography), as well as for the identification of potentially drainable collections or those affecting the growth plate. Furthermore, it is a non-irradiating test. As a limitation, it must be highlighted that its implementation involves sedation in non-cooperative patients. Furthermore, performing MRI after surgical drainage is difficult to distinguish between postsurgical changes or the persistence of signs of infection. Regarding its interpretation, MRI shows hypointense areas on T1 and hyperintense on T2. Specifically, in spondylodiscitis, a decrease in the size of the intervertebral disc is visualized, as well as T2 hyperintensity of the adjacent vertebral plates. On the other hand, fat suppression sequences allow the adipose tissue signal to be reduced, providing greater sensitivity for the detection of spinal edema. Finally, the penumbra sign (T1 hyperintensity in the transition area between the abscess and the bone marrow) is useful to differentiate Brodie abscesses from other lesions such as neoplasms. In general, the administration of intravenous contrast is not necessary, although the injection of gadolinium can be useful for the detection of intramedullary or intramuscular abscesses, a fact that can be useful in cases of complex interpretation (such as chronic OM with bone sequestration)[7].

Bone scintigraphy should be considered in those cases in which MRI is not available or when the location of the infectious focus is not clear based on history and physical examination. Generally, technetium 99 (Tc99m) is used as a tracer. Gallium-67 requires more irradiation, but is more sensitive, so it may be useful especially in neonates with a high suspicion of OM and normal Tc99m scintigraphy (in whom its sensitivity is lower). Bone scintigraphy with Tc99m consists of the intravenous administration of a radiotracer and the evaluation of uptake in three phases (flow phase at 2-5 seconds after the infusion, blood phase at 5-10 minutes and late phase at 2-4 hours). While focal hyperuptake of the tracer in the first two phases is common in any entity that involves increased local blood flow, hyperuptake in the third phase is suggestive of OAI. As an advantage, patients rarely require sedation for its performance. As drawbacks, it does not usually allow the detection of lesions that may require drainage (such as abscesses) and its specificity is lower than that of MRI, being able to visualize non-infectious uptake lesions, such as fractures and tumors[7].

Computed tomography is not a routine tool in the diagnosis of OAI, if MRI is available. Even so, it allows a better delimitation of the areas of bone destruction, which can be useful in debridement surgery of devitalized areas, as well as in the delimitation of areas of chronic osteomyelitis[2].

Finally, ultrasound is a highly useful tool in the diagnosis of SA, especially in those joints that are difficult to explore, such as the shoulder or hip. It is a test with a high negative predictive value, especially when performed beyond the first 24 hours of clinical presentation. It allows visualization of joint effusion in up to 95% of cases and its quantification (although the ultrasound characteristics of the fluid do not allow discrimination of the infectious or non-infectious etiology of the effusion), in addition to being used as a guide for performing arthrocentesis. Likewise, it allows the blood flow of the joint to be determined by Doppler technique, an increase in which is suggestive of SA. Finally, ultrasound can also be useful for identifying concomitant OM[2].

Differential diagnosis

The differential diagnosis of OAI should be made with:

- Other infections, such as: cellulitis, deep abscesses (such as those located in the psoas or obturator internus muscles), pyomyositis or congenital syphilis (which is associated with alterations of the long bones, which can cause pain and hypomobility).
- Non-bacterial infectious arthritis, such as that caused by viruses. The clinical picture can be accompanied by *rash* (such as by parvovirus or chickenpox). They are generally polyarticular.
- Transient synovitis, which typically occurs without fever.
- Reactive arthritis. It usually takes place after an infectious process of the upper respiratory tract, gastrointestinal tract (traditionally by *Shigella*, *Salmonella, Campylobacter*) or genitourinary (typically due to *Chlamydia trachomatis*).
- Recurrent multifocal chronic osteomyelitis. It is a non-infectious entity. It is characterized by bone pain of insidious onset, often involving multiple bones.
- Neoplasms. In particular, leukemia, Ewing´s sarcoma and osteosarcoma usually present with bone pain and fever.
- Bone infarction, essentially in a patient with sickle cell disease. Patients with Gaucher disease may also present pain crises due to ischemia.
- Complex regional pain syndrome. It usually occurs after a fracture or surgery. It is accompanied by pain, edema and limitation of joint mobility.
- Scurvy. In our environment, it is suspected above all in patients with an extremely restrictive diet, usually in the context of autism spectrum disorder or severe eating disorders. It presents with musculoskeletal pain, petechiae and hyperkeratosis.
- Caffey Disease. It is a hereditary disease with early onset, presenting with fever, subperiosteal hyperplasia and soft tissue edema.

