**Executive summary: Guidelines for the diagnosis and treatment of septic arthritis in adults and children, developed by the GEIO (SEIMC), SEIP and SECOT.**
**Resumen ejecutivo: Guía de diagnóstico y tratamiento de la artritis séptica en adultos y niños de GEIO (SEIMC), SEIP y SECOT.**

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**Guidelines for the diagnosis and treatment of septic arthritis in adults and children, developed by the GEIO (SEIMC), SEIP and SECOT.**


## ABSTRACT

Infection of a native joint, commonly referred to as septic arthritis, is a medical emergency because of the risk of joint destruction and subsequent sequelae. Its diagnosis requires a high level of suspicion. These guidelines for the diagnosis and treatment of septic arthritis in children and adults are intended for use by any physician caring for patients with suspected or confirmed septic arthritis. They have been developed by a multidisciplinary panel with representatives from the Bone and Joint Infections Study Group (GEIO) belonging to the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Paediatric Infections (SEIP) and the Spanish Society of Orthopaedic Surgery and Traumatology (SECOT), and two rheumatologists. The recommendations are based on evidence derived from a systematic literature review and, failing that, on the opinion of the experts who prepared these guidelines. A detailed description of the background, methods, summary of evidence, the rationale supporting each recommendation, and gaps in knowledge can be found online in the complete document.



Key words: septic arthritis, infectious arthritis, bacterial arthritis, native joint infection


**Guía de diagnóstico y tratamiento de la artritis séptica en adultos y niños de GEIO (SEIMC), SEIP y SECOT.**


## RESUMEN

La infección de una articulación nativa, generalmente denominada artritis séptica, constituye una urgencia médica por el riesgo de destrucción articular y las consecuentes secuelas. Su diagnóstico requiere un alto nivel de sospecha. Esta guía de diagnóstico y tratamiento de la artritis séptica en niños y adultos está destinada a cualquier médico que atienda pacientes con sospecha de artritis séptica o artritis séptica confirmada. La guía ha sido elaborada por un panel multidisciplinar en el que están representados el Grupo de Estudio de Infecciones Osteoarticulares (GEIO) de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC), la Sociedad Española de Infecciones Pediátricas (SEIP) y la Sociedad Española de Cirugía Ortopédica y Traumatología (SECOT); además han participado dos reumatólogos. Las recomendaciones se basan en la evidencia proporcionada por una revisión sistemática de la literatura y, en su defecto, en la opinión de los expertos que han elaborado la presente guía. En el texto completo online se hace una descripción detallada de los antecedentes, métodos, resumen de la evidencia, fundamentos que apoyan cada recomendación y las lagunas de conocimiento existentes.



Palabras clave: artritis séptica, artritis infecciosa, artritis bacteriana, infección de la articulación nativa

## RECOMMENDATIONS FOR DIAGNOSIS

### I. When should the diagnosis of septic arthritis (SA) in children and adults be considered?

1. All acute arthritis should be considered infectious until proven otherwise. A high index of suspicion for infectious arthritis is required because SA is a medical emergency and should be diagnosed as early as possible (**A-II**).
2. Suspect a diagnosis of SA in any patient with signs/symptoms of arthritis: joint pain, swelling, effusion, warmth, erythema, and/or restriction of movement in one or more joints,
   - with or without systemic signs/symptoms (fever, chills, shivering), and
   - with or without risk factors for SA (previous joint disorder, immunosuppressive conditions, recent joint procedures, bacteraemia) (**A-II**).
3. Increase clinical suspicion of SA in patients with acute monoarticular arthritis especially of large peripheral joints (knee and hip in particular) (**A-II**).
4. A diagnosis of SA should be considered especially in adults with acute monoarticular or polyarticular arthritis (usually involving two or three joints) with:
   - inflammatory joint diseases (mainly rheumatoid arthritis)
   - persistent bacteraemia, and/or
   - immunosuppression (**A-II**).
5. Maintain a high index of suspicion for the diagnosis of SA of axial joints (sternoclavicular, acromioclavicular, costochondral, symphysis pubis, sacroiliac and facet joints) because of their lower incidence and often non-specific clinical features (local pain and tenderness) (**A-II**).
6. In patients with subacute or chronic joint pain and swelling, consider a diagnosis of infectious arthritis caused by other infrequent organisms, such as mycobacteria or fungi, or infrequent bacteria (*Borrelia burgdorferi*, *Brucella* spp., *Coxiella burnetii*, *Bartonella* spp., *Legionella* spp., mollicutes [*Ureaplasma*/*Mycoplasma*], *Nocardia* spp., or *Tropheryma* whipplei) **(A-II).**

### II. What other possible diseases may be important to consider in patients with suspected SA?

1. In patients with suspected SA, we suggest considering alternative diagnoses, mainly the following:
   - Non-infectious arthritis, such as crystal-induced arthritis, post-traumatic arthritis, rheumatoid arthritis, and spondyloarthritis (including reactive arthritis, axial spondyloarthritis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease). In children or adolescents, consider juvenile idiopathic arthritis.
   - Infections of structures adjacent to the joint, such as bursitis, mainly in adults, and osteomyelitis or pyomyositis (typically around the pelvis and hip), mainly in children.
   - Various viral infections that can present with arthralgias and/or arthritis mimicking septic arthritis.
   - Transient synovitis and Perthes disease in children with hip involvement (**A-II**).
2. In adults with suspected SA, it is recommended to rule out crystal arthritis (gout, pseudogout) (**A-III**).
   **Comment**: It is possible to have concomitant infectious and crystal arthritis.

### III. What is the appropriate diagnostic evaluation and initial management of patients with suspected SA?

1. A complete history and physical examination are recommended in all cases of suspected SA (**A-III)**. This can help to differentiate between SA and other disorders and to identify pathogen-specific risk factors.
2. A diagnostic algorithm (Figure 1) showing laboratory and imaging tests (**B-III**) is provided. These are described in further detail in the following three sections.

### IV. What samples should be collected and what microbiological tests should be performed if SA is suspected?

1. Blood cultures are recommended in all patients with suspected SA and should be obtained prior to antibiotic administration whenever possible (**A-II**). For blood cultures positive for organisms that commonly cause endocarditis (such as *S. aureus*, viridans group streptococci, or enterococci), we suggest evaluation for endocarditis (**B-III**).
2. Synovial fluid (SF) samples should be taken as soon as possible in all patients with suspected SA, preferably before initiating antimicrobial therapy (**A-II**).

3. It is recommended to send the SF in a sterile container for Gram staining, culture and, when indicated, molecular studies (**A-II**). If there is enough fluid (e.g., more than 2 mL) for staining, culture, possible molecular studies and leukocyte count, we suggest bedside inoculation of blood culture bottles with SF (**B-II**).
4. In patients with suspected SA and negative SF cultures, we suggest obtaining a new sample of SF for microbiological staining and culture (including mycobacteria and fungi), molecular testing (see below) and histopathological analysis, especially if:
   - they do not respond to empirical therapy against typical SA pathogens and/or
   - mycobacteria or fungi are suspected (**B-II**).
5. Molecular methods (broad-range, multiplex or specific polymerase chain reaction [PCR]) for SF analysis or tissue biopsy:
   - These are not routinely recommended for all SF samples from patients with suspected SA (**D-III**).
   - Their use should be previously discussed with a microbiologist **(A-III)** and considered when SA is suspected in:
     - All children aged 6 months to 5 years: *Kingella kingae*-specific PCR (**A-II**)
     - Patients with negative SF culture receiving antibiotics before or at arthrocentesis: broad-range or multiplex PCR (**A-II**).
     - Patients with negative SF culture who do not improve with empirical antibiotics and/or with clinical and/or epidemiological suspicion of infection with *Neisseria gonorrhoeae* or fastidious/difficult-to-culture microorganisms, including *Brucella* spp., *Borrelia burgdorferi, Bartonella* spp*., Coxiella burnetii, Legionella* spp., *Ureaplasma* spp., *Mycoplasma* spp., and *Tropheryma whipplei*: targeted PCR (**B-II**).
6. Serological testing for *Brucella* spp. *B. burgdorferi, Bartonella* spp*., C. burnetii,* and/or *Mycoplasma* spp. is suggested in patients with negative SF culture, especially in the presence of risk factors and/or epidemiological, clinical or radiological evidence (**B-III**).
7. In patients with suspected mycobacterial or fungal joint infection, as much SF as possible should be sent in a sterile container for culture; synovial biopsy is also recommended because of its higher yield for these organisms (**A-III**).
8. In patients with suspected gonococcal arthritis, in addition to blood and joint cultures, we suggest *N. gonorrhoea* culture and nucleic acid amplification testing of genitourinary specimens and/or freshly voided urine, and, if clinically indicated, rectal and oropharyngeal swabs (**A-II**).

**V. What additional synovial fluid and blood/serum tests should be performed in patients with suspected SA?**

1. Recommended tests on SF: gross examination, leukocyte count and polymorphonuclear percentage (**A-II**). If the amount of SF is low, priority should be given to microbiological tests (**A-III**). **Comment:** There is no threshold to accurately diagnose SA or to differentiate SA from other acute arthritis, although the likelihood of SA rises with increasing leukocyte count and PMN percentage. SF leukocyte count >100,000/mm$^3$ or 50,000-100,000/mm$^3$ with > 90% PMN are suggestive of infection.
2. Additional markers: determination of SF glucose, lactate dehydrogenase (LDH), serum procalcitonin (PCT) and/or lactate (if available) are suggested, especially if previous initial data (including Gram stain) are inconclusive (**C-III**). **Comment:** Low glucose levels and elevated LDH, lactate and PCT levels are common in SA. These SF abnormalities are not reliably diagnostic of SA but may be useful in combination with other data.
3. Use of leukocyte esterase and glucose reagent strip tests in SF may be of value as a rapid screening tool (**B-II**).
4. SF should be examined for crystals to exclude microcrystalline arthritis in adults (**A-II**).
5. Recommended blood/serum tests at initial assessment: C-reactive protein (CRP), erythrocyte sedimentation rate, white blood cell (WBC) count and PMN percentage (**A-III**). **Comment**: These tests are non-specific and cannot diagnose SA or differentiate it from other forms of arthritis, but their performance can be improved in conjunction with clinical data and other SF analyses. They can also be used as a baseline for serial monitoring of treatment response, particularly CRP.
6. In adults, consider the determination of serum procalcitonin levels, if available. **Comment**: Although serum procalcitonin levels show low sensitivity, their high specificity may help differentiate between SA and other forms of arthritis (**B-II**).

7. We suggest a complete blood count and assessment of liver and kidney function as part of the evaluation of patient severity at presentation, as they could influence the choice and dose of antibiotics (**B-III**).

**VI. What is the role of imaging in patients with suspected SA?**

1. Plain radiographs of the affected joint at baseline are suggested in all patients (**B-II**). **Comment:** Although not usually helpful for a SA diagnosis, they can show pre-existing joint or bone disease, rule out other diagnoses, and can be used as a reference image to assess future joint damage. Additional imaging is not usually necessary (**D-III**).
2. Ultrasound is recommended to detect effusions when the physical examination is unclear, and to guide joint aspiration in joints that are difficult to examine, such as the hip or sacroiliac joint (**A-II**). In children with hip involvement and suspected transient synovitis, ultrasound of both joints is suggested, as bilateral hip effusion is a typical finding of transient synovitis of the hip that may support this diagnosis (**B-II**).
3. Magnetic resonance imaging (MRI) is recommended for a suspected diagnosis of SA of axial joints (**A-III**), and when further imaging is needed for suspected spread of infection from the joint to adjacent soft tissues, and/or osteomyelitis (more common in children's joints) (**A-II**). In children, MRI may be indicated to differentiate transient synovitis of the hip from SA if the diagnosis remains in doubt after the initial evaluation and investigation (**A-III**).
4. Computed tomography (CT) may be an alternative to MRI when the latter is not readily available (**A-II**), although CT should generally be avoided in children due to its high radiation index. CT may be an alternative to ultrasound to guide joint aspiration (**B-III**).
5. Nuclear medicine examinations are not recommended for the diagnosis of SA (**D-III**).

**RECOMMENDATIONS FOR TREATMENT**

**VII. General principles of management of SA**

1. As a general rule, patients with suspected or documented SA should be admitted to hospital (**A-II**). Some studies in children treated exclusively with oral outpatient antibiotics showed a favourable outcome when specific criteria were met (**BII**).
2. Joint drainage is recommended for peripheral bacterial arthritis (except for gonococcal and early mycobacterial infections, which do not usually require joint drainage) and for fungal arthritis (**A-II**).
3. We recommend joint drainage of large peripheral joints with pyogenic arthritis as soon as possible (**A-II**).
4. While most patients with early diagnosis of axial joint infection do not require surgery (**B-III**), drainage of adjacent abscesses and various types of surgery for concomitant osteomyelitis may be necessary, especially if diagnosis is delayed (**A-II**). MRI is recommended to assess the presence of these complications (**A-III**).
5. In haemodynamically stable patients without sepsis or septic shock and with clinical and laboratory findings of peripheral pyogenic arthritis, we recommend starting empirical antimicrobial therapy after obtaining blood cultures and SF aspirate, as well as intraoperative specimens if the patient is undergoing urgent surgery (**A-II**).
6. In patients with haemodynamic instability, sepsis or septic shock, we suggest obtaining blood and SF for culture before starting antimicrobial therapy, if this does not significantly delay initiation of antimicrobial therapy (< 45 min) (**B-III**).
7. We recommend that the definitive antibiotic regimen be based on the identified pathogen and its antimicrobial susceptibility or, if no pathogen is identified, on the most likely causative organism(s), to be discussed with an infectious disease specialist or clinical microbiologist whenever possible (**A-II**).
8. We suggest starting antimicrobial therapy intravenously **(B-III).**
9. It is recommended to switch to oral antibiotics after a few days (e.g., 2-7 days) of intravenous antibiotics in adults without endocarditis, with negative blood cultures and with clinical and laboratory improvement (provided that appropriate oral antimicrobials can be administered) (**A-II).** In children with a favourable clinical and analytical evolution after 2-4 days of intravenous antibiotics, switching to the oral route is strongly recommended (**A-I**).
10. Total duration of antimicrobial treatment in adults without endocarditis:

- For large peripheral joints after drainage, we suggest 3-4 weeks for *S. aureus* SA and gram-negative bacilli (GNB), 2-3 weeks for streptococcal arthritis and 1-2 weeks for gonococcal arthritis (**B-III**).
- A longer duration is recommended for SA of axial joints (6 weeks) and SA with adjacent osteomyelitis (**A-III**) and is also suggested for patients with immunosuppression or a slow/inadequate response to initial treatment (**B-III**).
- Two weeks are recommended for SA of the wrist or hand joints after surgical drainage (this recommendation may not apply to SA caused by methicillin-resistant *S. aureus* [MRSA]) **(A-I).**

11. Total duration of antimicrobial treatment in children:
    - We recommend 2-3 weeks for all uncomplicated SA in children, and 3-4 weeks for SA with osteomyelitis (**A-I**).
    - Longer therapy (4–6 weeks) may be required in:
        - Infections caused by MRSA (**B-II**), *Salmonella*, Enterobacterales or *Pseudomonas aeruginosa* (**B-III**)
        - SA of axial joints (**A-III**)
        - Newborns and young infants (<3 months) (**B-III**)
        - Immunocompromised children (**B-III**)

*Empirical antimicrobial therapy*

**VIII. What is the recommended initial empirical antimicrobial therapy for SA?**

1. Empirical therapy active against *S. aureus* is always recommended in any patient (adults and children) with suspected SA and negative SF Gram stain (**A-II**). Additional empirical antimicrobial coverage may be necessary for other pathogens (**A-III**).
2. In adults with negative SF Gram stain and no specific risk factors for special pathogens or resistant bacteria, we suggest coverage of *S. aureus,* streptococci and the more common GNB with:
    - Cloxacillin plus ceftriaxone or monotherapy with amoxicillin-clavulanate (**B-III**).
    - A glycopeptide or daptomycin combined with aztreonam or a fluoroquinolone in case of beta-lactam allergy (**B-III**).

    Other options should be considered in the presence of certain risk factors or clinical contexts (**B-III**).
3. In children without specific risk factors for special pathogens or resistant bacteria and with a negative SF Gram stain, we recommend treatment as follows (**A-II**):
    - < 3 months: cloxacillin or cefazolin + cefotaxime or gentamicin (avoiding 2 cephalosporins together).
    - 3 months to 2 years: cefuroxime; alternatively, cloxacillin + cefotaxime or amoxicillin-clavulanate
    - 2-4 years: cefazolin; alternatively, cefuroxime for coverage of *Haemophilus influenzae* and *Streptococcus pneumoniae* in under-vaccinated children.
    - > 4 years: cefazolin or cloxacillin

*Targeted antimicrobial therapy*

**IX. What is the definitive antimicrobial therapy for *Staphylococcus aureus* SA?**

**a) In adults**

1. For methicillin-susceptible *S. aureus*, intravenous cloxacillin or cefazolin is recommended (**A-II**). Initial addition of daptomycin may be considered (**C-III**). Patients allergic to beta-lactams can be treated with vancomycin or daptomycin (**A-II**)
2. Patients with MRSA SA can be treated with vancomycin or daptomycin (**A-II**) (initial combination of daptomycin plus a beta-lactam may be considered, **C-III**).
3. Sequential oral treatment with beta-lactams, levofloxacin, clindamycin or linezolid are possible options, depending on isolate susceptibility and beta-lactam allergy (**B-III**).
4. The use of rifampin for pure SA is not supported by pathogenesis or evidence. It could be considered in complicated cases with concomitant osteomyelitis (**A-III**)

**b) In children**

1. For methicillin-susceptible *S. aureus*, initial intravenous cefazolin or cloxacillin is recommended (**A-II**). Sequential oral treatment with a beta-lactam (i.e., cefadroxil) is recommended (**A-II**). Clindamycin

(**A-I**), linezolid, levofloxacin (children > 6 months), daptomycin (children > 1 year) or vancomycin are alternatives for beta-lactam allergy (**B-III**).
2. For MRSA, initial intravenous clindamycin is recommended if the isolate is susceptible (**A-I**). Otherwise, the most appropriate antibiotics are linezolid or daptomycin; a glycopeptide would be a valid but less suitable option (**B-III**). For sequential oral treatment, clindamycin (children > 6-8 years) (**AI**), cotrimoxazole (B-II), levofloxacin (> 6 months), or linezolid (**B-III**) are suggested, depending on isolate susceptibility.

**X. What is the definitive antimicrobial therapy for streptococcal SA?**

**a) In adults**

1. For SA caused by susceptible streptococci, penicillin is the drug of choice. Third-generation cephalosporins (ceftriaxone, cefotaxime) or ampicillin are good alternatives (**A-II**). In cases of allergy or reduced susceptibility, vancomycin, clindamycin, a fluoroquinolone, or linezolid may be used (**B-III**).
2. For the oral treatment phase, amoxicillin, cefuroxime, levofloxacin, or moxifloxacin are all good options (**A-III**)

**b) In children**

1. For group A and group B streptococci, and penicillin-susceptible *Streptococcus pneumoniae*, initial intravenous penicillin or ampicillin are the recommended drugs of choice (**A-III**).
2. Sequential oral treatment with amoxicillin is recommended (**A-III**).
3. Third generation cephalosporins (ceftriaxone, cefotaxime), levofloxacin (children > 6 months), clindamycin, linezolid or vancomycin are alternatives depending on isolate susceptibility and beta-lactam allergies (**C-III**).

**XI. What is the definitive antimicrobial therapy for SA caused by gram-negative bacilli?**

**a) In adults**

1. For SA caused by susceptible GNB, initial treatment with an intravenous second- or third-generation cephalosporin is recommended (**A-III**). For GNB isolates resistant to third-generation cephalosporins, consultation with an infectious disease specialist is recommended (**A-III**). Initial treatment with aztreonam or a fluoroquinolone is suggested for beta-lactam allergies (**B-III**).
2. Sequential oral treatment with ciprofloxacin is recommended whenever possible (**A-III**). Oral beta-lactams or cotrimoxazole are suggested alternative treatments, depending on the susceptibility of the GNB identified (**B-III**).

**b) In children**

1. *K. kingae* SA can be treated with penicillin or ampicillin. First- and second-generation cephalosporins or amoxicillin-clavulanate are good alternatives (**A-II**).
2. For SA caused by other GNB, antimicrobial selection should be based on susceptibility (**A-III**).

**XII. What is the directed therapy for SA caused by other less common microorganisms?**

- ***Candida* spp. septic arthritis**

1. In surgically treated cases, we suggest 6–8-weeks of therapy with an azole, echinocandin or liposomal amphotericin B (**A-III**).
2. In neonates with candida SA, an extent-of-disease study is suggested, including lumbar puncture and retinal examination (**B-II**).

- ***Mycobacterium tuberculosis* arthritis**

1. In patients with early diagnosis tuberculous arthritis (without large abscesses or bone sequestration), tuberculostatic treatment similar to that for tuberculosis at other sites is recommended. Some experts recommend longer treatment (9-12 months) (**B-III**).
2. It is suggested that treatment be supervised by an expert (**B-III**).

- **Gonococcal arthritis**

1. In adults, we recommend ceftriaxone 1g every 24h (first choice) or cefotaxime 1g intravenously every 8 hours (alternative) (**A-II**). After clinical improvement, we suggest switching to an oral agent guided by antimicrobial susceptibility testing: ciprofloxacin 500 mg/12h or cefixime 400 mg/12h (**B-III**). Patients with gonococcal arthritis should be screened for other sexually transmitted infections (**A-II**).
2. In children, we suggest 7 days of cefotaxime (neonates) or ceftriaxone (**B-III**).

**XIII. What is the treatment for culture-negative septic arthritis?**

1. We suggest that culture-negative SA be treated with antimicrobial therapy similar to empirical therapy in patients with Gram stain-negative SF (**B-III**).
2. In patients who are receiving or have recently received antibiotics, we advise considering antibiotic coverage to tailor antimicrobial therapy (**B-III**).
3. An accurate epidemiological assessment is required to rule out uncommon or fastidious microorganisms (**B-II**).

*Adjuvant treatment*

**XIV. Is any adjuvant treatment recommended for SA?**

1. In children, nonsteroidal anti-inflammatory drugs may be beneficial during the acute phase while the signs of inflammation are present (**A-III**).
2. In children with confirmed SA, early administration of a short course of intravenous corticosteroids may accelerate clinical recovery and reduce hospital stay (**B-I**). **Comment**: The potential impact of diagnostic delay on non-infectious arthritis and the long-term effects in SA are unclear.
3. In adults, corticosteroid use is not recommended for SA due to the lack of clinical evidence on its effects (**D-III**).

*Joint drainage*

**XV. What joint drainage procedures are recommended in patients with SA?**

1. Joint drainage to treat SA can be performed by closed-needle aspiration (repeated as necessary), arthroscopy or arthrotomy (open surgery) (**A-III**). We recommend tailoring the optimal drainage procedure to age, affected joint, extent of involvement, time course and other clinical data (**A-III**).
2. In adults, arthroscopic joint drainage with synovectomy is the suggested first-line procedure for SA of the knee (**B-II**). Needle aspiration is another treatment option (**B-II**). For the ankle, elbow or wrist, initial joint drainage may be by needle aspiration or arthroscopy (**B-III**). For the hip and shoulder, arthroscopy or arthrotomy is the suggested initial procedure (**B-II**). Open surgery is suggested for cases with unfavourable evolution after repeated aspiration or arthroscopic drainage (**B-III**).
3. In children, the suggested initial treatment procedure for uncomplicated SA of joints other than the hip is needle aspiration (**B-I**). For SA of the hip, knee, ankle, shoulder, elbow or wrist, arthroscopy is preferable to open surgery (**B-II**). We suggest joint drainage by arthrotomy as the first option for hip and shoulder SA in young children, and after more conservative procedures (needle aspiration or arthroscopy) have failed (**C-III**).

*Additional measures*

**XVII. What additional measures may be useful to improve the functional outcome of a patient with SA?**

Suggestions include**:**

1. Initiating physiotherapy after surgical joint drainage (**B-III**).
2. Early mobilisation of the affected joint, initially with passive movement (**B-III**). In children with hip arthritis, immobilisation in an abduction spica cast is reserved for cases of severe infection at risk of joint dislocation (**B-II**).
3. Early weight bearing -including partial weight bearing- is discouraged when the hip joint is affected (**D-III**)
4. Early partial weight bearing is suggested for patients with knee SA, once the pain is controlled (**B-III**)

**RECOMMENDATIONS FOR CLINICAL FOLLOW-UP**

**XVIII. How should patients be followed up and for how long?**

1. Outpatient follow-up with oral antimicrobial therapy (or outpatient parenteral antimicrobial therapy if oral treatment is not possible) is suggested once a favourable clinical and analytical evolution is established (**B-III**).

2. Clinical (joint pain, inflammation and function) and analytical (blood count, CRP and erythrocyte sedimentation rate) monitoring is suggested (**B-III**). While patients are receiving antibiotics, we suggest monitoring for possible associated adverse effects (**B-III**).
3. Outpatient follow-up by orthopaedic and infectious disease specialists is suggested at 1-2 weeks, 4–6 weeks and 3 months after discharge (**C-III**). We suggest a follow-up period of at least 1 year in adults at risk of long-term adverse outcomes and sequelae (such as those with impaired joint function and/or concomitant osteomyelitis) and in children (preferably by an experienced orthopaedic surgeon) (**B-III**). In infants with hip/physeal involvement, longer follow-up may be necessary (**B-III**).

## INTRODUCTION

Infectious arthritis is an infection of one or more joints caused by bacteria (including mycobacteria), fungi and viruses. Only a small number of viruses directly infect the joint, mainly as part of a self-limiting systemic infection. While the term septic arthritis (SA) usually refers to bacterial or fungal arthritis, bacteria are by far the most common agents of these infections. [1]

The annual incidence of SA is between 2 and 7 cases per 100,000 inhabitants in most Western European series. [2–7] Higher rates have been observed in other areas, such as Australasia. [8–10] Even though SA remains relatively rare in the general population, the overall incidence is increasing, due to the rising rate among older patients, who have more underlying co-morbidities and joint disorders, undergo more invasive procedures with increased use of immunosuppressive treatments. [5,6,11–13]

SA occurs when pathogens enter the joint space and proliferate. Microorganisms can enter a joint by haematogenous seeding, by direct inoculation (as a result of trauma or a surgical procedure), or by contiguous spread from adjacent soft tissue or bone infection. Most SA is acquired via the haematogenous route from a distant focus of infection, although often bacteraemia is not diagnosed and the source of the infection is not identified (primary bacteraemia). Direct inoculation can occur through mechanisms such as joint surgery, intra-articular injection, and penetrating trauma, including human and animal bites.[1,12,14,15]

*Staphylococcus aureus* is the leading cause of SA in all age groups, followed by streptococci and aerobic gram-negative bacilli, which cause arthritis mainly in neonates, the elderly, injecting drug users (IDU), and immunocompromised patients.[1] *Kingella kingae* is a common aetiology of SA in children <4 years.[16] Anaerobic organisms rarely cause SA but are more common when there is a history of penetrating trauma. Gonococcal, mycobacterial and fungal arthritis are currently rare in our setting. [6,17] Nevertheless, important differences may be observed depending on the patient's age, underlying conditions, and specific epidemiological circumstances. [1,12,14]

SA is considered a medical emergency due to its significant mortality, especially among adults, and its marked morbidity, mainly resulting in permanently impaired joint function if treatment is not promptly initiated. Mortality ranges from 2 to 15% in different series, depending on the baseline condition of the patient, aetiology and clinical presentation.[2,6,9–11,18–22] Permanent joint damage and impaired joint function have been reported in 23-33% of patients.[2,23] A recent Spanish study of patients with SA hospitalised in Spain between 2010 and 2019 found an in-hospital mortality of 3.7% for adults and no deaths in children.[24] Median hospital stay was 14 and 8 days for adults and children, respectively, and the mean admission cost was approximately €6,000 per patient. Total medical costs reached 12.7 million euros per year.[24]

There is a conspicuous lack of robust clinical evidence on the subject of SA. Many studies are retrospective, descriptive and have notable methodological weaknesses. There are few well-designed clinical trials comparing the efficacy and safety of different diagnostic and management strategies of SA, particularly in adults. Consequently, many questions about the optimal diagnosis and treatment of SA remain unanswered, and there is significant heterogeneity in the management of this infection.[25] There is also a paucity of clinical guidelines for the management of SA, particularly in adult patients.[26–29]

These clinical practice guidelines focus on infectious arthritis of native joints caused by bacteria, and include a brief section on tuberculous and candida arthritis. Prosthetic joint infections and arthritis of native joints caused by viruses are not dealt with in the present document. The primary aim of these guidelines is to provide evidence-based recommendations and, where this is not possible, consensus statements on the diagnosis and treatment of adults and children with SA. Management of SA involves a considerable number of specialists, including microbiologists, paediatricians, rheumatologists, orthopaedic surgeons, infectious disease specialists and emergency physicians, among others. The present guidelines are intended for use by any physician caring for patients with suspected or confirmed septic arthritis.

## METHODS

These guidelines were developed by a multidisciplinary panel representing the Bone and Joint Infection Study Group (GEIO) belonging to the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) (GEIO-SEIMC), the Spanish Society of Paediatric Infections (SEIP), and the Spanish Society of Orthopaedic Surgery and Traumatology (SECOT), along with two rheumatologists (JMN and JB). The GEIO-SEIMC, SEIP and SECOT nominated three coordinators (NB, JS and JCM), who selected the rest of the members of the panel of experts. The guidelines were written in accordance with SEIMC guidelines for consensus documents (www.seimc.org), as well as the recommendations of the AGREE collaboration (www.agreecollaboration.org) for evaluating the methodological quality of clinical practice guidelines.

Eighteen clinical questions were formulated under the three major headings of Diagnostics, Therapeutics and Follow-up. The coordinators assigned each clinical question to a subgroup of panellists. For each clinical question, all significant scientific literature was reviewed and summarised in comprehensive tables following the PICO system (P– Populations/People/Patient/Problem; I– Intervention(s); C-Comparison; O– Outcome). The criteria used to evaluate the strength of the recommendation and the quality of the evidence are summarised in Table 1. The coordinators wrote the first draft based on the sections submitted by each subgroup of panellists. The draft was reviewed by all members of the panel of experts, controversial issues were debated, and a final version was prepared. Before its final approval, the document was posted on the SEIMC intranet and left open for suggestions and comments from members. All authors have approved the contents of the document and the final recommendations. Possible conflicts of interest associated with all members of the panel of experts are listed at the end of the document.

## RECOMMENDATIONS FOR DIAGNOSTICS

### I. When should the diagnosis of septic arthritis in children and adults be considered?

Although the incidence of infectious arthritis of native joints is relatively low, it is associated with significant morbimortality, especially if treatment is not promptly instituted. Timely diagnosis of septic arthritis (SA) and appropriate treatment are essential to prevent irreversible joint damage and consequent long-term disability. For these reasons, SA should be considered a medical emergency, and a high index of suspicion of infection be maintained in all patients with arthritis [12,30]. It is advisable to consider patients with acute arthritis to have SA until proven otherwise [31]. Circumstances that should raise suspicion of SA are drawn from case series studies of patients with infectious arthritis.

SA can affect all ages but is more common in young children and older adults. Most cases in children develop before the age of five years, with a peak incidence in the under-3 age group.[16,32,33] Among adults, the incidence is increasing in line with the progressive ageing of the population.[12]

SA is monoarticular in 80-90% of cases, but more than one joint can be affected (up to 20% of patients) and an oligoarticular or polyarticular presentation does not therefore exclude the diagnosis of SA. [4,16,32,34–36] The risk for non-gonococcal pyogenic SA affecting more than one joint is higher in patients with rheumatoid arthritis (and other inflammatory joint diseases), immunosuppression and proven bacteraemia (positive blood cultures), especially when bacteraemia is persistent or frequent, as in endovascular infections and IDUs.[6,9,37–39]

Depending on the joint involved, infection can be classified as peripheral arthritis (joints in the appendicular skeleton) and SA of axial joints, which form part of the axial skeleton (the acromioclavicular, sternoclavicular, sternocostal, pubic symphysis, facet, and sacroiliac joints).[6] SA can also be classified as affecting large or small joints.[10]

In general, joints of the lower limbs (especially the knee and hip) are those most commonly involved, but any can be affected. In adults, large peripheral joints (especially the knee, shoulder and hip) are the most frequent sites, but some recent series have shown a marked incidence of small joint SA. [10,12,40] In

children, the large joints of the lower limbs are involved in up to 80-90% of SA, especially the knee (35-56%), hip (25-30%) and ankle (12-15%).[16,32,41] In infants, the hip may be the most frequently affected joint. [16,42,43]

Involvement of the axial skeleton is uncommon, except in IDUs.[44] However, recent series have reported infection of axial joints in 8-15% of non-IDU adults with SA, which suggests an increasing incidence. [6,45] In children, axial SA is a very infrequent infection compared to peripheral SA (< 5%). Among all types of axial SA, sacroiliitis is the most common in children,[46–48] although only about 100 cases have been reported to date.[47]

SA in adults can be considered an opportunistic disease that affects mainly elderly patients with underlying chronic conditions and pre-existing arthropathy (such as degenerative joint disease, rheumatoid arthritis, gout or calcium pyrophosphate arthritis). Risk factors for SA include diabetes mellitus, rheumatoid arthritis (RA), recent joint surgery or intra-articular corticosteroid injection, chronic liver or kidney disease, malignancy, IDU, skin lesions and skin and soft tissue infections. [10,12,36,49,50] A 10-fold higher incidence of SA has been reported in patients with RA compared to the general population [50]. In a recent study, SA was observed in 0.8% of patients with ankylosing spondylitis and seropositive RA during follow-up.[51] In patients with seropositive RA, tumour necrosis factor (TNF) inhibitors increased the risk for SA. The incidence of SA was most marked during the first year after starting TNF-inhibitor therapy for both ankylosing spondylitis and seropositive RA. [51] Patients with longstanding, erosive, seropositive RA are more likely to develop SA than those with less severe disease. The use of corticosteroids and other immunosuppressive drugs can mask systemic symptoms, such as fever; the local clinical features of SA, particularly when multiple joints are involved, may be difficult to distinguish from those due to an exacerbation of RA. [6] Since most SA cases are acquired by haematogenous spread, the presence of bacteraemia or infective endocarditis is an obvious risk factor for SA. In one recent study, small joint SA was associated with fewer comorbidities and was more often traumatic in origin than large joint SA. [10]

Previous trauma has traditionally been considered a risk factor for SA in children,[52] but more recent papers have questioned this assumption.[53] Children with SA caused by *K.* kingae often have a concomitant or recent viral infection involving the oral, respiratory or gastrointestinal mucosa. [54] *K. kingae* commonly colonises the nasopharynx of infants and young children. Mucosal damage due to viral infections can lead to bacterial invasion of the bloodstream and dissemination to joints. Other risk factors include immunodeficiencies, hemoglobinopathies (*Salmonella* spp.) and previous wound or environmental exposure (i.e., animal handling). Newborns are especially susceptible to developing SA, some risk factors being prematurity, previous central venous catheter, bacteraemia or candidaemia, and skin infections.

The presence of the above risk factors should raise suspicion of SA.

The classic presentation of SA is acute arthritis of short duration (1-2 weeks in adults, <5 days in children), with local inflammatory findings (joint pain, swelling, effusion, warmth and/or erythema) and decreased range of motion in the affected joint (except when occult joints, such as the sacroiliac, are involved).[12] This presentation would be typical of most SA caused by *S. aureus*, streptococci and gram-negative bacilli. Nevertheless, many patients present only pain and loss of function in the affected joint. Limping or refusal to walk is typical in children when the lower limbs are affected, and refusal to use the affected joint when it is in the upper extremity. When the hip is involved, it is often held in flexion, external rotation and abduction, and the pain may be referred to the knee.[55,56] Of note, in children, there is considerable overlap between the symptoms of SA, osteomyelitis (including vertebral osteomyelitis) and pyomyositis.