Treatment

Intravenous antibiotic therapy should be started early in case of clinical suspicion and maintained for at least 2-3 days. In arthritis, the purulent fluid must be drained early.

In the same way as the diagnosis, the treatment of OAI must be approached in a multidisciplinary manner. There are three main pillars of treatment: surgical, medical and rehabilitative. Although they are explained separately, the three approaches are complementary, not exclusive, and often simultaneous[1].

Surgical treatment

It is an indisputable part of the treatment of SA, while it is a resource in cases of complicated OM.

The surgical approach in OM is rare. It is reserved for those cases complicated by sequestrations or purulent collections that require drainage, taking into account that small periosteal abscesses tend to resolve with medical treatment. In any case, if a surgical approach is required, it is imperative to collect samples for its study, whether of purulent material or even through bone biopsy[11].

The surgical objective in SA is to reduce the amount of synovial fluid in the affected joint. This fact is not only important from a diagnostic point of view (as described above), but it also allows intra-articular pressure to be rapidly reduced (which improves pain control and reduces the risk of sequelae due to vascular compromise), and facilitates the performance of antibiotic therapy by reducing the bacterial load through the evacuation of purulent material. Therefore, its implementation should be considered early.

There are two main approaches which are mentioned below.

Arthrocentesis

It consists of needle puncture of the joint to extract synovial fluid, generally using ultrasound guidance. The technique also allows for joint lavage.

Its main advantage lies in its less invasiveness and simplicity. On the other hand, it can be performed without the need for deep sedation, especially in older patients. Furthermore, in case of fluid reaccumulation, the technique could be repeated. For all these reasons, it is considered the technique of choice in the majority of SA cases[11].

Arthrotomy

It consists of the surgical opening of the affected joint, which allows effective washing of the purulent material, with the consequent placement of a surgical drain for 48-72 hours.

It is an invasive technique, with a higher complication rate. Furthermore, its performance is associated with a subsequent increase in CRP concentrations, which may involve a longer duration of intravenous antibiotic therapy and, therefore, a longer hospital stay. However, its greater effectiveness in removing purulent material makes it the technique of choice in cases of complicated SA: repeated fluid reaccumulation with the need for multiple arthrotomies, cases of penetrating trauma (in order to ensure the removal of possible foreign bodies), concomitant OM with the need for surgical drainage, progression times longer than 5-6 days (the greater density of the purulent fluid may make it difficult to drain by arthrocentesis), or poor prognostic factors, such as marked elevation of acute phase reactant or SA caused by MRSA or Panton-Valentine leukocidin-producing (PVL-SA) *S. aureus*.

It is also the technique of choice in neonates with SA, due to insufficient evidence on the effectiveness of arthrocentesis in this age group. On the other hand, in the past, arthrotomy was indicated in all cases of SA in the shoulder or hip. Even so, more and more evidence demonstrates the correct effectiveness of arthrocentesis also in large joints, so that the performance of one technique or another in such locations should be chosen based on the orthopedic surgeon's experience.

Arthroscopy is an alternative approach to arthrotomy that aims to achieve the same objective, but with less invasiveness. Even so, the small size of the joints, as well as the young age of the affected patients, can make this approach extremely difficult[11].

Medical treatment

Although it is not decisive for the prognosis of OAI, it is very important to ensure correct analgesic treatment, and oral paracetamol or ibuprofen can be used in case of mild pain, or intravenous metamizole and paracetamol in moderate pain. It is especially important to ensure correct pain control in the case of performing potentially painful techniques such as arthrocentesis[11].

On the other hand, it is important to mention that there is not enough evidence to recommend the widespread use of glucocorticoids as an adjuvant therapy for OM. Although some studies suggest that they could relieve pain and reduce fever, they could interfere with the diagnosis of arthritis of non-infectious etiology or mask the clinical progress of the infection. Therefore, its use should be restricted to those cases of confirmed infections with a large inflammatory component[11].

Finally, it is essential to start antibiotic treatment early in any case of suspected OAI after obtaining adequate microbiological samples. Classically, long regimens of intravenous antibiotic therapy had been recommended. In recent years, there is growing evidence on the non-inferiority of administering short courses of intravenous antibiotic therapy[12]. There are even recent publications that report a correct clinical evolution in patients treated exclusively with oral antibiotic therapy[13,14]. Thus, in a retrospective analysis carried out in Paris, pediatric patients with OM without signs of severity were retrospectively analyzed. Of them, 19 received oral treatment from the beginning, while 26 received intravenous treatment initially. Of the former, none presented complications, and only one presented radiological sequelae, with subsequent spontaneous resolution[14]. On the other hand, at the Hospital La Paz (Madrid), a prospective analysis was carried out on 25 patients between 1 month and 14 years of age with uncomplicated OAI who received only oral treatment. None of them presented complications or sequelae[13]. Although these are promising results, it must be taken into account that the patients in the aforementioned studies present good prognostic factors, such as decreased CRP concentrations[14], greater etiology of *K. kingae* and less of *S. aureus*[13], as well as little involvement of the hip and shoulder[13].

Currently, the first randomized clinical trial in Pediatrics in this regard is being carried out in Denmark, which includes patients between 3 months and 18 years of age with uncomplicated OAI, comparing those who receive initial oral antibiotic therapy or intravenous antibiotic therapy for at least 3 days and until clinical and analytical improvement is observed. The results of the study, which have not been published yet, will provide greater knowledge about the possibility of starting, on a preliminary basis, oral antibiotic therapy[15]. For the moment, and in the

Table III. Dosage of the most frequently used antibiotics in the treatment of osteoarticular infections[11,20]

Antibiotic	*Route*	*Dose in mg/kg/day*	*Maximum daily dose*	*Daily doses*	*Observations*
Amoxicillin	Oral	80-100	6 g	3-4	
Amoxicillin clavulanic	Oral	80-100 (max.)	Amox: 4-6 g Clav: 15 mg/kg (or 375 mg)	3	
	IV	100 (max.)		3-4	
Ampicillin	IV	150-200	12 g	3-4	
Cefadroxil	Oral	60-90	4 g	3	
Cefazolin	IV	100-150	6 g	3-4	
Cefotaxime	IV	150-200	12 g	3-4	
Ceftaroline	IV	<2 months: 18	1,200-1,800 mg* 1,800 mg if: ≥12 years and ≥33 kg	3	*30 mg/kg/day (maximum 1,800 mg/day) if *S. aureus* with MIC ≥2 mg/L. Variable dosage in renal failure
		2 months-2 years: 24-30*			
		≥2 years: 36			
Ceftazidime	IM/IV	150	6 g	3	
Ceftriaxone	IM/IV	75-100	4 g	1-2	Avoid administration below 15 days of life
Cefuroxime	Oral	60-90	3 g	3	
	IV	150-200	6 g		
Ciprofloxacin	Oral	30	750 mg/dose	2	
	IV		400 mg/dose	23	
Clindamycin	Oral	30-40	1,350 mg	3-4	In life-threatening cases, up to 4.8 g daily have been administered intravenously
	IV		2.7 g		
Cloxacillin	IV	150-200	12 g	4-6	
Daptomycin	IV	2-6 years: 8-10 6-12 years: 7 ≥12 years: 4-6		1	350 and 500 mg vials
Gentamicin	IM/IV	6-7.5		1	
Levofloxacin	Oral	6 months-5 years: 20 ≥5 years: 10	750 mg	<5 years: 2 ≥5 years: 1	
	IV		500 mg		
Linezolid	Oral/IV	30	600 mg/dose	3	≥12 years: 600 mg/12 h
Penicillin G	IM/IV	240,000-400,000 U/kg/day	4,000,000 U/dose	4-6	
Rifampicin	Oral/IV	15-20	600 mg	1-2	
Teicoplanin	IM/IV	6-10	400 mg	1	First 3 doses: 10 mg/kg/12 h
Cotrimoxazole	Oral	10-15	160 mg/dose*	2	Trimethoprim dosage. *Up to 320 mg IV every 6 hours in severe cases
	IV			2-4	
Vancomycin	IV	45-60	2-4 g	3-4	Valley levels in SARM close to 15-20 µg/ml

Amox: amoxicillin; Clav: clavulanic acid; h: hours; IM: intramuscular route; IV: intravenous route; U: units.

absence of sufficient evidence to definitively support this practice, the Spanish Society of Pediatric Infectology recommends starting intravenous antibiotic therapy[11].

Regarding the choice of antibiotic therapy, it must be taken into account that some drugs, such as penicillin and metronidazole, have poor bone penetration. On the other hand, the rest of beta-lactams have a moderate penetration, so their use implies administering higher doses than those indicated in infections of another location, as shown in table III.