The low incidence of SA of axial joints may be one of the reasons why its diagnosis is often delayed; and most patients also present with concomitant osteomyelitis. Non-specific signs and symptoms make clinical diagnosis difficult; pain is often the only local symptom, and tenderness in the affected or adjacent areas the only sign. Axial SA is more common in patients with risk factors such as IDU or presence of a central catheter line, frequently with a concomitant diagnosis of bacteraemia and even

endocarditis.[45,57,58] Consequently, to make a timely diagnosis of SA of axial joints, high suspicion is necessary, especially in the absence of typical risk factors.[6]

Systemic signs and symptoms of infection, such as fever or rigours, are less frequent than might be expected in patients with SA. The presence of fever varies between 30%-60% of cases in adults.[21,59] A low-grade fever is more common than fever > 38-39ºC, especially in the elderly and patients with immunosuppressive treatments. [40] Up to 30-40% of children with SA may not present with fever.[16,32] In newborns and young infants, only non-specific symptoms may be present. Indeed, it is well established that the presence of fever is not a reliable indicator of an infected joint. [12,60] A study that systematically analysed the likelihood ratios of all signs or symptoms used to distinguish SA from other causes of an acutely painful or swollen joint found that the sensitivity of fever as a diagnostic test for non-gonococcal bacterial arthritis was only 57%.[49] This suggests that almost half of patients with SA will not present with fever and consequently that the absence of fever does not rule out infection. In that particular study, no clinical feature was significantly specific for SA. [49]

Gonococcal SA has traditionally been described as a particular form of SA. It is found in patients with disseminated gonococcal infection. Clinical findings associated with disseminated gonococcal infection can be divided into two groups: 1) "arthritis-dermatitis syndrome", a triad of tenosynovitis, dermatitis (usually painless skin lesions) and polyarthralgia without purulent arthritis, or 2) a purulent arthritis, in which signs and symptoms may be indistinguishable from those described above under bacterial SA. A small number of patients with purulent arthritis may also have tenosynovitis or skin lesions. The percentage of SA cases due to *Neisseria gonorrhoeae* at the present time is low, but the increasing incidence of sexually transmitted infections may lead to an upsurge in this diagnosis.[10,45] This infection typically affects adolescents and young sexually active patients.[12] Gonococcal SA may also occur in newborns presenting with non-specific prodromal symptoms of poor feeding, irritability and fever.

Subacute and chronic infectious arthritis are much less frequent. They may be caused by *Mycobacterium tuberculosis* and non-tuberculous mycobacteria, a variety of fungi (*Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans/gattii*, *Sporothrix* spp., endemic fungi such as *Blastomyces* sp, *Coccidioides immitis/posadasii*, and *Histoplasma* spp., among others), as well as some infrequent bacteria (such as *Borrelia burgdorferi*, *Brucella* spp., *Coxiella burnetii*, *Bartonella* spp., *Legionella* spp., mollicutes [*Ureaplasma*/*Mycoplasma*], *Nocardia* spp., or *Tropheryma* whipplei).[61–77]

RECOMMENDATIONS

1. All acute arthritis should be considered infectious until proven otherwise. A high index of suspicion for infectious arthritis is required because SA is a medical emergency and should be diagnosed as early as possible (**A-II**).
2. Suspect a diagnosis of SA in any patient with signs/symptoms of arthritis: joint pain, swelling, effusion, warmth, erythema, and/or restriction of movement in one or more joints,
   - with or without systemic signs/symptoms (fever, chills, shivering), and
   - with or without risk factors for SA (previous joint disorder, immunosuppressive conditions, recent joint procedures, bacteraemia) (**A-II**).
3. Increase clinical suspicion of SA in patients with acute monoarticular arthritis, especially of large peripheral joints (knee and hip in particular) (**A-II**).
4. A diagnosis of SA should be considered especially in adults with acute monoarticular or polyarticular arthritis (usually involving two or three joints) with:
   - inflammatory joint diseases (mainly rheumatoid arthritis)
   - persistent bacteraemia, and/or
   - immunosuppression (**A-II**).
5. Maintain a high index of suspicion for the diagnosis of SA of axial joints (sternoclavicular, acromioclavicular, costochondral, symphysis pubis, sacroiliac and facet joints) because of their lower incidence and often non-specific clinical features (local pain and tenderness) (**A-II**).
6. In patients with subacute or chronic joint pain and swelling, consider a diagnosis of infectious arthritis caused by other infrequent organisms, such as mycobacteria or fungi, or infrequent bacteria (*Borrelia*

*burgdorferi*, *Brucella* spp., *Coxiella burnetii*, *Bartonella* spp., *Legionella* spp., mollicutes [*Ureaplasma*/*Mycoplasma*], *Nocardia* spp., or *Tropheryma* whipplei) **(A-II).**

**II. What other possible diseases may be important to consider in patients with suspected septic arthritis?**

The differential diagnosis of SA is wide and includes any patient with an acutely painful joint which may be caused mainly by crystalline and inflammatory arthropathies, trauma, neoplasm, and infection. Although some clinical features such as fever or rigours are suggestive of infection, other entities (mainly microcrystalline arthropathies) can mimic the symptoms of SA. In the absence of fever, an infectious origin should still be considered, especially in immunosuppressed and elderly patients. A detailed clinical history and examination can help to distinguish between different diseases. It should be emphasised that diagnosis is not always initially obvious, but becomes apparent during follow-up.[78]

The diagnostic alternatives to SA are summarised in Table 2. There are some common causes in both paediatric and adult populations, such as trauma, infections other than SA or certain inflammatory joint diseases, while other diagnoses are characteristic of a particular age range or group, such as crystal arthritis in adults or hip synovitis in children.

a) Differential diagnosis in children and adults

- Mechanical causes of acute monoarthritis, trauma.

Any injury can produce low-grade acute synovial inflammation and joint effusion. Inflammatory signs may be increased by hemarthrosis, which should be especially considered in cases of anticoagulant therapy, haemophilia or fractures affecting the joint. Penetrating injuries (foreign bodies, thorns) can also give rise to acute monoarthritis.

- Viral arthritis

A wide spectrum of viral infections[79] can manifest with acute arthralgia and arthritis, often concomitantly with febrile illness and resolve along with other manifestations of disease. In many patients, viral arthritis is self-limiting and does not cause permanent joint damage, but some may experience disabling joint symptoms. Viruses can cause arthritis directly by infecting the synovium, or indirectly through host immune-mediated responses. The most frequently reported viruses are enteroviruses (coxsackie virus and echovirus), hepatitis virus, parvovirus B19, rubella, alphaviruses (such as Chikungunya), flaviviruses (Zika and dengue viruses), mumps virus, adenovirus and herpesvirus infections.

- Bursitis

Inflammation and infection of musculoskeletal bursae may present with joint pain, swelling, erythema and fever.[80,81] Joint range of motion is usually reasonably well preserved, which helps to distinguish bursitis from SA, but this may not always be obvious. The most common locations for bursitis are the olecranon and patella and should be distinguished from SA of the elbow and knee, respectively. Localised tenderness and fluctuant swelling at the site of the bursa may help to establish the diagnosis.

b) Differential diagnosis in adults

In most cases, SA presents as monoarthritis, and the main problem in making a differential diagnosis arises with crystal arthritis.[14,82] In patients with involvement of axial joints (i.e., sternoclavicular, sacroiliac), spondylarthritis should be considered. Special care should also be taken to differentiate SA from other infectious processes affecting periarticular soft tissues, such as bursitis.

Generally speaking, fever in non-infectious arthritis is usually better tolerated than in SA. The presence of cutaneous erythema over the affected joint supports the diagnosis of SA, but again, it may be absent, while it can also be present in some non-infectious cases (i.e., crystal arthritis). Of note, any arthropathy may be complicated at some point by septic arthritis, which is of particular importance in patients with RA.[14,50,83,84]

- Crystal arthritis

The clinical presentation of crystal arthritis (i.e. gout, pseudogout) may be very difficult to distinguish from SA because the clinical picture is similar.[85] Patients present with acute onset symptoms and usually very intense local signs of inflammation. Low grade fever may also be found. Some clues that incline in favour of crystal arthritis are:[1,85]

- Location: the first metatarsophalangeal joint is very typical of gout.
- The patient's medical records: patients with gout may be under hyperuricaemia treatment (i.e., allopurinol, febuxostat) or medical stress (hospitalisation, diuretic treatment), and may have had previous episodes. Patients should be checked for the presence of tophaceous deposits.
- Patients with pseudogout (chondrocalcinosis) are usually older and may also have had previous arthritis.
- Plain radiography: chronic tophaceous gout may present with loss of joint space and characteristic erosions at the joint margins; linear cartilage calcification on an anteroposterior knee radiograph, or calcification around the triangular ligament of the hand (usually bilateral and symmetrical) are typical of chondrocalcinosis.

The cellular and biochemical characteristics of crystal arthritis may also be indistinguishable from SA.[86] Crystal arthritis may even present with grossly purulent synovial fluid (SF) and a synovial white blood cell count (WBC) greater than 50,000/mm$^3$.[1,78,87–89] Although rare, cases of concomitant crystal and septic arthritis have been described.[90–92] Nor does a previous history of crystal arthritis preclude SA at any given time, so that joint aspiration should be performed to search for both crystals and microorganisms.[86]

- Spondyloarthropathies

This is a heterogeneous group of inflammatory diseases affecting young patients (20-40 years old) involving the axial skeleton (spine and axial joints, especially the sacroiliac joints) and includes: axial spondyloarthritis (radiographic axial spondyloarthritis, also known as ankylosing spondylitis, and non-radiographic axial spondyloarthritis), reactive arthritis, psoriatic arthritis, and enteropathic arthritis. Peripheral joint involvement is not uncommon and may be the first event of the disease. Although an oligoarticular presentation is the characteristic pattern, the only manifestation, either initial or definitive, may be monoarthritis. Arthritis may precede other signs and symptoms more typical of spondyloarthropathy and so forms part of the differential diagnosis of SA. Some clinical clues may be important in making the diagnosis:[1]

- Look for a history of back and sacroiliac pain.
- Explore the skin thoroughly for signs of psoriasis, including the submammary and intergluteal folds, and behind the ears.[86] *Keratodermia blennorrhagica* (vesicles on the palms and soles resulting in hyperkeratotic plaques) and painless oral ulcers are typical of reactive arthritis.
- Nail changes are closely related to the development of arthritis. Dactylitis and distal interphalangeal joint involvement are characteristic of psoriatic arthritis.
- An episode of enteric or urogenital infection, usually 1 to 4 weeks before joint inflammation, is typical of reactive arthritis. Development of circinate balanitis (fragile vesicles leaving superficial erosions on the glans penis) is typical of reactive arthritis.
- Other extra-skeletal sites of involvement, such as conjunctivitis or uveitis, lung involvement or signs and symptoms of inflammatory bowel disease.

- Rheumatoid arthritis (RA)

In the setting of patients with RA, distinguishing a flare from infection may be difficult. Indeed, it is common for the diagnosis of SA in rheumatoid patients to be delayed.[83,84] SA is usually monoarticular, while a flare up of RA frequently involves several joints. However, polyarticular SA can occur, this being more likely when there is a predisposing condition such as RA.[50,86,93] Patients with RA who develop SA

usually have longstanding and advanced stages of disease, and rheumatoid nodules are not uncommon.[83,84] However, SA can also occur in patients with less advanced disease, especially if they are receiving immunosuppressive treatment and biological therapy. In the setting of these new therapies, the rate of polyarticular SA among patients with RA has decreased.[93]

So-called pseudoseptic arthritis is a special condition that occasionally occurs in RA. Patients present with fever, a joint with marked inflammatory signs, and the SF may be grossly purulent with >50,000 WBC/mm$^3$. The levels of acute phase reactants are usually high and other joints may be involved in the flare-up, which usually shows rapid improvement, negative cultures and allows rapid removal of antibiotics with no signs of relapse.[94,95]

- Osteoarthritis

Degenerative joint disease is very common in the general population. Although osteoarthritis usually behaves as a chronic, progressive disease, acute episodes of joint inflammation and synovial effusion can occur, especially following overuse or minor trauma.[86] In such cases, there is no fever or erythema, but since osteoarthritis normally occurs among the elderly, the differential diagnosis with SA should be borne in mind. Joint aspiration will reveal low synovial inflammation (usually less than 2,000 WBC/mm$^3$).[88,96] The clinician should look for other signs of osteoarthritis, such as deformities, instability, Heberden and Bouchard nodes, and involvement of the first carpometacarpal joint, along with radiological signs of degenerative skeletal disease.[97]

c) <u>Differential diagnosis in children</u>

- Transient synovitis of the hip

Transient synovitis of the hip is a very common condition of unknown cause.[98] It usually develops between 3 and 6 years of age and affects boys twice as often as girls. Both transient synovitis and SA of the hip can present with acute onset pain, hip flexion, abduction and external rotation and refusal to bear weight.[99] Limping and irritable hip with no fever is more compatible with transient synovitis. A history of non-weight bearing and a temperature above 38.5 °C are reliable clinical signs that differentiate it from SA. Many authors use a SF cut-off value of 50,000 WBCs/mm$^3$, erythrocyte sedimentation rate (ESR) > 40 mm/h, and C-reactive Protein (CRP) > 20 mg/L to distinguish SA from transient synovitis. However, the synovial WBC count may be lower, especially in immunosuppressed children or those previously treated with antibiotics. A CRP value > 20 mg/L and refusal to bear weight may be more reliable to distinguish transient synovitis of the hip from SA.[100] Radiographs are unremarkable. Ultrasonography shows a small amount of joint effusion. Aspiration is rarely necessary when the presentation is typical, with no fever or laboratory evidence of systemic inflammation. The symptoms resolve within 7 days, although some patients experience relapses.

- Juvenile idiopathic arthritis.

Juvenile idiopathic arthritis is by far the most common cause of chronic monoarthritis.[101] This diagnosis should be considered in all patients with monoarthritis for more than 6 weeks. Typically, symptoms have a gradual onset (over weeks). It may be oligoarthritic (< 4 joints) or polyarthritic, usually with a symmetrical pattern and often with extra-articular symptoms. SF testing may be necessary to exclude SA when it presents as monoarthritis. White blood cell counts are often lower when compared to SA. A synovial WBC count above 50,000/mm$^3$ lacks the sensitivity to rule out SA. Patients with infection usually have a much higher CRP than those with juvenile idiopathic arthritis.[102]

- Other infections[103]

- **Pyomyositis** is twice as common as SA in children presenting with an acutely irritable hip. The SF aspiration is usually non-septic (synovial leukocyte count < 50,000 WBC/mm$^3$, negative Gram stain and cultures) as it is an extra-articular infection. It is important to distinguish between SA and pyomyositis because arthrocentesis performed through infected muscles can contaminate the joint. There are no significant CRP, ESR, and serum WBC differences between the two entities, and body

temperature and weight-bearing do not differ significantly either. The two conditions can only be differentiated by ultrasound and magnetic resonance imaging (MRI) (diagnostic tool of choice).

- **Osteomyelitis**. SA in children may occur in isolation, but is often associated with subperiosteal abscesses, intramuscular abscesses and osteomyelitis.[104][105] Children with osteomyelitis tend to have symptoms for longer than those with SA, but the appearance and examination of a patient having SA with adjacent infections is very similar to that of a patient with isolated SA. In one study, independent predictors of adjacent infection were age above 3.6 years, CRP > 13.8 mg/L, duration of symptoms >3 days, platelets < 314,103 cells/mL, and absolute serum neutrophil count > 8,600 cells/$mm^3$.[105] The presence of three or more of these indicators was associated with an increased risk of infection adjacent to a septic joint, and performing MRI was recommended. However, the false-negative rate of this model indicated that less than 10% of patients with adjacent infections would be misclassified as low risk.[105]

- **Cellulitis:** Rapid development of swelling, redness and pain within hours to a day. Erythema usually precedes the onset of pain and, compared to SA, normally extends over larger areas. The skin is oedematous and tender, and lymphangitis may be present. The patient may be able to bear weight and move the underlying joint.

- Post-infectious arthritis

**Post-streptococcal reactive arthritis.**[101] Post-streptococcal reactive arthritis is a well-known entity distinct from rheumatic fever that can cause arthritis. Hip involvement occurs in 90% of cases. Joint symptoms develop within 1 to 2 weeks after the streptococcal infection, with acute onset of symmetrical or asymmetrical arthritis, which is usually polyarticular, nonmigratory and can be persistent or recurrent. Extra-articular manifestations, such as vasculitis or glomerulonephritis, may also present.

**Reactive arthritis.** This is similar to reactive arthritis in adults following recent infection of the gastrointestinal or genitourinary tract (see above).

- Malignancy

The frequency of arthritis revealing malignant disease is difficult to assess, but appears to be low. Acute leukaemia and lymphoma are the most common malignant causes of monoarthritis.[106] Other tumours may start as monoarthritis, with osteoid osteoma, synovial haemangioma and villonodular synovitis among those that are benign, and Ewing's sarcoma and neuroblastoma among the malignant.

RECOMMENDATIONS

1. In patients with suspected SA, we suggest considering alternative diagnoses, mainly the following:
    - Non-infectious arthritis, such as crystal-induced arthritis, post-traumatic arthritis, rheumatoid arthritis, and spondyloarthritis (including reactive arthritis, axial spondyloarthritis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease). In children or adolescents, consider juvenile idiopathic arthritis.
    - Infections of structures adjacent to the joint, such as bursitis, mainly in adults, and osteomyelitis or pyomyositis (typically around the pelvis and hip), mainly in children.
    - Various viral infections that can present with arthralgia and/or arthritis mimicking SA.
    - Transient synovitis and Perthes disease in children with hip involvement (**A-II**).
2. In adults with suspected SA, it is recommended to rule out crystal arthritis (gout, pseudogout) (**A-III**).
   **Comment**: It is possible to have concomitant infectious and crystal arthritis.

### III. What is the appropriate diagnostic evaluation and initial management of patients with suspected septic arthritis?