Additionally, the choice of empirical antibiotic therapy must ensure correct coverage of the most common germs involved depending on the age range. In general terms, correct coverage of *S. aureus* and *Streptococcus pyogenes* must be ensured in all groups[7]. It is not necessary to ensure coverage of MRSA in patients in the community without a specific risk of infection with this microorganism. In any case, it should be assumed that strains resistant to methicillin are also resistant to other beta-lactams (except ceftaroline) [11]. On the other hand, in patients younger than three months, correct coverage of *Streptococcus agalactiae* and gram-negative bacilli must be

Table IV. Empirical intravenous antibiotic therapy for osteoarticular infections (OAI) depending on age and in special situations[4,11]

	Profile	*Antibiotherapy*	*Comment*
General indication	<3 months	Cloxacillin+ cefotaxime/ ceftriaxone/gentamicin	– Cefazolin is an alternative in patients older than 1 month in whom central nervous system involvement has been ruled out
	3 months-5 years	Cefuroxime	– In order to ensure correct coverage of *S. aureus*, *Kingella*, pneumococcus and *H. influenzae*
	>5 years	Cefazolin	– This regimen could be used in patients over 2 years of age correctly vaccinated against pneumococcus and *H. influenzae*
Special situations	Risk of methicillin-resistant *S. aureus* (MRSA)[a]	Clindamycin +/– rifampin Alternatives: – Vancomycin[b] +/– rifampicin – Daptomycin[c] +/– rifampicin – Linezolid +/– rifampicin – Ceftaroline +/– rifampicin	– Combine with a beta-lactam in children under 5 years of age to ensure coverage against *Kingella* – The experience of using cotrimoxazole for the treatment of OAI due to MRSA is scarce, so it should be used with caution
	Severe infection	Vancomycin (or linezolid) + beta-lactam with *S. aureus* coverage +/- rifampicin	– severe sepsis, septic shock or suspected septic pulmonary embolisms – Vancomycin offers worse coverage for methicillin-sensitive *S. aureus*
	Risk of OAI due to penicillin-non-susceptible pneumococcus	Cloxacillin + ceftriaxone/ cefotaxime	– Patients under 2 years of age with incomplete antipneumococcal regimen – Patients with risk factors for severe pneumococcal disease (nephrotic syndrome, asplenia...)
	Risk of OAI due to *Salmonella*[d]		
	Chronic granulomatous disease		– In case of poor progress, think about atypical germs, such as *Aspergillus* and *Serratia*
	Risk of OAI due to *Enterobacteriaceae*		– Patients with severe uropathy or recent abdominal intervention
	Risk of OAI due to *Pseudomonas*[d]	Cloxacillin + ceftazidime	
	Prosthesis superinfection	Vancomycin/linezolid/quinolone +/- rifampicin	
	Allergy to beta-lactams	Clindamycin	– Alternatives: cotrimoxazole and quinolones

[a] *Admission to the intensive care unit, mother colonized by S. aureus from highly endemic countries.*
[b] *In cases of recent contact with a health center, as well as in areas where reported clindamycin resistance rates are greater than 10%.*
[c] *Daptomycin should be considered only in patients over 1 year of age and without lung involvement, in whom glycopeptides or clindamycin cannot be used.*
[d] *See table I.*

ensured. *Kingella kingae* should also be covered in patients under 5 years of age. This germ has a correct sensitivity to cefazolin, while the use of clindamycin, cloxacillin or vancomycin in monotherapy should be avoided. Finally, in those under 2 years of age or those not properly vaccinated, coverage for pneumococcus and *Haemophilus influenzae* must be ensured. Based on these precepts, the recommendation for empirical antibiotic therapy is collected in table IV[11].

As soon as the isolation of the microorganism is available, antibiotic therapy should be adjusted to the lowest possible spectrum. However, in up to half of the cases, the causative etiological agent is not identified, in which case empirical antibiotic therapy should be maintained assuming a correct response to treatment is observed. The response to treatment is considered to be optimal when the fever subsides, the symptoms of bone pain or functional impotence subside and the CRP decreases. The absence of a decrease in CRP after 4-5 days after the start of treatment and in the absence of previous surgery should raise suspicion of a complication.

In case of lack of response to treatment, the development of a complication (such as abscesses), resistance to treatment or an alternative diagnosis should be considered. In such cases, the blood analysis and the imaging test should be repeated, taking into account that the interpretation of the images obtained by MRI in a patient who has recently undergone surgery may be difficult. Likewise, atypical microorganisms should be suspected, such as *Brucella, Bartonella* or mycobacteria[4].

There is no minimum number of days that must be guaranteed for intravenous antibiotic therapy. In patients older than three months, even in those older than one month who present with uncomplicated OAI, sequential oral-intravenous treatment could be performed if they have remained fever-free for 48 hours, have shown clear clinical improvement, and with decrease in CRP levels of at least 30%[11]. Even if concomitant bacteremia is found, intravenous antibiotic treatment can also be shortened to 4-7 days, as long as clinical improvement is observed and in the absence of complications[16]. On the contrary, patients under one month of age should complete the treatment intravenously (given that antibiotic absorption may be erratic). In cases of complicated infections or those caused by aggressive bacteria, such as MRSA or *Staphylococcus aureus* that encode the Panton Valentine leukocidin virulence factor (PVL-SA), a duration of intravenous antibiotic therapy of at least 10-14 days should be ensured[11].