History and physical examination are the first steps in the diagnostic evaluation of any patient with suspected disease. However, a systematic review of the literature by Margaretten *et al* in 2007, based on 14 studies, found that the history and physical examination did not significantly change the pre-test

probability of SA in patients with an acutely painful, swollen joint.[49] Two studies showed that joint pain and swelling were reasonably sensitive for SA, but there were no studies assessing their specificity. Nevertheless, these two symptoms would describe the population in which SA should be considered. The risk factors that seemed to be most helpful for predicting SA (age older than 80 years, diabetes mellitus, RA, recent joint surgery, hip or knee prosthesis and skin infection) were only useful when present (increasing the likelihood of SA) but did not substantially lower the likelihood of infection when they were absent. Laboratory blood test results, such as peripheral WBC count, ESR, and CRP, had high sensitivity but very poor specificity. Synovial WBC count and percentage of polymorphonuclear (PMN) cells were the most useful for identifying SA while waiting for Gram stain and culture test results. Progressively higher synovial WBC counts increased the likelihood ratio (LR) of SA (for counts <25,000/mL, LR 0.32; ≥25,000/mL, LR 2.9; >50,000/mL, LR, 7.7; and for counts >100,000/mL, LR 28). A synovial PMN cell count of at least 90% is suggestive of SA, while a PMN cell count of less than 90% lowers the likelihood of infection. However, the authors acknowledged that the main limitations of their review were the lack of high-quality studies and the difficulty of establishing an ideal gold standard for SA.[49]

Mathews *et al* also published a systematic review of the literature on the diagnosis and management of SA in native joints in 2008.[60] They found that SA almost invariably presents for up to two weeks as one or more hot, painful, swollen and restricted joints. In this circumstance, infectious arthritis should be assumed until proven otherwise. The absence of fever or raised WBC does not reliably exclude the diagnosis, nor does a negative SF culture. According to their conclusions, the overall judgement of an experienced clinician would be superior to any laboratory or radiological investigation for diagnosing SA. In addition, demographic and risk factors (old age, prior hospitalisation, trauma or leg ulcers) may be predictive of the likely infective pathogen or atypical organisms, so that a careful history is useful to guide antibiotic choice.[60]

In 2011, Carpenter *et al* performed a systematic review describing the diagnostic characteristics of history, physical examination, and bedside laboratory tests for nongonococcal bacterial arthritis. Some studies on prosthetic joint infection were included[107]. Recent joint surgery or cellulitis overlying a prosthetic hip or knee (which would be useful for prosthetic, but not native joint infections) were the only findings on history or physical examination that significantly alter the post-test probability of SA. Joint pain (sensitivity 85%-100%) and tenderness (sensitivity 100% in a single study) may be sufficiently sensitive, but their overall diagnostic accuracy remains inconclusive without the corresponding specificity data. Serum tests did not significantly alter the post-test probability of SA, and extreme values of synovial WBC (>50,000/ml) increased but did not decrease the probability of SA. The authors found that the overall quality of evidence for the diagnosis of non-gonococcal SA was relatively low. The majority of the 32 studies included were retrospective hospital-based case series derived from administrative data and with no control group. No randomized clinical trials were available.[107]

A subsequent prospective study of 105 patients with suspected SA (38, 26% with SA) corroborated that no single clinical sign or laboratory test (excluding bacteriologic testing) on its own was conclusive for differentiation between SA and non-SA.[108] However, in the multivariate analysis, the authors found that the association of several factors, particularly chills, the absence of a history of crystal-induced arthritis, radiological findings compatible with SA, and the appearance and cellularity of SF, may be suggestive of SA.[108]

A recently published systematic review and meta-analysis by Dey *et al* evaluated the utility of serum and SF markers in the diagnosis of acute hot native joints.[109] The overall aim of this review was to identify tests that were able to identify or exclude SA in acute hot native joints. A total of 49 articles were included: prospective cohorts (25); prospective cross-sectional studies (2); prospective case–control (1); retrospective cohorts (18); retrospective cross-sectional studies (2); retrospective case–control studies (5); and a mixed retrospective and prospective cohort (1); four studies included a partial or complete paediatric cohort. This review identified many biomarkers with good individual diagnostic utility but suboptimal accuracy for exclusion of SA. A panel of several SF and/or serum tests is required to optimise rapid assessment of hot joints.[109]

Despite the above-mentioned limitations, the first step for an appropriate diagnostic evaluation of patients with suspected SA should be a thorough history and physical examination. This can help to differentiate between SA and other conditions and to identify pathogen-specific risk factors. In addition, several laboratory tests, and usually at least one imaging test, should be performed. These tests are described in greater detail in the following three sections. An algorithm is provided that may be useful to guide the diagnostic work-up and initial management of patients with suspected SA (Figure 1). This algorithm has been proposed by the authors and its potential utility has not been demonstrated; hence it should be used at the discretion of the treating physicians as an additional tool.

RECOMMENDATIONS

1. A complete history and physical examination are recommended in all cases of suspected SA (**A-III)**. This can help to differentiate between SA and other disorders and to identify pathogen-specific risk factors.
2. A diagnostic algorithm (Figure 1) showing laboratory and imaging tests (**B-III**) is provided. These are described in further detail in the following three sections.

## **IV**. **What specimens should be collected and what microbiological tests should be performed if septic arthritis is suspected?**

Since most cases of SA are haematogenous in origin, every effort should be made to obtain blood cultures, with or without the presence of fever, before starting antibiotics, to increase the probability of detecting associated transient bacteraemia that may yield the cause of the infection.[101] The percentage of patients with positive blood cultures in non-gonococcal pyogenic arthritis varies from 25% to 70%, depending on the study, although in most studies it is around 50%.[2,4,6,8,11,20,23,110–112] High blood volume is more likely to yield a positive blood culture, which is critical in children.[101,113–115] In general, the recommended minimum volume is 2 ml for neonates, 4 ml for young children and up to 20-40 ml for adolescents.[114]

A sample of SF should be taken as soon as possible from all patients with suspected SA, preferably before antimicrobial treatment is started.[49] Sampling is usually performed with blind fine-needle aspiration or guided by imaging methods, usually fluoroscopy, US or CT, depending on the location to be studied and the availability of imaging techniques. SF should be tested by Gram stain and microbiological culture. SF Gram stain has a low sensitivity (30-65%), but is higher for *S. aureus.*[12,116] In children, where the sample volume is commonly low, prior cytocentrifugation to concentrate the organisms may improve sensitivity.[117] In any case, a positive Gram stain is very useful for starting empirical antimicrobial therapy.

SF aspiration resulting in a positive culture, if performed with the appropriate technique, is very likely to be a real infection, especially when there is a compatible clinical syndrome.[28] Culture of synovial tissue is more sensitive than culture of SF in cases of SA caused by fungi or *M. tuberculosis*.

In gonococcal SA, less than 50% of SF cultures are positive. Diagnosis is usually based on a clinical syndrome compatible with disseminated gonococcal infection, and isolation or detection of *N. gonorrhoeae* from cultures or nucleic acid amplification tests on cervical, urethral, rectal, or oropharyngeal samples. Bacteraemia is uncommon in disseminated gonococcal infection, despite the frequency of polyarticular involvement.[118,119]

In approximately 20% to 50% of cases of SA, no causative organism is identified. This is often due to treatment with antibiotics prior to arthrocentesis, insufficient volume (low inoculum), the inhibitory effect of SF, and microorganisms with special growth requirements.[120] Therefore, SF should be incubated for at least 5 days, and if possible, inoculated into blood culture bottles in order to increase the sensitivity.[17,121–127]

Broad-spectrum polymerase chain reaction (PCR) followed by DNA sequencing is theoretically able to detect the presence of any bacteria (16sRNA gene) or fungus (18s and 28s rDNA or ITS genes) in

clinical samples.[116,128] Various multiplex PCR and PCR assays targeting different microorganisms are under development.[116,129–131]

Targeted PCR has been shown to have higher sensitivity than broad-spectrum PCR (16sRNA gene) in children with *K. kingae* SA.[132–134] In fact, PCR has higher sensitivity than culture for this pathogen.[135,136] A recent study showed that, in children with SA, obtaining a blood culture barely increased the yield of bacterial isolation if SF was evaluated by bacterial PCR.[16] Increased awareness of *K. kingae* aetiology in young children with SA, and implementation of an appropriate protocol including the use of molecular techniques may improve the diagnosis and optimal management of this infection.[16] It has been suggested that whenever a specific *K. kingae* PCR is available, inoculation into blood culture bottles may not be necessary in children, where it is very common to obtain very small quantity of SF.[16,28] However, since culture is still needed to determine the antimicrobial susceptibility of the isolate, a positive culture result should be attempted whenever possible.

The advantage of multiplex PCR is its potential for rapid diagnosis of the aetiology of infection, especially when there has been prior use of antimicrobials (and the risk of culture-negative SA is higher).[16,136–139] Rapid results can make a clinical impact on patient management. The results observed in a number of studies have been variable.[16,28,120,131] An increased yield of positive results was detected using a recently marketed multiplex PCR compared to routine culture.[131] However, organisms not included in the panel may be clinically significant, limiting the value of these tests. Cultures will continue to be necessary for antimicrobial susceptibility testing and the diagnosis of pathogens not targeted by the PCR.[131,140] In overall terms, therefore, the addition of molecular techniques can play a role as a complementary diagnostic tool in selected culture-negative cases of suspected SA.

Newer molecular techniques such as next generation sequencing (NGS) determine the DNA sequence of a complete bacterial genome in a single sequence run; from these data, information on resistance and virulence is obtained, as well as for typing, which is useful for the study of outbreaks.[141] Consequently, in patients with SA, NGS is likely to play an important role in the diagnosis in the near future.

RECOMMENDATIONS

1. Blood cultures are recommended in all patients with suspected SA and should be obtained prior to antibiotic administration whenever possible (**A-II**). For blood cultures positive for organisms that commonly cause endocarditis (such as *S. aureus*, viridans group streptococci, or enterococci), we suggest evaluation for endocarditis (**B-III**).
2. SF samples should be taken as soon as possible in all patients with suspected SA, preferably before initiating antimicrobial therapy (**A-II**).
3. It is recommended to send the SF in a sterile container for Gram staining, culture and, when indicated, molecular studies (**A-II**). If there is enough fluid (e.g., more than 2 mL) for staining, culture, possible molecular studies and leucocyte count, we suggest bedside inoculation of blood culture bottles with SF (**B-II**).
4. In patients with suspected SA and negative SF cultures, we suggest obtaining a new sample of SF for microbiological staining and culture (including mycobacteria and fungi), molecular testing (see below) and histopathological analysis, especially if:
   - they do not respond to empirical therapy against typical SA pathogens and/or
   - mycobacteria or fungi are suspected (**B-II**).
5. Molecular methods (broad-range, multiplex, or specific PCR) for SF analysis or tissue biopsy:
   - These are not routinely recommended for all SF samples from patients with suspected SA (**D-III**).
   - Their use should be previously discussed with a microbiologist **(A-III)** and considered when SA is suspected in:
     - All children aged 6 months to 5 years: *Kingella kingae*-specific PCR (**A-II**).
     - Patients with negative SF culture receiving antibiotics before or at arthrocentesis: broad-range or multiplex PCR (**A-II**).
     - Patients with a negative SF culture who do not improve with empirical antibiotics and/or with clinical and/or epidemiological suspicion of infection with *Neisseria gonorrhoeae* or fastidious/difficult-to-culture microorganisms, including *Brucella* spp., *B. burgdorferi, Bartonella*

spp., *C. burnetii, Legionella* spp., *Ureaplasma* spp., *Mycoplasma* spp., and *T. whipplei*: targeted PCR (**B-II**).

6. Serological testing for *Brucella* spp. *B. burgdorferi, Bartonella* spp., *C. burnetii,* and/or *Mycoplasma* spp. is suggested in patients with culture-negative SF, especially in the presence of risk factors and/or epidemiological, clinical or radiological evidence (**B-III**).
7. In patients with suspected mycobacterial or fungal joint infection, as much SF as possible should be sent for culture in a sterile container; synovial biopsy is also recommended because of its higher yield for these organisms (**A-III**).
8. In patients with suspected gonococcal arthritis, in addition to blood and joint cultures, we suggest *N. gonorrhoea* culture and nucleic acid amplification testing of genitourinary specimens and/or freshly voided urine, and, if clinically indicated, rectal and oropharyngeal swabs (**A-II**).

## V. What additional synovial fluid and blood/serum tests should be performed in patients with suspected SA?

The basis for a definitive diagnosis of SA is identification of the pathogen in SF (and sometimes only in blood cultures). However, around 20% of SF cultures in patients with SA are negative. In addition, the sensitivity of Gram stain is low, and cultures often take a few days to become positive. The search for surrogate blood and SF biomarkers could enable clinicians to make a correct diagnosis earlier. It is both clinically and financially advantageous therefore to find effective methods to differentiate septic from non-septic joints, and multiple studies suggest the usefulness of various biochemical markers.[109] Several meta-analyses have analysed the diagnostic value of these markers. A major problem that often arises when conducting a meta-analysis is heterogeneity and when analysing laboratory data in patients with clinical suspicion of SA, there is considerable methodological heterogeneity in patients and control groups. Microbiological tests in the diagnosis of SA are not always positive, but in some publications, a positive SF culture was mandatory.[96,142–153] Various clinical and microbiological criteria were also accepted in different studies: diagnostic suspicion of SA without culture confirmation [108,154–157], positive Gram stain in SF,[158] positive blood cultures,[159] SA together with osteomyelitis,[160] and native joint SA together with prosthetic joint infection.[107] Lack of homogeneity is also evident in the selection of controls with a wide range of non-infectious inflammatory and non-inflammatory arthropathies: osteoarthritis,[144,146,153,154,161] hemarthrosis,[161] RA, [146,153,155,157,159,161] microcrystalline arthropathies (gout and pyrophosphate disease),[143,146,147,153–155] spondyloarthropathies,[153,155] and lupus.[153] The percentage of these conditions also shows considerable variation, depending on the publication.

Serum markers like WBC count, CRP and ESR have good sensitivity at multiple thresholds, but poor specificity.[107,109,149,152,153,159,162] In fact, ESR and CRP have sensitivities of >90% for SA when low thresholds are used.[162] In one prospective study, ESR > 15 mm and CRP > 15 mg/L had sensitivities of 94% and 92% (but specificities of 23% and 18%) respectively.[108] Thus, a diagnosis of SA cannot be made on the basis of these tests, although their performance can be improved in conjunction with clinical data and SF analyses.[161,163] They can also be used as a baseline for sequential monitoring of response to treatment, particularly CRP, which is expected to normalise 1-2 weeks after starting treatment.[164–167]Although ESR can also be monitored, serum values may remain elevated for days or weeks after the resolution of inflammation.[165] Interestingly, Pyo et al compared the delta neutrophil index (a value corresponding to the fraction of immature circulating granulocytes) in 149 patients with SA and 194 with acute gout attack within 24 h after hospitalisation.[143] The authors suggest that SA should be considered a high priority in patients with delta neutrophil index levels ≥1.9%, particularly when the diagnosis between acute gout attack and SA is doubtful. No other studies have analysed this marker.

Procalcitonin (PCT) has been studied in both serum and SF in recent years. With respect to serum PCT levels, Shen *et al* performed a systematic review and meta-analysis of the diagnostic performance of serum PCT in the identification of osteomyelitis and SA.[168] Seven studies (4 with prospective cross-sectional designs and 3 retrospectives) published between 1998 and 2012 were included, two of them in paediatric populations. A pooled sensitivity of 67% and specificity of 90% was reported with a cut-off value > 0.5 ng/mL. A subgroup analysis with a lower cut-off value (0.2–0.3 ng/mL) improved sensitivity to 90% but with no significant change in specificity. The authors recommend that PCT can be used as a rule-in test at the cut-off value of 0.5 ng/mL and as a rule-out test at the cut-off value of 0.3 ng/mL. The

results also indicated that PCT was more sensitive in adults.[168] Several additional prospective studies evaluated the diagnostic value of serum PCT to differentiate SA and other causes of acute arthritis in adult patients. Most studies used a serum PCT cut-off point of 0.5 ng/mL and found high specificity (ranging from 86% to 99%) but low sensitivity (35%-65%).[142,146,159,169,170] Based on these results, serum PCT has poor sensitivity but is a very specific marker of bacterial arthritis. Hügle *et al* used a serum PCT cut-off point of 0.25 ng/ml and reported a sensitivity of 93% and specificity of 75%.[145] The authors concluded that SA is unlikely in a patient with serum PCT <0.25 ng/ml. Of these studies, those comparing the diagnostic performance of serum CRP and PCT obtained better results with PCT.[143,157142,170] A recent systematic review on the diagnosis of osteomyelitis and SA in children using serum PCT included four studies. The authors concluded that serum PCT can be used as a biomarker for the diagnosis of osteomyelitis, but that there is no direct evidence to support the diagnosis of SA.[172]

Aspiration of an affected joint often reveals SF that is purulent and low in viscosity. Abdullah *et al.* found that gross analysis of SF had 94% sensitivity and 58% specificity for determining whether SF was inflammatory or non-inflammatory.[173] In another prospective study of 71 patients with suspected SA, the macroscopic appearance of SF, as assessed by the clinician, was a valid parameter for excluding SA when the fluid was clear (null sensitivity) or for considering it when it was purulent (LR 4.7).[108] In the same study, SF cellularity was considered to be the best non-bacteriological test for the diagnosis of SA. [108] In another prospective study, synovial WBC count was found to be one of the most accurate tests available for SA.[174] In the review of the literature by Margaretten *et al*, the probability of a diagnosis of SA increased with an increase in the synovial WBC count. A synovial PMN cell count of at least 90% was suggestive of SA, while a PMN cell count below 90% decreased the likelihood of infection [49] In the meta-analysis performed by Carpenter *et al,*[107] the pooled sensitivity and specificity values of SF leukocyte count > 100,000 leukocytes/mL were 18% and 99%, respectively; [96,152,175] between 50,000 and 100,000 leukocytes/mL, they were 56% and 90% respectively. [96,149,151,152,155,159] Nevertheless, there is no WBC count or PMN percentage threshold to accurately diagnose SA or to differentiate between SA and other acute arthritis, but, because of their high specificity, low cost, rapid determination and simplicity, and despite their limitations, WBC and percentage of PMN in SF have been widely used, and are currently recommended as markers suggestive of infection in patients with acute arthritis.[176] If the amount of SF is very low, priority should be given to microbiological testing. Low SF volume is common in children and these markers are not systematically recommended in this population for this reason.[28] It is important to bear in mind that the patient's immune status may affect these findings, resulting in lower synovial WBC counts in immunocompromised individuals.[27]

Various studies have analysed the diagnostic value of synovial PCT levels in SA, with different results. [146,159,169,171] While one study did not find that synovial PCT was useful to discriminate between infectious and non-infectious arthritis in clinical practice,[159] other studies reported that synovial PCT at 0.5 ng/ml had a similar specificity, but a higher sensitivity than serum PCT for diagnosis of SA.[146,169] Saeed *et al* showed that synovial levels < 0.5 ng/ml or > 4.5 ng/ml could exclude or support, respectively, a diagnosis of an infectious process.[171]

Several studies have been conducted in the last few years on the potential role of leukocyte esterase (LE) and glucose reagent test strips in the diagnosis of SA. These strips are commonly used with urine samples to screen for possible urinary tract infection. Increased levels of LE, an enzyme secreted by neutrophils, are found during inflammatory processes. The LE strip test has been useful to confirm or rule out infections in various body fluids and effusions (peritoneal and cerebrospinal fluid, pleural effusions). Decreased glucose concentrations in SF are known to be suggestive of infection. In a German report, Omar et al used LE and glucose reagent strips in SF obtained from 19 and 127 patients with septic and aseptic arthropathies, respectively.[177] Considering SA when the LE reading was positive (++ or +++) and the glucose reading was negative yielded sensitivity of 89%, specificity of 99.2%, positive predictive value (PPV) of 94.4%, and negative predictive value (NPV) of 98.4%.[177] In a more recent study, the same research group prospectively evaluated SF from 455 patients with atraumatic joint effusions using LE and glucose strip tests.[178] A positive LE reading combined with a negative glucose reading detected SA with 85% sensitivity, 100% specificity, 100% PPV and 98% NPV. A positive synovial LE reading alone detected SA with 82% specificity, 95% sensitivity, 47% PPV, and 99% NPV. In a study comparing patients with culture-positive SA and juvenile idiopathic arthritis, the sensitivity,

specificity, PPV, and NPV of the synovial LE test were 80.8%, 78.6%, 70% and 86.8% respectively.[179] In a prospective cohort of 25 children with suspicion of SA, a positive LE strip test ("++" and "+++" readings) yielded a sensitivity, specificity, PPV and PNV of 100%, 83%, 95%, and 100%, respectively.[180] Furthermore, all 25 patients with an aseptic SF (from children undergoing surgery for developmental dysplasia of the hip) had negative test results ("−" and "+" readings).[180] Based on these studies, LE and glucose strip tests could be a low-cost tool to rapidly diagnose or rule out SA. Interestingly, a recent systematic review and meta-analysis analysed eight SF tests, all of which were used to differentiate septic from non-septic joints; of these, LE had the highest pooled sensitivity (0.94) and good pooled specificity (0.74).[109]

Synovial lactic acid has also been studied as a biomarker of SA. In a study by Shu et al, D-lactic acid levels ≥10 mmol/l showed high specificity (97%).[156] Lenski and Scherer compared septic and gouty arthritis and found levels >10 mmol/l only in infected individuals.[147] In a series of 52 patients (15 infected), levels >12 mmol were raised in all SA patients and in only 1/37 non-infected cases.[154] In a large cohort studied by Gobelet *et al* (n=383), the results overlapped: 29.5% of seropositive RA and 19% of crystal-induced arthritis had levels > 9.4 mmol/l.[161] Overlapping data were also found in another study by Arthur et al.[157] D-lactic acid, an optical isomer of L-lactic acid, is basically a product of bacterial metabolism, and human cells produce insignificant amounts of it. Gratacós *et al* studied D-lactic levels in patients with infectious and non-infectious arthritis. Using a cut-off value of 0.05 mM, overall sensitivity was 85% and specificity 96%.[151] Although the determination of D-lactic acid is not expensive and does not require special equipment, it may not be feasible at all institutions.

Regarding synovial levels of glucose, lactate dehydrogenase (LDH) and proteins, Margaretten *et al* [49] found that low glucose was quite specific (85%) but not very sensitive (51%), LDH > 250 U/l had a sensitivity of 100%, but specificity of 51%, and proteins > 3g/dl were neither specific nor sensitive.

Cytokine levels in SF have been studied in patients with SA, with different results.[152,153]

Microscopic studies for crystals in SF in patients with acute arthritis are mandatory because they are the gold standard for the diagnosis of crystal arthropathies. However, positivity does not exclude a diagnosis of infection, and concomitant microcrystalline and septic arthropathy has been described in the literature.[181]

A recently published systematic review and meta-analysis on the diagnosis of acute hot joints demonstrated that many single tests with individual diagnostic utility had suboptimal accuracy for exclusion of native joint infection, and that a combination of several tests was required to optimise rapid assessment of the hot joint.[109]

RECOMMENDATIONS.

1. Recommended tests on SF: gross examination, leukocyte count and PMN percentage (**A-II**). If the amount of SF is low, priority should be given to microbiological testing (**A-III**). **Comment:** There is no threshold to accurately diagnose SA or to differentiate it from other acute arthritis, although the likelihood of SA rises with increasing leukocyte count and PMN percentage. SF leukocyte counts >100,000/mm$^3$ or 50,000-100,000/mm$^3$ with > 90% PMN are suggestive of infection.
2. Additional markers: determination of SF glucose, LDH, PCT and/or lactate (if available) are suggested, especially if previous initial data (including Gram stain) are inconclusive (**C-III**). **Comment:** Low glucose levels and elevated LDH, lactate and PCT levels are common in SA. These SF abnormalities are not reliably diagnostic of SA but may be useful in combination with other data.
3. Use of leukocyte esterase and glucose reagent strip tests in SF may be of value as a rapid screening tool (**B-II**).
4. SF should be examined for crystals to exclude microcrystalline arthritis in adults (**A-II**).
5. Recommended blood/serum tests at initial assessment: CRP, ESR, WBC count and PMN percentage (**A-III**). **Comment**: These tests are non-specific and cannot diagnose SA or differentiate it from other forms of arthritis, but their performance can be improved in conjunction with clinical data and other SF analyses. They can also be used as a baseline for sequential monitoring of treatment response, particularly CRP.

6. In adults, consider the determination of serum procalcitonin levels, if available. **Comment**: Although serum procalcitonin levels show low sensitivity, their high specificity may help differentiate between SA and other forms of arthritis (**B-II**).
7. We suggest a complete blood count and assessment of liver and kidney function as part of the evaluation of patient severity at presentation, as they could influence the choice and dose of antibiotics (**B-III**).

### VI. What is the role of imaging in patients with suspected SA?

In the early stages of SA, radiographic findings are usually normal. They can detect soft tissue swellings or joint effusions in knees, elbows, and ankles, but cannot reliably identify joint effusions in hips, shoulders, wrists, or small joints.[182] In a prospective study of 123 patients with suspected hip joint effusion, the sensitivity of plain film radiography was only 27.8% versus 100% sensitivity of ultrasonography (US).[183] Therefore, in terms of isolated SA (without adjacent chronic osteomyelitis), plain radiographs have limited usefulness [32,184]. Plain radiographs can reveal the progression of SA to periarticular osteopenia, joint space narrowing secondary to cartilage destruction, loss of continuity of the white cortical line as bone destruction begins, and marginal erosions when the bone is further destroyed. More advanced infections may present with nonspecific erosions and/or uniform joint space narrowing.[185] According to the literature, and mainly based on expert recommendations, radiographs should be used for the initial evaluation of SA, although plain radiographs are often normal.[186] Radiographs are safe, inexpensive, easy to obtain, and widely available.[187] They provide an anatomical assessment of the affected joint, can identify osteomyelitis, subluxation, the presence of foreign bodies or gas, and can suggest alternative diagnoses such as neuropathic arthropathy, fracture or tumour.[186–188] Radiographs are also useful to assess the state of the joint at diagnosis, as SA in adults frequently occurs in joints with previous disease. In short, plain radiography is considered an important baseline test in all patients to rule out other conditions and to evaluate subsequent changes. In most patients, additional imaging tests are unnecessary.[186]

Ultrasound (US) is a low-cost, widely available, non-invasive technique that does not use ionising radiation, can be rapidly performed, and does not require sedation, which is of special interest in children. US has high sensitivity for the diagnosis of joint effusions, which are a hallmark of SA. The absence of hip joint effusion virtually excludes SA; a false negative rate of 5% has been reported in patients with shorter duration of symptoms (<24 hours).[189190] In a retrospective comparative study (compared to MRI) evaluating joint effusion of the knee, US correctly identified 78 of 96 patients with effusion, showing a sensitivity, specificity, PPV and NPV of 81%, 100%, 100% and 78% respectively.[191] In a more recent cadaver model study, Berona et al. reported a sensitivity and specificity of 86% and 90%, respectively.[192] In children, a sensitivity of 86% for detection of joint effusion has been reported,[193] with a false negative rate of only 2.5% in patients with less than 24 h of symptoms. Some experts recommend US in all children with suspected SA, unless it is easily diagnosed by physical examination.[28,32] However, US does not sufficiently differentiate between SA and toxic synovitis of the hip in children due to its low specificity.[194–196] For this reason, bilateral exploration of the hips is recommended, as bilateral effusion is typical of synovitis but not of SA.[184] US guidance can also be used for diagnostic or therapeutic aspiration and/or drainage [184,197–199]. In deep joints such as the hip, US-guided arthrocentesis has many advantages over conventional fluoroscopic techniques: visualization of needle position is generally easier for intra-articular placement, involves less needle manipulation and no irradiation. US can also be useful for the diagnosis of soft tissue and periarticular complications such as abscesses, pyomyositis or tenosynovitis.[193,200]

Magnetic resonance imaging (MRI) is a highly sensitive and specific procedure for the diagnosis of SA and is the modality of choice in patients with SA and suspected adjacent bone and/or soft-tissue infection.[187] MRI can identify osteomyelitis, subperiosteal abscesses, and intramuscular abscesses, which, in children, are frequently associated with SA (40-68%) and are often clinically indiscernible.[105,201–203] In addition, MRI is the most sensitive and specific imaging technique for assessing SA of axial joints, as a high percentage of these cases can be complicated by adjacent osteomyelitis and soft tissue complications.[204,205] MRI findings in SA include joint effusion and synovial enhancement, and if the infection progresses, cartilage loss, bone erosion and bone marrow oedema.[206] However, some of

these findings may also be present in non-septic arthropathies, which are common in adults. In a case-control study of 19 septic versus 11 non-septic arthritis, Graif *et al* found that the combination of bone erosions and bone marrow oedema was highly suggestive of SA,[207] although a subsequent study showed that these signs were also present in patients with RA.[208] In a later study with 50 cases and 22 controls, Karchevsky *et al* found that synovial enhancement was almost invariably present in septic cases (98%, n = 47), but present in only 23% (n = 5) of controls.[209] After synovial enhancement, peri-synovial oedema and joint effusion showed the highest correlation with the clinical diagnosis of SA.[209] In children, MRI has a sensitivity and specificity of 97% and 92%, respectively, for a diagnosis of SA.[210] In addition, a recently published systematic review and meta-analysis found that MRI findings -especially bone marrow changes- were useful for differentiating between SA and transient synovitis in children with painful hips after excluding other causes.[211]

MRI offers advantages, such as multiplanar imaging and lack of ionizing radiation, but also drawbacks, which include potential difficulty in distinguishing between infection and inflammation, artifacts in patients with orthopaedic hardware, the need for sedation or anaesthesia in young children, and patient contraindications, such as MRI-incompatible devices, or severe claustrophobia.[187] MRI is also very expensive and not widely available, which can lead to a delay in the diagnosis and treatment of SA. Because of these disadvantages, unless there is suspicion of associated osteomyelitis or abscesses, lack of improvement or suspicion of complications, MRI is not recommended initially. Some authors have proposed clinical and laboratory-based algorithms to decide whether MRI is necessary for the diagnosis of adjacent musculoskeletal infection in SA in children that would change the management or prognosis; [105,212] other authors however, have not validated these algorithms in other geographical regions due to potential differences in regional microbiology and specific anatomical factors.[213]

Although not routinely required in the evaluation of suspected bacterial arthritis, computed tomography (CT) may be helpful, if MRI is not available, for assessing areas of complex or difficult-to-examine anatomy, or when adjacent osteomyelitis is suspected. CT features of SA include joint effusion and bone erosions around the joint.[214] Compared to MRI, CT is often more widely available, image acquisition is faster and does not require sedation or anaesthesia; however, due to its high radiation, MRI is often preferred in children when osteomyelitis is suspected.[187] CT may also be an alternative to US for guiding joint aspiration.

A radionuclide scan is of limited use for the diagnosis of SA.[186,215] On 3-phase bone scans, early images may show increased activity with hyperperfusion and hyperaemia on flow and blood pool phases. Delayed images may be normal or have increased activity limited to the articular surfaces.[215] According to recent evidence-based guidelines on criteria for determining appropriate imaging examinations, there is no evidence to support bone scans for the initial evaluation of SA.[186] Compared with US, CT, and MRI, a bone scan has poor spatial resolution and lacks specificity.[186] These techniques also involve a significant amount of radiation exposure.[216] Nevertheless, it is useful when it is difficult to pinpoint the exact location of the infection or if multiple foci are suspected.[186,187] There is insufficient information to support a role for 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) without or with integrated CT in the diagnosis of SA.

RECOMMENDATIONS

1. Plain radiographs of the affected joint at baseline are suggested in all patients (**B-II**). **Comment:** Although not usually helpful for a SA diagnosis, they can show pre-existing joint or bone disease, rule out other diagnoses, and can be used as a reference image to assess future joint damage. Additional imaging is not usually necessary (**D-III**).
2. US is recommended to detect effusions when the physical examination is unclear, and to guide joint aspiration in joints that are difficult to examine, such as the hip or sacroiliac joint (**A-II**). In children with hip involvement and suspected transient synovitis, ultrasound of both joints is suggested, as bilateral hip effusion is a typical finding of transient synovitis of the hip that may support this diagnosis (**B-II**).
3. MRI is recommended for a suspected diagnosis of SA of axial joints (**A-III**) and when further imaging is needed for suspected spread of infection from joint to adjacent soft tissues and/or osteomyelitis

(more common in children's joints) (**A-II**). In children, MRI may be indicated to differentiate transient synovitis of the hip from SA if the diagnosis remains in doubt after initial assessment and investigation (**A-III**).

4. CT may be an alternative to MRI when the latter is not readily available (**A-II**), although CT should generally be avoided in children due to its high radiation index. CT may be an alternative to ultrasound to guide joint aspiration (**B-III**).
5. Nuclear medicine examinations are not recommended for the diagnosis of SA (**D-III**).

## RECOMMENDATIONS FOR TREATMENT

### VII. General principles of management of septic arthritis

The cornerstones of SA treatment include appropriate joint drainage and antimicrobial therapy. Most of the specific recommendations for the management of SA are detailed in other sections, but some general principles are discussed in this section.

SA entails significant morbidity and mortality, the latter, especially among adults. SA is often associated with bacteraemia and may present with sepsis and septic shock in some cases. Apart from the possible effect on mortality, delayed treatment of SA can lead to potentially irreversible joint damage. For these reasons, SA is a medical emergency and early recognition and treatment are crucial to outcome. Patients with suspected or confirmed SA are normally hospitalised. Joint drainage should be performed as soon as possible and empirical antibiotics are usually started intravenously.[28]

Joint damage is caused by bacterial enzymes and toxins, the host inflammatory response to pathogens, and tissue ischaemia caused by reduced synovial blood flow as a result of the increased joint pressure. Neutrophils release reactive oxygen species and proteases, and cytokines activate metalloproteinases that digest cartilage. Appropriate drainage of the affected joint is essential to eliminate pus, bacterial inoculum, bacterial virulence factors and harmful enzymes that damage the cartilage, and to reduce intraarticular pressure. Joint aspiration (arthrocentesis) should be performed as soon as SA is considered. Early and aggressive therapy with appropriate joint drainage to relieve joint pressure provides the best results.[49]

While joint drainage is considered a critical part of the treatment of SA in large peripheral joints, it may not be necessary in certain specific circumstances. In the case of axial SA, joint drainage is often not indicated due to the lower probability of functional sequelae, less accessible location, and the different characteristics of these joints. Diagnostic delay and findings of concomitant marginal bone erosions, common in axial joint SA, is a clinical scenario more likely to be considered osteoarthritis (concomitant SA and osteomyelitis) than pure SA, with frequent adjacent abscesses.[6] In such cases, additional imaging techniques are usually necessary. MRI is considered the better option for assessing the presence of osteomyelitis and fluid collections. CT may be useful for guided aspiration of the joint and/or adjacent abscesses. Osteomyelitis and large abscesses may require surgical treatment. By contrast, peripheral large joint SA in adults is commonly limited to the joint itself, and abscesses in the vicinity are unusual.[6]

A medical approach can also be considered when SA involves small peripheral joints (i.e. interphalangeal) or is caused by specific pathogens (at initial stages), such as *M. tuberculosis* and *Neisseria spp*. Indeed, the scenario of gonococcal arthritis has conventionally been treated with a short course of appropriate antimicrobial therapy and surgical procedures are rarely indicated. [217,218]

As a general principle of the antimicrobial therapy of SA, in the peripheral joint setting, the most important target is planktonic bacteria (free-living bacteria with active metabolism and rapid replication).[219] Synovial tissue has no basement membrane and is richly vascularised, so that most of the available antibiotics show good penetration into the synovial membrane and good diffusion in SF (serum concentration of 80%), usually reaching favourable concentrations, especially in inflamed joints. [220] In the setting of SA of the axial skeleton, usually with adjacent osteomyelitis, it may be more important to target intracellular and biofilm bacteria (in the less metabolically active, stationary phase of growth).