If the microorganism causing the infection has been isolated, the oral antibiotic that is effective against it and, at the same time, has the narrowest possible spectrum will be chosen. If it could not be identified, the one with coverage similar to that of the intravenous antibiotic will be administered, as proposed in table V.

Finally, it is important to determine the total duration of treatment. It should be at least 10-14 days for SA and 20 days for uncomplicated OM cases. On the contrary, longer treatments must be carried out in cases such as: OAI caused by *Salmonella* (especially in patients with sickle cell disease), MRSA or PVL-SA; and in those OM that require drainage or that affect the spine or pelvis. In such scenarios, treatment should be prolonged up to 3-4 weeks in SA and 4-6 weeks in OM. Be that as it may, given that these are prolonged treatments, possible adverse effects of antibiotics, such as cytopenias, hepatitis, diarrhea or other signs of toxicity, must be closely monitored, as well as the correct control of the infection, with analytical monitoring being recommended (blood count and CRP) every 10-14 days[11].

Rehabilitative treatment

Initially, the patient must remain at rest and with immobilization of the affected joint in a functional position (with continuous traction or a cast)[17]. From the beginning, however, it is advisable to consult rehabilitation so that isometric exercises can be carried out early, in order to prevent the development of atrophies and deformities. Subsequently, the patient can move on to passive mobilizations and active movements.

Follow-up and sequelae

The development of a local complication should be suspected in the presence of persistent fever or lack of resolution of the local symptoms.

After discharge, close follow-up must be guaranteed to ensure correct adherence to treatment. It is recommended to carry out clinical controls at the end of antibiotic treatment and after one month. In cases of complicated OAI, with axial or pelvic involvement, as well as in those younger than

Table V. Empirical oral antibiotic therapy for osteoarticular infections depending on age and depending on the causative germ

	Age/germ profile	*Antibiotherapy*
Empirical treatment	Children under 2 years	Cefuroxime-axetil or amoxicillin-clavulanate
	Over 2 years	Cefadroxil
Targeted treatment	Methicillin-sensitive *S. aureus*	Cefadroxil
	Methicillin-resistant *S. aureus*	Clindamycin, ciprofloxacin or cotrimoxazole. Linezolid without resistance to clindamycin
	Haemophilus influenzae	Cefuroxime-axetil or amoxicillin-clavulanate
	Streptococcus pneumoniae	Amoxicillin
	Streptococcus pyogenes	
	Streptococcus agalactiae	
	Kingella kingae	

three months, closer follow-up may be necessary. In this context, a control x-ray should be considered 2-3 weeks after SA to rule out signs of OM or other complications, especially SA of the hip and shoulder. In the long term, it is indicated to monitor for signs of limb dysmetria[11].

In our environment, complications/sequelae in OAI with early diagnosis range between 5 and 10%, being observed more frequently in infants under 3 months in SA that affect the shoulder or hip, as well as in OAI caused by virulent germs such as MRSA or PVL-SA[11].

Complications of OAI are rare (around 10% of cases), but they must be suspected in circumstances, such as persistent fever or poor control of the infectious focus. Acute complications of OAI can be local or systemic. The most common local complication is the extension of the primary focus to adjacent tissues, such as pyomyositis and the formation of abscesses (subperiosteal, intramedullary...), which can cause sustained fever and persistent bacteremia. The occurrence of deep vein thrombosis is rare, but potentially severe, typically observed in adolescents with OM of the femur or tibia; especially, in those cases caused by MRSA[18]. Systemic complications are rare and include sepsis, as well as the development of pulmonary thromboembolism in the setting of deep vein thrombosis.

Regarding sequelae, the most common complication is avascular necrosis of the bony epiphyses, followed by limb dysmetria; especially if the OAI has affected the physis of a long bone. Other chronic complications are: collapse of the vertebral bodies, pathological breakage of long bones and chronic osteomyelitis. Chronic osteomyelitis is typically described in patients who have not received optimal antibiotic coverage, and is defined by the duration of symptoms of more than 2 weeks in the context of radiological evidence of devitalized bone[11].

Role of the Primary Care pediatrician

Although OAI require diagnostic and hospital management at first, Primary Care pediatricians play a critical role in early detection and referral in cases of suspected osteoarticular infection, thus allowing prompt initiation of targeted treatment with the least morbidity and sequelae that this entails. Furthermore, this role is also very important in the follow-up of patients, in order to facilitate correct adherence to oral antibiotic treatment, as well as in the early detection of signs of complications.