Empirical antimicrobial therapy should normally be initiated once clinical suspicion of SA has been established, after obtaining reliable samples for culture whenever possible, as highlighted in section IV. The severity of the clinical presentation of infection should be taken into account when deciding on when to start antibiotics. In haemodynamically stable patients without sepsis or septic shock, empirical antimicrobial therapy can be started after obtaining blood cultures and SF aspirate, as well as intraoperative specimens if the patient is undergoing urgent surgery. However, in patients with haemodynamic instability, sepsis or septic shock, it is well known that delay in starting antimicrobial treatment is associated with higher mortality.[221] In such cases, in accordance with the Guidelines for Management of Sepsis and Septic Shock 2021, we suggest obtaining blood and SF for culture before starting antimicrobial therapy, if this does not significantly delay initiation of antimicrobial therapy (< 45 min).[221]

Empirical antibiotics are usually started intravenously and subsequently switched to the oral route. The duration of intravenous administration reported in case series ranges from 1 to 4 weeks. [2,4,20,112,222–224] However, intravenous antibiotics have typically been given for up to 2 weeks, followed by a switch to oral treatment if there was an oral option and the clinical signs, symptoms, and inflammatory markers were settling. [12,31,124,225–227] The need for a minimum duration of intravenous antibiotics is not well defined, but is probably less relevant than in other infections as synovial tissue is well vascularised and antibiotics usually reach good concentrations, especially in cases of high bioavailability.

Retrospective data suggest that regimens with an early switch to oral antibiotics (≤ 7 days) with good bioavailability are as effective as prolonged parenteral regimens of 8–21 days and even ≥21 days, both in children and adult patients.[112,132,228] In a randomised trial demonstrating non-inferiority of 2 vs. 4 weeks of antibiotics for surgically-drained arthritis (64% hand joints), the median number of days of intravenous antibiotics was 1-2 days. [229] A multicentre, open-label, parallel-group, randomised controlled non-inferiority clinical trial involving 1,054 patients with bone and joint infections demonstrated that switching to oral antibiotic therapy within 7 days after definitive surgery was noninferior to continuation with intravenous antibiotics when used during the first 6 weeks; however, this clinical trial did not include patients with uncomplicated SA.[230]

In the paediatric population, several studies dealing with route of administration have been published. Two published prospective studies evaluating short intravenous therapy followed by oral antibiotics for the treatment of osteoarticular infections in children concluded that two to five days of intravenous therapy followed by oral therapy was appropriate for the cure of these infections. [232,234] However, some experts consider that SA caused by certain bacteria such as methicillin-resistant *S. aureus* (MRSA) or Panton-Valentine leukocidin (PVL)-positive strains may require a longer duration of both intravenous and oral therapy, based on the severity of osteoarticular infections caused by these microorganisms and the increased rate of complications. [28,232–235] A recent prospective multicentre study in Spain studied whether an exclusively oral treatment in selected children might be appropriate. [236] In a comparison of 893 children managed with initial intravenous antibiotic therapy and 64 patients exclusively treated with oral antibiotics (in the same hospital), complications were found in 8% of patients in the first group versus no patients in the second group. The authors concluded that an exclusively oral administration could be a safe option in selected children with bone and joint infections.[236] Some of these criteria would be: children between 3-36 months, absence of underlying disease, mild clinical symptomatology and low inflammatory parameters. In addition, there should be an outpatient clinic available with professionals experienced in these infections. These results need to be confirmed in further studies.

The definitive antibiotic regimen should be based on the pathogen identified and its antimicrobial susceptibility or, if no pathogen is identified, on the most likely causative organism(s).[237] It is recommended that treatment be discussed with an infectious disease specialist or clinical microbiologist whenever possible. [238]

The optimal duration of antimicrobial treatment in the setting of SA is not well established. Published evidence on the appropriate total duration of antibiotic treatment in SA is scarce and mainly based on case series or retrospective cohort studies and expert opinion.[6,12,17,31,124,226,227,239,240]. Duration of

antimicrobial therapy in SA can vary depending on the joint affected, microbial aetiology, other patient characteristics (age, immunosuppression) and the infection (osteomyelitis, abscesses).

In a retrospective observational study including 169 episodes of SA (75% involving large joints and 52% caused by *S. aureus*), Uçkay *et al* observed no difference in failure rate between patients treated for more or less than 28 days, and no differences either in patients who were treated for less than 15 days. [112] Encouraged by these results, the same researchers conducted a randomised trial, which demonstrated the non-inferiority of 2 versus 4 weeks of antibiotics for surgically-drained arthritis.[229] Nevertheless, these results should be interpreted with caution, because 64% of the sample were hand joints (in fact, non-inferiority was only demonstrated for wrist and hand SA), with under-representation of large joints and staphylococcal SA.[241] There were no cases of MRSA SA in this clinical trial.

Thus, while short courses of antimicrobials can be used for SA of peripheral joints (2-4 weeks),[12,31,124,226,227] longer courses are usually recommended for SA of the axial skeleton in adults (6-8 weeks) and children (4-6 weeks). [28,47] Longer treatments may also be necessary in adults with associated osteomyelitis, patients with immunosuppression and a slow/inadequate response to initial treatment, and in newborns and young infants (<3 months).

Expert opinion generally recommends 3 to 4 weeks of treatment for staphylococcal SA. [242,243] In reality, the duration of treatment is not reported in many case series, and when available, usually ranges between 4 and 8 weeks. [2,4,20,112,222–224,244–247] Some old papers report even longer treatments. [248–250]

Available data on the duration of treatment for streptococcal arthritis is scarce, and is not mentioned in all studies. It ranges from 2 weeks, as proposed by some authors, [229] to 4-6 weeks in most of the published series [6,14,251–255] or 12 weeks reported in older case series. [256] For pneumococcal SA, the recommendations vary between 4-6 weeks, with successful results reported after shorter treatments.[257–260] Lotz *et al,* in a recent retrospective observational study including 73 episodes of streptococcal and enterococcal SA recorded between 2003-2015, described a median antibiotic treatment duration of 6 weeks (4 intravenous, 2 oral) for large peripheral joints and 4 weeks (3 intravenous, 1 oral) for small ones (hands, feet).[254] They found no significant differences in survival or functionality either between them or the different streptococcal species; no case received less than 20 days of intravenous therapy, and up to 30% of patients were treated exclusively by this route. The authors found that shorter treatment was not predictive of poor outcome and that duration of antibiotic treatment could probably be shortened.

In the paediatric population, several studies have been published addressing the duration of antibiotic treatments. A randomised controlled clinical trial concluded that the outcomes of children with SA, mostly due to *S aureus,* randomised to receive 7 days of intravenous therapy (n=11) were the same as children receiving 14 days of intravenous therapy (n=10).[261] Two other published prospective studies evaluating short intravenous therapy followed by oral antibiotics concluded that two to five days of intravenous therapy followed by oral therapy for a total of 2-3 weeks was effective for the cure of osteoarticular infections in children.[28,231,262] In *K. kingae* SA, the recommended duration of antibiotic treatment varies from 10 to 14 days.[54,263] Longer treatment may be necessary for *Salmonella* SA (complications often develop),in immunocompromised children, those with underlying diseases, in the case of hospital-acquired infections, or newborns.[27,42,264] One series of *P. aeruginosa* SA of the foot in children reported the need for longer duration of antibiotic therapy plus an aggressive surgical approach.[265]

RECOMMENDATIONS

1. As a general rule, patients with suspected or documented SA should be admitted to hospital (**A-II**). Some studies in children treated exclusively with oral outpatient antibiotics showed a favourable outcome when specific criteria were met (**BII**).
2. Joint drainage is recommended for peripheral bacterial arthritis (except for gonococcal and early mycobacterial infections, which do not usually require joint drainage) and for fungal arthritis (**A-II**).
3. We recommend joint drainage of large peripheral joints with pyogenic arthritis as soon as possible (**A-II**).

4. While most patients with early diagnosis of axial joint infection do not require surgery (**B-III**), drainage of adjacent abscesses and various types of surgery for concomitant osteomyelitis may be necessary, especially if diagnosis is delayed (**A-II**). MRI is recommended to assess the presence of these complications (**A-III**).
5. In haemodynamically stable patients without sepsis or septic shock and with clinical and laboratory findings of peripheral pyogenic arthritis, we recommend starting empirical antimicrobial therapy after obtaining blood cultures and SF aspirate, as well as intraoperative specimens if the patient is undergoing urgent surgery (**A-II**).
6. In patients with haemodynamic instability, sepsis or septic shock, we suggest obtaining blood and SF for culture before starting antimicrobial therapy if this does not significantly delay initiation of antimicrobial therapy (< 45 min) (**B-III**).
7. We recommend that the definitive antibiotic regimen be based on the identified pathogen and its antimicrobial susceptibility or, if no pathogen is identified, on the most likely causative organism(s), discussed with an infectious disease specialist or clinical microbiologist whenever possible (**A-II**).
8. We suggest starting antimicrobial therapy intravenously **(B-III).**
9. It is recommended to switch to oral antibiotics after a few days (e.g., 2-7 days) of intravenous antibiotics in adults without endocarditis, with negative blood cultures and with clinical and laboratory improvement (provided that appropriate oral antimicrobials can be administered). (**A-II).** In children with a favourable clinical and analytical evolution after 2-4 days of intravenous antibiotics, switching to the oral route is recommended (**A-I**).
10. Total duration of antimicrobial treatment in adults without endocarditis:
    - For large peripheral joints after drainage, we suggest 3-4 weeks for *S. aureus* SA and gram-negative bacilli (GNB), 2-3 weeks for streptococcal arthritis and 1-2 weeks for gonococcal arthritis (**B-III**).
    - A longer duration is recommended for SA of axial joints (6 weeks) and SA with adjacent osteomyelitis (**A-III**), and is suggested for patients with immunosuppression or a slow/inadequate response to initial treatment (**B-III**).
    - Two weeks are recommended for SA of the wrist or hand joints after surgical drainage (this recommendation may not apply to SA caused by methicillin-resistant *S. aureus* [MRSA]) **(A-I).**
11. Total duration of antimicrobial treatment in children:
    - We recommend 2-3 weeks for all uncomplicated SA in children, and 3-4 weeks for SA with osteomyelitis (**A-I**).
    - Longer therapy (4–6 weeks) may be required in:
        - Infections caused by MRSA (**B-II**), *Salmonella*, Enterobacterales or *Pseudomonas aeruginosa* (**B-III**).
        - SA of axial joints (**A-III**).
        - Newborns and young infants (<3 months) (**B-III**).
        - Immunocompromised children (**B-III**).

*Empirical antimicrobial therapy*

**VIII. What is the recommended initial empirical antimicrobial therapy for SA?**

No clinical trials have compared the efficacy of different antibiotics in SA, except for one in paediatric age groups, and there are no studies on the registration of antibiotics in this indication. The few experimental models available, and the trial mentioned above found no differences in results when they compared antibiotics of different classes or mechanisms of action. Consequently, the decision on empirical treatment should be based on epidemiological information and the context of the patient which may determine a specific aetiology.

The empirical treatment of SA should be based on the organism identified in the SF Gram stain, or, if the Gram stain is negative, on the likelihood of the organisms involved and current local susceptibility patterns, further modified by the results of SF culture and/or blood cultures (when positive).[12,31,124] The most frequent causative organism of SA in adults and children is *S. aureus*, responsible for approximately 35–53% of SA in adults (Table 3), followed by group A and B streptococci, which are

especially prevalent among the elderly and those with chronic diseases. Arthritis caused by *Streptococcus pneumoniae* is not exceptional. Approximately 10-20% of SA cases in adults are caused by gram-negative bacilli, which are generally limited to immunocompromised patients, IDUs and hospital-acquired infections.[6,36] SA can also be caused by atypical bacteria, fungi or mycobacteria. [266,267] The use of an antimicrobial with good anti-staphylococcal activity is the cornerstone of empirical treatment of SA. In connection with the empirical coverage of methicillin-resistant *S. aureus* (MRSA), it should be noted that rates of MRSA in community-acquired SA are high in North America but lower in Europe, including Spain. [6,247,268] Additional empirical antimicrobial coverage may be necessary for other pathogens, depending on patient-specific risks.

The inferiority of vancomycin to beta-lactam antibiotics in different settings has led to controversies over what empirical treatment should be given when trying to cover MRSA, as the patient would receive suboptimal treatment until antibiogram availability if the strain is ultimately methicillin-susceptible. Discussion of this point is beyond the scope of this document given the absence of specific information on SA. Possible alternatives would include a beta-lactam combined with vancomycin, daptomycin, or the use of new cephalosporins active against MRSA, such as ceftaroline or ceftobiprole.

When a GNB aetiology is suspected (i.e. in the elderly, hospital-acquired infections, immunosuppressed patients, IDUs), empirical treatment should include a third-generation cephalosporin such as ceftriaxone (2 g intravenously every 24 hours), cefotaxime (2 g intravenously every 8 hours); or ceftazidime if *P. aeruginosa* is suspected.[12,124,226,227,239] Amoxicillin/clavulanate acid or piperacillin/tazobactam (if *P. aeruginosa* is considered a likely pathogen) are alternative options if polymicrobial infection is suspected, i.e. in diabetic patients with small joint infections in the feet or toes. [12,17,227,239] For patients allergic to penicillins or cephalosporins, aztreonam or fluoroquinolones are alternative options. [12,124,227] However, an assessment of the probability of multidrug-resistant GNB should be made, and if it is high, treatment should be started with a carbapenem until susceptibilities are confirmed. [269,270]

Based on the above criteria, when the Gram stain is negative and in the absence of specific risk factors for particular pathogens or resistant bacteria, initial empirical treatment in adults may consist of cloxacillin plus ceftriaxone or monotherapy with amoxicillin-clavulanate, which provides coverage for methicillin-susceptible *S. aureus*, streptococci and Enterobacterales. In patients with a history of beta-lactam allergy, daptomycin (or a glycopeptide) may be used combined with aztreonam or a fluoroquinolone.

Other options should be considered for certain risk factors or clinical settings (Table 4).

Special considerations for children

In children, the most frequent microorganism at all ages is also *S. aureus.* [28,32] Recent reports suggest that *K. kingae* may be more frequent in children aged 6 months to 5 years, [1,16,27,134,139,271–273] but *S. aureus* remains a common aetiology. Hence, *S. aureus* should always be included in the empirical treatment of SA (unless the Gram stain is positive and suggests other pathogens). In young children, empirical treatment should include adequate coverage against *K. kingae*, usually provided by empirical therapy with first- or second-generation cephalosporins recommended for SA. [28,263] *K. kingae* colonises the oropharynx from 6 months of age, reaches a peak of 10-12% in the second year of age, especially in children attending day-care centres, and decreases in older children. [136] *K. kingae* enters the bloodstream via the colonised mucosa, facilitated by concomitant viral respiratory infections, [274,275] hand, foot and mouth disease, or herpetic gingivostomatitis which damages the pharyngeal epithelium. [136] However, the probability of children carrying *K. kingae* going on to develop osteoarticular infection is less than 1% and depends on *K. kingae* clones with virulent strains, such as broad-spectrum RTX (repeat-in-toxin), cytotoxin, and other cofactors. [16,276] In nursing infants, group B streptococci and Enterobacterales (especially *Escherichia coli*) are also important. [28,32] Group A streptococci are also a frequent cause of SA in older children and adolescents. *Salmonella*, although very unusual, is more common in children with hemoglobinopathies such as sickle cell disease, and in young children. [277,278]

In children, the age range is especially important as the aetiology of SA can change significantly at different ages. The bacteria most commonly associated with SA in children are as follows:

- 0-3 months: *S. aureus*, Group B streptococcus (GBS) and *E. coli* (or other Enterobacterales). Unusual: *N. gonorrhoeae*, *Candida albicans*.
- 3 months to 4 years: *S. aureus*, *Kingella kingae*, Group A Streptococcus (GAS) and *S. pneumoniae* (especially in non-vaccinated children < 2 years). *Haemophilus influenzae* type B (Hib) may be frequent in areas where the vaccine is not available.
- > 4 years: *S. aureus*, GAS.
- Adolescents: The possibility of *N. gonorrhoeae* and *N. meningitidis* should be considered.

As empirical therapy, there should always be an antibiotic with high activity against MSSA (e.g., a beta-lactam) until this microorganism can be ruled out. *K. kingae* is resistant to antibiotics directed against *S. aureus* commonly used in bone and joint infections in children, such as clindamycin and cloxacillin, but is usually susceptible to most beta-lactams, including penicillin, amoxicillin, and ampicillin, and only rarely is it beta-lactamase-producing.

A prospective study performed in children showed that the four antibiotics studied (ampicillin, methicillin, penicillin and cephalothin) enter joint fluid at concentrations well above the *in vitro* inhibitory levels of the bacteria that usually cause SA. All these antibiotics appeared to be suitable for treating this infection in children. [279]

European guideline recommendations for the empirical treatment of MRSA SA in children are as follows:

- Use clindamycin in cases at high risk of MRSA SA or if the rate of MRSA infection is > 10-15% of the *S. aureus* infections in the setting.
- Use vancomycin when the rate of clindamycin resistance is > 10-15% or when the clinical presentation is severe. As vancomycin has not shown optimal results in some studies of bone and joint infection, some experts recommend it in combination (e.g.,with clindamycin) or prefer the use of other antimicrobials (linezolid or daptomycin).

Based on the above considerations, in the absence of specific risk factors for particular pathogens or resistant bacteria, the recommended initial empirical treatment in children is as follows:

- < 3 months: cloxacillin/cefazolin + cefotaxime/gentamicin, avoiding the use of 2 cephalosporins together.
- 3 months to 2 years: cefuroxime. Alternative: cloxacillin + cefotaxime or amoxicillin-clavulanate.
- 2-4 years: cephazolin or cefuroxime (the latter for under-vaccinated children).
- > 4 years: cephazolin, cloxacillin or clindamycin, depending on local epidemiology.

RECOMMENDATIONS

1. Empirical therapy active against *S. aureus* is always recommended in any patient (adults and children) with suspected SA and negative SF Gram stain (**A-II**). Additional empirical antimicrobial coverage may be necessary for other pathogens (**A-III**).
2. In adults with negative SF Gram stain and no specific risk factors for special pathogens or resistant bacteria, we suggest coverage of *S. aureus,* streptococci and the more common GNB with:
   - Cloxacillin plus ceftriaxone or monotherapy with amoxicillin-clavulanate (**B-III**).
   - A glycopeptide or daptomycin combined with aztreonam or a fluoroquinolone in case of beta-lactam allergy (**B-III**).

   Other options should be considered in the presence of certain risk factors or clinical contexts (**B-III**).
3. In children without specific risk factors for special pathogens or resistant bacteria, and with a negative SF Gram stain, we recommend treatment as follows (**A-II**):
   - < 3 months: cloxacillin or cefazolin + cefotaxime or gentamicin (avoiding 2 cephalosporins together).

- 3 months to 2 years: cefuroxime; alternatively, cloxacillin + cefotaxime or amoxicillin-clavulanate.
- 2-4 years: cefazolin; alternatively, cefuroxime for coverage of *Haemophilus influenzae* and *Streptococcus pneumoniae* in under-vaccinated children.
- > 4 years: cefazolin or cloxacillin.

*Targeted antimicrobial therapy*

**IX. What is the definitive antimicrobial therapy for *Staphylococcus aureus* SA?**

In general, *S. aureus* is the most common causative organism of native joint arthritis in adults and children,[1,82] which probably has to do with its ability to produce bacteraemia, its virulence and its tropism for bone and joints. [280] Definitive therapy should focus on the anti-staphylococcal activity of the antibiotic and its penetration into SF, and bone tissue when appropriate. Here we address these issues and the role of rifampin.

a) <u>What antibiotics should be used in staphylococcal SA?</u>

Strong recommendations cannot be made as there have been no comparative trials specifically addressing the treatment of staphylococcal SA.[270] The choice is based mainly on accumulated experience, sub-analyses in some comparative studies, and on pharmacokinetic and pharmacodynamic aspects.

Experience over the last decade has focused on anti-staphylococcal beta-lactams (i.e. cloxacillin, cefazolin) and glycopeptides.[4,20,59,223,244] Since the overall oral bioavailability of β-lactams is low, these drugs should usually be administered intravenously, at least during the first days of treatment. Synovial penetration of semi-synthetic penicillins (i.e., cloxacillin) appears to be lower than that of aminopenicillins or cephalosporins, [281,282] but long experience and outcomes would support their intravenous use against methicillin-susceptible *S. aureus.* A prospective study in 13 children with osteoarticular infection (3 with SA) showed that adequate synovial concentrations were achieved with orally given cephalexin.[283] Finally, the recently introduced ceftaroline and ceftobiprole are broad-spectrum cephalosporins with intrinsic activity against MRSA that require further consideration both as empirical and tailored antibiotics in the setting of SA.[270,284,285]

The arrival of new anti-staphylococcal agents in recent years has led to changes in the treatment of staphylococcal infections, mainly in the field of bacteraemia, which may also have had an effect on the treatment of SA.[286,287] Daptomycin is a bactericidal drug with activity against both methicillin-susceptible and methicillin-resistant strains. Reported experiences with this antibiotic in the setting of SA have been favourable,[288,289] with daptomycin concentrations in SF being approximately 50% of those in plasma.[290] Experts recommend administration at high doses (i.e. ≈10 mg/kg/d) and in combination with a second drug (i.e. beta-lactam, fosfomycin) to enhance activity and prevent resistance development.[291] A retrospective observational study observed better outcomes for *S. aureus* infection in adults with daptomycin compared to vancomycin, especially when the vancomycin MIC was ≥ 2 µg/mL.[292] In addition, some studies in adults have shown suboptimal efficacy of vancomycin in MRSA infections.[293]

Linezolid has high bioavailability and joint penetration and also has activity against MRSA.[281] Although prolonged use is associated with haematological and neurological toxicity, reports of linezolid for the treatment of SA have been successful. [294,295]

In children, there are no well-designed studies on glycopeptides, linezolid or daptomycin for the treatment of staphylococcal SA. A randomised, evaluator-blinded, multicentre study sponsored by MSD tested the safety of daptomycin in children with S. *aureus* bacteraemia (10% MRSA).[296] As a secondary objective, daptomycin was compared with other antibiotics (vancomycin and cefazolin) and no differences in efficacy were observed. Twenty-two children (27%) had bone and joint infections (9 SA). Based on this study and a previous observational study evaluating children with gram-positive infections treated with daptomycin, [297] this antimicrobial can be used in children with MRSA SA.

Clindamycin is a bacteriostatic agent that inhibits the production of bacterial proteins. It has been recommended for use as sequential oral treatment or as an alternative to beta-lactams or glycopeptides [243]. A prospective, quasi-randomized controlled trial in children with osteoarticular infections (84% MSSA), half of them with SA, showed that treatment with clindamycin had efficacy similar to that of first-generation cephalosporins [298]. An old prospective study performed in 31 children with bone and joint infections (12 children with SA) showed appropriate concentrations of clindamycin in serum (8-32-fold in excess of the MICs of all organisms isolated) and SF (60-85% of the serum concentrations measured), making this antibiotic suitable for the treatment of SA in children.[299]

Fluoroquinolones are bactericidal antibiotics with excellent bioavailability and penetration into SF (≈100% of plasma concentration).[281] A multicentre clinical trial showed the non-inferiority of administration of fluoroquinolones plus rifampin to flucloxacillin or vancomycin.[300] The satisfactory experience with this family of antibiotics among adults with orthopaedic-related infections supports their use in SA.

As sequential oral treatment, co-trimoxazole may be a suitable therapy for SA in children, based on a retrospective study conducted in children with acute osteomyelitis, 40% of them with *S. aureus* infection, including MRSA.[301] Oral co-trimoxazole was given as oral treatment following initial intravenous treatment.

b) What is the role of rifampin in staphylococcal SA?

Use of rifampin-based combinations is well established in the setting of biofilm and foreign body-associated staphylococcal infection, and is recommended in clinical scenarios where biofilm development is common, such as prosthetic joint infection and chronic osteomyelitis.[302–305] However, as pure native joint infections do not involve clinically relevant biofilm formation, the use of rifampin combinations in this setting is questionable. Indeed, the use of rifampin is not commonly reported. Apart from this, concerns about potential antagonism between rifampin and its companion drug would advise against its use in planktonic infections with potentially associated bacteraemia, such as SA.[306,307]

In adults, use of rifampin could be considered in situations where not only the joint is involved, but also the subchondral bone tissue. Bone involvement in the infection may be more frequent in chronic cases with delayed diagnosis, or in previously severely damaged joints. Bone tissue may also be involved in SA of small joints of hands and feet, or in some axial joints (i.e., sternoclavicular and sacroiliac joint, and pubic symphysis).

In children, there is no evidence to support the use of rifampin for staphylococcal SA,[28] even though bone involvement is fairly common in the setting of SA. Some authors might recommend the addition of this antibiotic in cases of MRSA or toxin-producing *S. aureus*, or where there is prosthetic material, all based on adult or experimental studies. [305] On the other hand, some authors would consider linezolid a suitable treatment for these situations, although experience in children is limited.[308,309]

RECOMMENDATIONS

**a) In adults**

1. For methicillin-susceptible *S. aureus*, intravenous cloxacillin or cefazolin is recommended (**A-II**). Initial addition of daptomycin may be considered (**C-III**). Patients allergic to beta-lactams can be treated with vancomycin or daptomycin (**A-II**).
2. Patients with MRSA SA can be treated with vancomycin or daptomycin (**A-II**) (an initial combination of daptomycin plus a beta-lactam may be considered, **C-III**).
3. Sequential oral treatment with beta-lactams, levofloxacin, clindamycin or linezolid are possible options, depending on isolate susceptibility and beta-lactam allergy (**B-III**).
4. The use of rifampin for pure SA is not supported by pathogenesis or evidence. It could be considered in complicated cases with concomitant osteomyelitis (**A-III**).

**b) In children**

1. For methicillin-susceptible *S. aureus*, initial intravenous cefazolin or cloxacillin is recommended (**A-II**). Sequential oral treatment with a beta-lactam (i.e., cefadroxil) is recommended (**A-II**). Clindamycin

(**A-I**), linezolid, levofloxacin (children > 6 months), daptomycin (children > 1 year) or vancomycin are alternatives for beta-lactam allergy (**B-III**).

2. For MRSA, initial intravenous clindamycin is recommended if the isolate is susceptible (**A-I**). Otherwise, the most appropriate antibiotics are linezolid or daptomycin; a glycopeptide would be a valid but less suitable option (**B-III**). For sequential oral treatment, clindamycin (children > 6-8 years) (**AI**), cotrimoxazole (B-II), levofloxacin (> 6 months), or linezolid (**B-III**) are suggested, depending on isolate susceptibility.

**X. What is the definitive antimicrobial therapy for streptococcal septic arthritis?**

Since it was first reported in 1940 by Ranz et al.,[310] the proportion of cases of SA due to streptococci (SSA) has been increasing and is now the second most frequent cause after *S. aureus,*[6,11] or coagulase-negative staphylococci when arthritis is secondary to an invasive intraarticular process (intraarticular injection, ligamentoplasty) where the percentage is variable (3.3%-18%).[11,311] However, there is little knowledge on clinical characteristics specific to SSA or across streptococcal species, and most of what is available comes from small retrospective cohort studies that reveal a predominance of beta-haemolytic streptococci*,* especially GAS and Group B streptococci (GBS). A progressive increase in cases attributable to *S. agalactiae* (GBS) has been reported over the last three decades, mainly in women, elderly patients and those with a significant burden of underlying conditions (diabetes, RA, hepatopathy or neoplasms).[251,253,256] S. *pneumoniae* is an uncommon, but not rare, cause of SA in adults. In the most important published series, the incidence of pneumococcal SA relative to other aetiological agents varies from 0%-10%, decreasing progressively from the 1970s-1980s to 3-4% today.[257,259,260]. Similarly, according to different reviews, the incidence of invasive pneumococcal disease also ranges from 0.6%-2.2%, and usually occurs in patients with underlying joint disease, immunosuppression or chronic debilitating conditions such as alcoholism.

In children, there are no good studies evaluating SA caused by streptococci. Most are non-comparative retrospective epidemiological studies. GBS are bacteria found in a high proportion of young infants (< 3 months) with SA, which usually presents with other infections at this age. In a large retrospective study of 71 infants < 3 months with bone and joint infections, GBS accounted for 45% of isolates, although the authors did not specify the type of osteoarticular infection.[42] In children older than 5 years, the second cause of SA after *S. aureus* is GAS, whereas *S. pneumoniae* is very unusual in places where the anti-pneumococcal vaccine has been introduced (< 5% of cases). In a retrospective analysis of a large prospective study, 97 children were identified with pneumococcal SA, representing 3.3% of all SA evaluated over a 15-year period. There was a decrease in pneumococcal SA during the study period, probably related to the introduction of the anti-pneumococcal vaccine in the study population.[312] Sixty per cent of children were < 2 years of age. Another retrospective study evaluating 43 children with pneumococcal osteoarticular infections found that 74% had SA, 72% were < 2 years old, and only 7/39 (18%) children had received the PCV-7 vaccine. [313] The data taken together indicate that pneumococcal SA is very unusual and mostly occurs in unvaccinated children under 2 years of age. Wounds and lesions, varicella lesions in particular, may be risk factors for the development of GAS SA.[28]

Regarding clinical presentation, SA caused by beta-haemolytic streptococci is characterised by an abrupt onset, accompanied by bacteraemia in 50-60% of cases, and multiple joint involvement has frequently been described (30-40%) in published series. Skin lesions seem to be the most common portal of entry, and additional extra-articular manifestations such as pneumonia, infected vascular catheter or endocarditis are found in 50% of cases[254,256] SSA is a predominantly monomicrobial infection, whereas polymicrobial cases are mainly associated with diabetic foot infection, as reported in one series.[253].

In infants, GBS SA is usually a consequence of sepsis or bacteraemia related to the immaturity of the immune system and colonisation from the birth canal. The clinical presentation can be subtle, with decreased range of motion of a limb, or irritability, or it can be part of a severe clinical sepsis.[27] Children with GAS or *S. pneumoniae* usually have the classic clinical presentation of fever, pain and decreased range of motion of the involved joint. The clinical presentation of GAS may be more severe than that of *S. pneumoniae*.

The prevalence of antibiotic-resistant streptococci has increased worldwide, mainly in the case of *S. pneumoniae*, with low susceptibility to penicillin or resistance. The rate of resistance to quinolones has remained stable, around 2-3%, in recent years. GAS is susceptible to penicillin, ampicillin and cephalosporins, but increased resistance to macrolides, clindamycin and tetracyclines has been observed, which may complicate antibiotic treatment in allergic patients. To date, resistance to vancomycin has not been detected.

Few studies in the literature describe the antibiotic regimen used in the medical treatment for SSA cases. All of them consider bactericidal antibiotics against the infecting organisms to be necessary and recommend the intravenous route for the initial phase. Penicillin is recommended for antimicrobial treatment in the setting of SA, and is the drug of choice in all published series. Third-generation cephalosporins (ceftriaxone, cefotaxime) or ampicillin are good alternatives to either vancomycin or clindamycin in cases of reduced susceptibility or allergy. Amoxicillin, cefuroxime, levofloxacin or moxifloxacin are options for the oral treatment phase. [251,254,256]

In children, the rate of penicillin- or cefotaxime-resistant *S. pneumoniae* outside the central nervous system is very low in Spain, at around 3% for invasive pneumococcal infection.[314] In the United States, the rates of resistance to beta-lactams are also very low, varying between 3-6% of cases of pneumococcal SA. [312] Hence, beta-lactams (especially penicillin or ampicillin/amoxicillin) are the first-line treatment for pneumococcal SA in children.[19] For GAS and GBS, penicillin is the first-line treatment recommended by most experts; for penicillin-allergic children, clindamycin may be a suitable alternative for streptococci SA.[37]

There are no comparative studies evaluating antibiotic therapy in children with SA caused by streptococci and all evidence is expert opinion and personal experience. Nevertheless, relapses or treatment failure following the general recommendations of different guidelines for acute SA are very rare.[26,28] Beta-lactams or clindamycin have been shown to be sufficient for effective treatment of acute SA in children,[33,298] and should be the primary therapy, depending on susceptibility.

RECOMMENDATIONS

**a) In adults**

1. For SA caused by susceptible streptococci, penicillin is the drug of choice. Third generation cephalosporins (ceftriaxone, cefotaxime) or ampicillin are good alternatives (**A-II**). In cases of allergy or reduced susceptibility, vancomycin, clindamycin, a fluoroquinolone or linezolid may be used (**B-III**).
2. For the oral treatment phase, amoxicillin, cefuroxime, levofloxacin, or moxifloxacin are all good options (**A-III**).

**b) In children**

1. For group A and group B streptococci, and penicillin-susceptible *Streptococcus pneumoniae*, initial intravenous penicillin or ampicillin are the recommended drugs of choice (**A-III**).
2. Sequential oral treatment with amoxicillin is recommended (**A-III**).
3. Third generation cephalosporins (ceftriaxone, cefotaxime), levofloxacin (children > 6 months), clindamycin, linezolid or vancomycin are alternatives depending on isolate susceptibility and beta-lactam allergies (**C-III**).

## XI. What is the recommended definitive therapy for septic arthritis caused by gram-negative bacilli?

In adults, gram-negative bacilli (GNB) are the third most frequent cause of SA after *S. aureus* and streptococci, with Enterobacterales and *P. aeruginosa* being the most commonly reported GNB organisms.[3,12,17,31,315,316] Among Enterobacterales, *E. coli* is the organism most commonly involved, but there have also been reports of SA caused by *Klebsiella* spp., *Enterobacte*r spp., *Proteus* spp., *Salmonell*a spp., *Morganella* spp., *Citrobacter* spp., and *Serratia s*pp.[317] One recent study reported that up to 22% of osteoarticular infections (including SA) diagnosed in very young infants (< than 3 months) were caused by Enterobacterales, which were the third most common cause of SA at this age.[42] Among

non-fermenting GNB, *P. aeruginosa* has been implicated as a cause of SA following invasive procedures, and as a cause of SA of the knee following anterior cruciate ligament surgery or intra-articular injections.[317] *Burkholderia cepacia* and *Acinetobacter baumannii* have also been implicated as causative pathogens following invasive procedures; *Burkholderia pseudomallei* is highly endemic in South and Southeast Asia and northern Australia.[317,318] *Salmonella* spp. is frequently associated with sickle cell disease in children.[28] *Haemophilus* spp. and *K. kingae* can also cause arthritis in certain population groups. *Haemophilus* spp. is now extremely rare since the introduction of Hi conjugate vaccines[28], but has previously been reported as a cause of SA in the elderly and children.[3,12,239] In addition to Hib, other non-typeable *H. influenzae* strains can cause SA in children.[28] *K. kingae* is increasingly recognised as an invasive pathogen in children, causing osteoarticular infections that affect large joints (knee, ankle, hip, and shoulder), although small joints may also be involved.[11,16,263] Several recent PCR studies showed that *K. kingae* may be the most frequently isolated bacterium in children aged 6-48 months, with frequencies up to 23% in children younger than 3 months.[16,132,134,264,319] Improved diagnostic techniques, with the recent addition of a new real-time PCR assay targeting the malate dehydrogenase gene of *K. kingae* which shows higher sensitivity than PCR targeting the RTX toxin locus, could explain, at least in part, the increased frequency of this diagnosis.[320]

GNB are more frequently seen as a cause of SA in immunosuppressed patients and the elderly, perhaps because of the increased prevalence of comorbidities such as diabetes, as well as potential sources of infection such as cutaneous ulceration, urinary tract infection, or recent abdominal surgery.[12,17,31,239] Many cases of GNB SA are the result of the haematogenous seeding of native joints from healthcare-associated bloodstream infections.[317] Although SA is usually monomicrobial and affects large joints, in diabetic patients with foot ulcers, the small joints of the foot are frequently involved and infection is often polymicrobial, including *P. aeruginosa* and other GNB.[17]

The recommended definitive therapy for GNB SA should be based on microbiological results.[12,31,227] Initial intravenous treatment with a second- or third-generation cephalosporin could be used in most cases, with aztreonam or a fluoroquinolone as alternatives for beta-lactam allergies. Based on published experience in prosthetic joint infection, an antibiotic regimen including fluoroquinolones is recommended whenever possible when switching to oral treatment.[321] As an alternative, given that these infections are usually acute and no foreign material is involved (and thus little or no biofilm is present), a beta-lactam or cotrimoxazole may be suitable, particularly in the case of quinolone resistance or intolerance.[322] Resistance to standard antibiotics in GNB infection is often associated with extended-spectrum β-lactamase, AmpC or carbapenemase production; co-expression of different resistance mechanisms to other antibiotic classes is frequent. In this scenario, guided antibiotic treatment should be discussed with infectious disease specialists/microbiologists.[12,227,270] Tigecycline, new cephalosporins (ceftolozane-tazobactam or ceftazidime–avibactam) or antibiotic combinations that include meropenem alone or with colistin or fosfomycin could be alternative options.[269]

In the particular case of children, a position statement was recently published including the treatment recommendations of the Spanish Association of Paediatrics-Spanish Society of Paediatric Infectious Diseases (AEP-SEIP) in multidrug-resistant bacterial infections.[323] For *K. kingae* SA, the initial drug treatment is usually penicillin or ampicillin once the culture results and antibiotic susceptibility of the isolate are available.[28,263] Nevertheless, even if *K. kingae* is detected by PCR and antibiotic susceptibility is not available, it may be appropriate to switch to penicillin since most strains of these bacteria are susceptible.[28,324] In a series of 62 children with proven invasive *K. kingae* infections (42 with positive blood culture results, 20 with positive SF culture results), patients were treated with intravenous cefuroxime (150 mg/kg per day) or cefazolin (100 mg/kg per day).[54] *K. kingae* SA is usually mild, with a low rate of complications compared to *S. aureus* SA.[16,132,325] A recent retrospective study showed that children with *K. kingae* SA treated initially with oral antibiotics and without hospitalisation had a favourable outcome.[325] These children were closely monitored after arthrocentesis and none developed complications or sequelae. There is no clear evidence on the treatment of other GNB SA in children. Therefore, the general recommendations for treatment of invasive disease caused by these bacteria may be followed, although it seems prudent to prolong the duration of antibiotic treatment, as many of these children may be immunocompromised or have severe underlying diseases.[323]

RECOMMENDATIONS

**a) In adults**

1. For SA caused by susceptible GNB, initial treatment with an intravenous second- or third-generation cephalosporin is recommended (**A-III**). For GNB isolates resistant to third-generation cephalosporins, consultation with an infectious disease specialist is recommended (**A-III**). Initial treatment with aztreonam or a fluoroquinolone is suggested for beta-lactam allergies (**B-III**).
2. Sequential oral treatment with ciprofloxacin is recommended, whenever possible (**A-III**). Oral beta-lactams or cotrimoxazole are suggested alternative treatments, depending on the susceptibility of the GNB identified (**B-III**).