Conflict of interest

There is no conflict of interest in the preparation of the manuscript. Declaration of interests: none.

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The asterisks show the interest of the article in the authors' opinion.

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Consensus document prepared by various Spanish scientific societies, which very pragmatically issues recommendations focused on the diagnosis of pediatric osteoarticular infection.

– Saavedra-Lozano J, Calvo C, Carol RH, Rodrigo C, Núñez E, Obando I, et al. SEIP-SERPE-SEOP Consensus document on the treatment of uncomplicated acute osteomyelitis and septic arthritis. An Pediatr. 2015; 82: 273.e1-e10.

Second part of the aforementioned document. In this section, the management of osteoarticular infections is agreed upon, such as the antibiotic therapy of choice or the indications for a surgical approach.

– Peltola H, Pääkkönen M. Acute osteomyelitis in children. N Engl J Med. 2014; 370: 352-60.

Very interesting review on acute osteomyelitis. Furthermore, the document cites the trial carried out by the same authors, which demonstrated the safety of performing short intravenous treatments.

– Gutiérrez K. Bone and joint infections in children. Pediatr Clin North Am. 2005; 52: 779-94.

This is a review that describes in detail the most relevant aspects of both osteomyelitis and septic arthritis in Pediatrics.

– Woods CR, Bradley JS, Chatterjee A, Copley LA, Robinson J, Kronman MP, et al. Clinical Practice Guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics. J Pediatric Infect Dis Soc. 2021; 10: 801-45.

This is the guide of the American Society of Pediatric Infectious Diseases. It provides a comprehensive and up-to-date review of pediatric osteomyelitis, outlining potential future challenges we may face.

– Alcobendas Rueda R, by Inocencio Arocena J. Differential diagnosis of arthritis. Diagnóstico diferencial de artritis. Pediatría Integr. 2022; 3: 125-31. Available in: https://www.pediatriaintegral.es/wp-content/uploads/2022/xxvi03/01/n3-125-131_RosaAlcobendas.pdf.

Very practical article that reviews the possible causes of joint inflammation, also proposing recommendations on how to carry out the initial diagnostic approach.

Clinical case

A 2-year-old male was referred to the Emergency Department from his outpatient clinic, due to progressive limping and irritability of 6 days' duration. Two days before, the patient had presented an isolated fever peak of 38.7ºC, subsequently remaining afebrile. He had presented with catarrhal symptoms and dyspeptic stools the previous week. They report no history of trauma. On the third day of the onset, he went to his pediatrician, who diagnosed the condition as transient synovitis of the hip. Today they consulted again, due to complete refusal to walk, from where they referred the patient to the Emergency Department.

Personal history: healthy boy, without previous hospital admissions. The patient has not been vaccinated due to family decision. He attends daycare.

Family history: there is no history of relevance.

Constants taken in the Emergency Room: weight: 12 kg. Temperature: 37.6ºC. Heart rate: 105 bpm. RR: 25 rpm.

Physical examination: Stable pediatric assessment triangle. Normal cardiopulmonary auscultation. Soft and depressible abdomen. No neurological focality or meningeal signs. The left knee was edematous and hot, with pain on palpation and mobilization of the joint. Non-explorable gait due to pain.

Additional tests: x-ray of both legs: Normal. Blood tests: hemoglobin: 11.6 g/dl (normal value 11.5-13.5); platelets: 411,000/ml (150,000-500,000); leukocytes: 17,500/ml (5,000-13,000); neutrophils: 10,600/ml (1,500-7,000); erythrocyte sedimentation rate 29 mm/h (<15); C-reactive protein 25.4 mg/L (<15); and procalcitonin: 0.03 ng/ml (<0.07).

Ultrasound of left knee: suprapatellar joint effusion, organized with multiple septa, bulging of the suprapatellar tendon with synovial thickening.

Joint fluid examination: purulent appearance with 91,165 leukocytes/ml (<200), 95% polymorphonuclear cells (<25) and glucose 13 mg/dl (80-100).

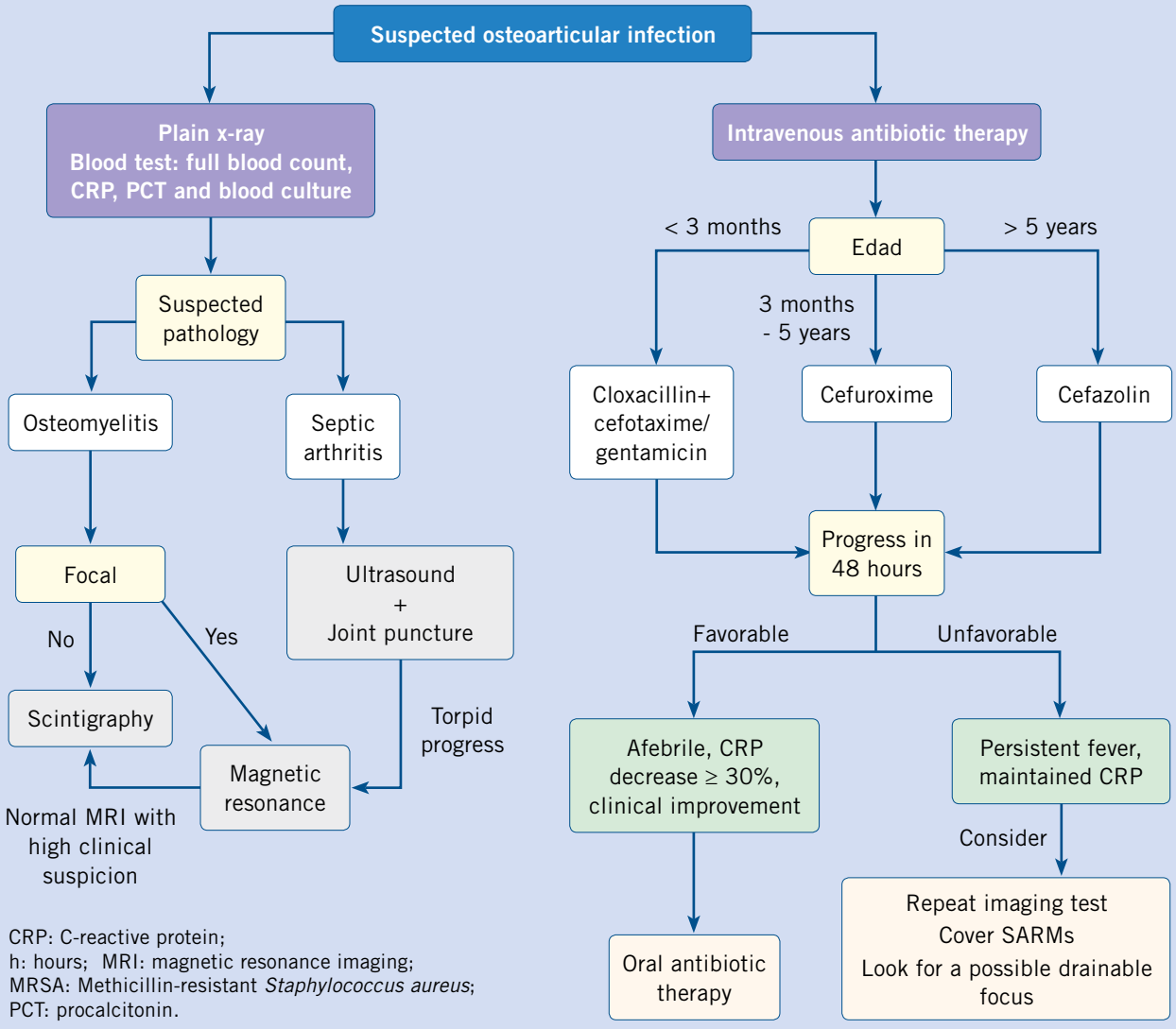
Progress: Septic arthritis was suspected, and ultrasound-guided arthrocentesis performed urgently, with aspiration of purulent-looking fluid. Empirical antibiotic therapy with intravenous cefuroxime was initiated.

After 72 hours, the patient remains afebrile, presenting resolution of the inflammatory signs of the knee and recovering walk without showing signs of lameness. PCR for *Kingella kingae* in joint fluid is positive. Blood culture and joint fluid culture remain negative. A control blood test is performed, which shows a normalization of the leukocyte count (11,700/ml) and C-reactive protein (12 mg/L). Given the optimal progression, the patient is discharged from the hospital.

Accreditation quiz

The Accreditation Questionnaires for FC topics can be done at "On line" through the web: www.sepeap.org and www.pediatriaintegral.es. To obtain the single continuous training accreditation from the accreditation system for health professionals for the entire national health system, 70% of the questions must be answered correctly. The accreditation questionnaires on the different issues in the journal may be carried out during the period stated in the online questionnaire.

Diagnostic-therapeutic algorithm for osteoarticular infection in Pediatrics



CRP: C-reactive protein;
h: hours; MRI: magnetic resonance imaging;
MRSA: Methicillin-resistant *Staphylococcus aureus*;
PCT: procalcitonin.

Accreditation quiz

Subsequently, the following accreditation quiz of Pediatría Integral collects questions on this topic, which must be answered online through the website: www.sepeap.org.
In order to obtain certification by the Spanish "formación continuada" national health system for health professionals, 70% of the questions must be answered correctly. The accreditation quizzes of the different numbers of the journal may be submitted during the period indicated in the "on-line" quiz.

Osteoarticular infections

33. Which of the following statements that refer to the epidemiology of osteoarticular infections is CORRECT?

a. Neonates are at special risk for osteoarticular infections.

b. The most affected joints are the knee and hip.

c. These are more common infections in the adult population than in the pediatric population.

d. In Pediatrics, the concomitant presentation of septic arthritis with osteomyelitis occurs in less than 5% of cases.

e. The bones most commonly affected are the vertebrae and the pelvis.

34. Which of the following relationships is INCORRECT, regarding the risk factors associated with a specific agent?

a. Neonates - *Streptococcus agalactiae*.

b. Patients from the United States - *Staphylococcus aureus* resistant to methicillin.

c. Piercing wound - *Pseudomonas aeruginosa*.

d. Patient over 5 years old - *Kingella kingae*.

e. Sickle cell anemia - *Salmonella* spp.

35. Which of the following statements regarding the diagnosis of osteomyelitis is INCORRECT?

a. Signs suggestive of osteomyelitis can be visualized using ultrasound.

b. Computed tomography is not part of the first choice tests for the diagnosis of osteomyelitis in our environment.

c. Radiography should be considered in any case of suspected osteomyelitis.

d. Magnetic resonance imaging is especially useful in detecting cases of discitis and pelvic osteomyelitis.

e. Gadolinium scintigraphy is the test of choice in cases of suspected osteomyelitis in which the x-ray is normal.

36. Which of the following answers is CORRECT regarding the treatment of osteoarticular infections?

a. Fever persisting 72 hours after starting antibiotic treatment is common and should not suggest a complication.

b. The surgical approach is part of the standard treatment of acute uncomplicated osteomyelitis.

c. It is advisable to keep the affected joint immobilized for the duration of the antibiotic treatment.

d. Arthrocentesis is a technique that can also be performed on large joints such as the hip and shoulder.

e. Arthrotomy is preferable to arthrocentesis in patients older than 3 months.

37. Which of the following statements is CORRECT about antibiotic treatment of osteoarticular infections?

a. In correctly vaccinated patients over 5 years of age, the empirical treatment of choice is a penicillinase-resistant beta-lactam.

b. There is no evidence about the exclusive use of oral antibiotic therapy in the treatment of osteoarticular infections.

c. Correct coverage must be ensured against *Staphylococcus aureus* resistant to methicillin in all patients over 15 years of age.

d. If the clinical and analytical progress is correct, oral antibiotic therapy may be started after having completed a minimum of 5 days of intravenous antibiotic therapy.

e. In cases of complicated osteomyelitis, such as those that require drainage or those that affect the spine or pelvis, a minimum of three weeks of total antibiotic therapy must be completed.

Clinical case

38. What OTHER ENTITIES should be considered in a preschool patient with limping and pain referred to the knee?

a. Reactive arthritis of the knee.

b. Bone fracture in the context of child abuse.

c. Transient synovitis of the hip.

d. a and b are correct.

e. All are correct.

39. Which of the following statements regarding the diagnosis of septic arthritis is INCORRECT?

a. Arthrocentesis is reserved for those cases that progress torpidly or in those patients with risk factors, such as the absence of vaccination.

b. Performing an MRI is dispensable in those cases in which the ultrasound shows arthritis signs and the progression is optimal.

c. The absence of sustained fever and marked elevation of acute phase reactants is common in osteoarticular infections produced by *Kingella kingae*.

d. The absence of isolation of *Kingella kingae* in cultures is not uncommon, so molecular diagnostic techniques increase the probability of identifying the causative agent.

e. The decrease in C-reactive protein levels in cases of osteoarticular infection with adequate progression usually occurs earlier than the decrease in the erythrocyte sedimentation rate.

40. What would be the OPTIMAL antibiotic treatment upon discharge and its duration?

a. Cloxacillin until completing 14 days of antibiotic therapy.

b. Oral cefuroxime-axetil until completing 7 days of antibiotic therapy.

c. Amoxicillin until completing 14 days of antibiotic therapy.

d. Clindamycin until completing 21 days of antibiotic therapy.

e. Amoxicillin-clavulanic acid until completing 21 days of antibiotic therapy.

Accreditation quiz

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