**b) In children**

1. *K. kingae* SA can be treated with penicillin or ampicillin. First- and second-generation cephalosporins or amoxicillin-clavulanate are good alternatives (**A-II**).
2. For SA caused by other GNB, antimicrobial selection should be based on susceptibility (**A-III**).

## XII. What is the directed therapy for septic arthritis caused by other less common microorganisms?

When SA does not follow the expected clinical course and no microorganism is isolated, the possibility of unusual pathogens should be considered. This is particularly relevant in specific populations or those with particular epidemiological risk factors, such as immunocompromised subjects, healthcare-acquired infections or contact with a person with tuberculosis.

- ***Candida* spp. septic arthritis**

*Candida* spp. is a rare cause of SA in adults. It is commonly acquired (approximately 80% of cases) by the haematogenous route as a late manifestation of candidemia.[326] About 20% develop following traumatic inoculation. The evolution of candida SA is frequently indolent and may be diagnosed late in the disease. Unfortunately, there is no evidence-based standard treatment regimen for patients with candida native joint infections due to the heterogeneous spectrum of diseases and the relatively low frequency of this disease.[71] In an analysis of 112 previously published cases, 2 (4%) of those treated with surgery and antifungal therapy died versus 12 (14%) of those treated only with antifungal agents;[326] these results however should be interpreted with caution due to possible survival bias. Nevertheless, despite the higher mortality among those who received medical treatment alone, the authors reported no significant differences in therapeutic response between those who received combined medical and surgical treatment versus medical treatment alone.[326] According to the 2016 IDSA guidelines, surgical drainage is indicated in all cases of candida SA (strong recommendation; moderate quality of evidence).[327]

The preferred antifungal agent is unknown, as all published experience is based on case reports, with documented cures with amphotericin B, fluconazole, and echinocandin therapy. The optimal duration of antifungal treatment is not well established. A recent study with a limited number of cases (23 patients) showed high cure rates with a 6-8 week course of antifungal therapy if aggressive surgical intervention was performed. [328] ESCMID and IDSA guidelines recommend a total duration of antifungal therapy of at least 6 weeks.[327,329]

In children, candida SA is very rare, usually occurring in premature infants, immunocompromised children or in cases with medical or surgical devices.[71,326] This infection is frequently a healthcare-associated infection. In Gametlous's review of 40 children with candida SA, the majority of the children were < 12 months old (70%). Neonates frequently have polyarticular involvement, with the knee being the most commonly affected joint.

In children, the recommended medical treatment for candida SA is based on adult studies and experience with other systemic infections caused by these microorganisms, as the evidence in children

is scarce, with no comparative studies. It may be necessary to rule out other sources of infection, especially in neonates (with lumbar puncture and dilated retinal examination).[327]

- ***Mycobacterium tuberculosis***

Bone and joint tuberculosis (TB) currently accounts for 2.2–4.7 % of all TB cases in Europe and the USA and around 10–15 % of extrapulmonary tuberculosis.[330,331] Half of the cases involve the spine. Peripheral osteoarticular TB refers to extraspinal skeletal TB affecting the joints or bones. The knee, ankle and wrists are the most frequently affected joints in adults, usually with an indolent clinical course. Refractory monoarthritis or oligoarthritis with negative SF cultures should raise suspicion. The clinical non-specificity often results in late diagnosis. [61] Adjacent bone is often involved, which may influence the duration of treatment.

Although it is difficult to specify the burden of TB bone and joint infections in children, up to 25-35% of childhood TB cases are extrapulmonary, and 1.5% of these are osteoarticular infections.[332] As in adults, the most commonly affected bones are the vertebrae, especially of the dorsal spine. The peripheral joints are much less involved, with hip and knee (8% each) being those most frequently infected.[1]

In adults, TB arthritis can be cured with medical therapy (without surgery) if it is started in early stages of the disease. Indeed, the key to successful management of bone and joint TB is early diagnosis and treatment.[333] However, surgery is often necessary in advanced disease.[330] The recommended antituberculous therapy for bone and joint involvement is similar to that for pulmonary TB; for pan-susceptible TB, treatment consists of four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) given for a total of 2 months, followed by two drugs (isoniazid and rifampicin) for a minimum of 4 months.[334] Ethambutol may be stopped once the susceptibility of the bacteria is known. Duration of therapy is controversial. IDSA guidelines recommend 6-9 months of treatment, but there is limited evidence to support this recommendation. [335] Some experts recommend longer treatment (9-12 months).[330] In addition, therapy may be extended to 9 to 12 months in patients who initially present with a significant disease burden or when their net state of immunosuppression is high.[331] Sequelae are common, particularly in patients with extensive bone or soft tissue involvement and joint damage at diagnosis. Surgery (drainage, arthrodesis, prosthesis) may be required to cure the infection, control pain, or improve joint function.[333]

There are no well-designed studies evaluating TB SA in children and most of the recommendations are based on results in adults and expert opinions. In children, the Spanish Guidelines recommend 6–9 months of treatment for extrapulmonary TB.[336]

In cases of TB SA with resistant strains, more complex regimens are required, and for longer periods of time; consultation with an infectious disease specialist is warranted.

**Gonococcal arthritis**

Disseminated gonococcal infection (DGI) usually manifests as two major clinical syndromes: arthritis-dermatitis syndrome and localised purulent arthritis. Approximately 0.5% to 3% of patients infected with *N. gonorrhoeae* develop DGI. There are very few recent epidemiological data analysing the incidence of DGI in patients with arthritis, but historical data showed that up to 14% of SA cases were due to *N. gonorrhoeae.* [12,14] A study including patients with DGI from 1975 to 2008 observed a threefold decrease in incidence from the 1980s to the early 2000s.[337] However, an increasing incidence of gonococcal arthritis is currently observed, paralleling the overall increase in sexually transmitted infections. [218] In our setting, more than half of *N. gonorrhoeae* isolates are now resistant to fluoroquinolones; worldwide, decreased susceptibility to cefixime (MIC≥ 0.5) and clinical failures in gonococcal urethritis have been reported.

In neonates and sexually active adolescents with suspected SA, consider the possibility of *N. gonorrhoea*. In neonates, the symptoms are nonspecific, whereas in adolescents, they occur as part of a DGI.

Evidence on the choice of antibiotics or duration of antibiotic treatment for *N. gonorrhoea* SA is scarce, and to the best of our knowledge, no randomised trials have been conducted. In a recent review of 112 patients with a DGI, the only available information was that the clinical response to intravenous antimicrobial therapy was rapid (median of 3 days), and similar between pregnant and nonpregnant women, [337] supporting that this infectious arthritis is easily treated. The recommended treatment is based on guidelines and expert opinion.[338] Ceftriaxone 1g iv/day or cefotaxime 1g/8h is the treatment of choice. After clinical improvement, treatment can be switched at 48-72h to ciprofloxacin 500 mg/12h or cefixime 400 mg/12-24h if the isolate is susceptible. The recommended duration of treatment has been 1 week for arthritis-dermatitis syndrome and two weeks for purulent arthritis. The management of purulent arthritis rarely requires surgical drainage.[36] According to CDC guidelines, if chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.[338] In any case, screening for other STIs should be performed.

Although evidence in children is sparse, both ceftriaxone (25 to 50 mg/kg/day, intravenously or intramuscularly, in a single daily dose for 7 days) and cefotaxime (25 mg/kg, every 12 hours for 7 days) are the treatments of choice for newborns and adolescents with SA. The treatment should be extended to 10-14 days if meningitis is documented. Cefotaxime is preferred for infants with hyperbilirubinemia. Empirical use of fluoroquinolones for gonorrhoea is no longer recommended because of the increased prevalence of quinolone-resistant *N. gonorrhoeae*, and cefixime is not recommended as a first-line therapy. Treatment may be switched to oral antibiotics, guided by susceptibility testing, 24-48 hours after substantial clinical improvement. Sequelae are very rare.

RECOMMENDATIONS

- ***Candida* spp. septic arthritis**

1. In surgically treated cases, we suggest 6–8-weeks of therapy with an azole, echinocandin or liposomal amphotericin B (**A-III**).
2. In neonates with candida SA, an extent-of-disease study is suggested, including lumbar puncture and retinal examination (**B-II**).

- ***Mycobacterium tuberculosis* arthritis**

1. In patients with early diagnosis tuberculous arthritis (without large abscesses or bone sequestration), tuberculostatic treatment similar to that for tuberculosis at other sites is recommended. Some experts recommend longer treatment (9-12 months) (**B-III**).
2. It is suggested that treatment be supervised by an expert (**B-III**).

- **Gonococcal arthritis**

1. In adults, we recommend ceftriaxone 1g every 24h (first choice) or cefotaxime 1g intravenously every 8 hours (alternative) (**A-II**I). After clinical improvement, we suggest switching to an oral agent guided by antimicrobial susceptibility testing: ciprofloxacin 500 mg/12h or cefixime 400 mg/12h (**B-III**). Patients with gonococcal arthritis should be screened for other sexually transmitted infections (**A-II**).
2. In children, we suggest 7 days of cefotaxime (neonates) or ceftriaxone (**B-III**).

**XIII. What is the treatment for culture-negative septic arthritis?**

Patients with clinical findings of SA but negative SF cultures is a frequent scenario in clinical practice. The percentage of culture-negative SA in adult patients ranges widely in different series from 7% to 59%,[3,21,224,339,340] with a mean of around 20%,[339] depending on the population included and the clinical and laboratory diagnostic methods used. In children, this percentage may be somewhat higher (25-35%);[33,41,298] in one series of SA without osteomyelitis, it was as high as 69%.[341] This may be due in part to the relevance of *K. kingae* in children under 2 years old in some areas of the world. *K. kingae* is a fastidious microorganism and may not have been identified in some series.[16,132,273] In the setting of culture-negative SA in adults, the role of microorganisms with fastidious growth requirements (such as *N. gonorrhoea*, *M. tuberculosis* or Lyme disease) is small, because they are unusual and can often be suspected on the basis of specific clinical and epidemiological characteristics.

The approach adopted to rule out certain rheumatic diseases that mimic SA should be thorough and precise.[339] In a retrospective study involving 198 patients admitted with arthritis, who were diagnosed

and treated as septic, at least 14% (diagnosed with culture-negative SA) subsequently developed rheumatic arthritis.[339] Consequently, the authors suggest that when no microorganism is identified, the diagnosis of SA should remain presumptive and that follow-up is necessary to screen for other diseases, especially rheumatic diseases.

Concomitant or prior antibiotic administration may be responsible for negative cultures. If so, this is one of the most important factors to consider when deciding on antimicrobial therapy[21,342]. In the only prospective study comparing the characteristics of culture-negative and culture-positive SA cases, more patients in the former group (29%) had received antibiotics in the previous week than those in the culture-positive SA group (15%), although this difference was not statistically significant.[21] Otherwise, the clinical findings and outcomes of patients with culture-positive and culture-negative SA were found to be similar, although culture-negative SA cases required fewer surgical interventions to be cured[21]. Most authors reported milder findings and better outcomes for patients with culture-negative SA,[224,340,343,344,] especially in children.[33,41,132,298,345]

Once other diseases have been ruled out, most cases of culture-negative SA cannot be explained either by the effect of antibiotics or by the particular growth requirements of the microorganisms involved.[21,342] In fact, the aetiology of culture-negative SA would mostly be the same as that of culture-positive SA, and the likelihood of a negative culture could be influenced by the balance between bacterial load and host immunity.[21,342] In some retrospective series comparing culture-positive and culture-negative cases, the most frequently isolated microorganisms in culture-positive SA were staphylococci and streptococci, as in other series.[33,41,224,298,340,343,344] In a study of 36 adults with culture-negative SA, they received the first-line antibiotics (cefazolin, cloxacillin, clindamycin) and treatment was successful in 70% of cases.[340] In children with culture-negative SA without osteomyelitis, failure was observed in only 9% and was unrelated to the empirical antibiotics used.[341]

In general, based on the above considerations, patients with culture-negative SA can be managed with antibiotic treatment regimens similar to those recommended empirically for patients with culture-positive SA and no Gram-stained microorganisms. If immunosuppression is not present and the epidemiological circumstances mean that the isolation of multidrug-resistant organisms is unlikely, it seems reasonable to use first-line antibiotics.[340,342] An accurate evaluation of epidemiological aspects is particularly necessary to exclude less frequent aetiologies or unusual, difficult-to-grow microorganisms on the spectrum of antibiotic treatment. In patients who are receiving or have recently received antibiotics, it is advisable to take antibiotic coverage into account in order to tailor antimicrobial therapy. According to some authors, the duration of antibiotic treatment for culture-negative SA can be shortened to two weeks in adult patients,[342] and to ten days in children.[33,298,342]

RECOMMENDATIONS

1. We suggest that culture-negative SA be treated with antimicrobial therapy similar to empirical therapy in patients with Gram stain-negative SF (**B-III**).
2. In patients who are receiving or have recently received antibiotics, we suggest considering antibiotic coverage to tailor antimicrobial therapy (**B-III**).
3. An accurate epidemiological assessment is required to rule out uncommon or fastidious microorganisms (**B-II**).

*Adjuvant treatment*

**XIV. Is any adjuvant treatment recommended for SA?**

In SA, once the bacteria colonise the synovial membrane and start to proliferate, a host inflammatory response is induced.[346] Although bacterial products and toxins can directly increase tissue damage in the infected joint,[347,348] it is the inflammatory response which is responsible for most joint injury. [349] Bacterial endotoxins can trigger the release of certain cytokines (such as tumour necrosis factor and interleukin-

1), which could stimulate proteinase production by synovial cells and chondrocytes, enhancing leukocyte migration; neutrophil elastases have been shown to increase cartilage matrix degradation in the joint. [350–352] The inflammatory process increases intra-articular pressure, reducing blood flow and resulting in cartilage and synovial ischaemia and necrosis. If left untreated, inflammation can lead to further cartilage and underlying bone destruction and progress to other surrounding tissues.

Permanent joint damage and poor joint function have been described in 23-33% of patients.[2,23] In children, it is estimated that 10-25% have residual dysfunction after SA, although recent studies in developed countries show a much lower percentage (5-10%).[32] Sequelae of SA include bone growth abnormalities, rigidity, chronic inflammation or joint pain and joint instability.[28]

Reducing inflammation or modulating the host immune response at the site of infection may prevent damage to the joint and thus preserve its anatomy and function. A number of approaches aimed at attenuating microbial virulence factors or the host inflammatory response have been studied in experimental and animal models in an attempt to improve the outcome in infected joints.[346] However, corticosteroids are the only drugs that have been studied in clinical trials in children with SA,[353] and no appropriate studies have been conducted with these agents in adults. It is generally accepted that nonsteroidal anti-inflammatory drugs are of benefit in patients with SA,[28] but no studies have been conducted with these drugs. Other authors have evaluated treatment with agents that modulate bone remodelling and thus modify bone and joint damage,[354,355] and immunomodulators such as IL-10 and anti-TNF.[356,357]

a) Animal models

A number of animal models have been developed to investigate the effect of anti-inflammatory drugs on the outcome of SA.

Stricker *et al* studied the effect of betamethasone on the cartilage of rabbits with *S. aureus* SA.[358] There were 3 experimental groups: antibiotics alone for 12 days (Group 1), antibiotics + steroids for 4 days (Group 2) and antibiotics plus a single intra-articular dose of betamethasone (Group 3). The SF and cartilage of the three groups were analysed on day 14. Rabbits in group 2 showed significantly less articular cartilage proteoglycan loss than groups 1 and 3. The somewhat lower dose of steroids in group 3 may have accounted for its lower effectiveness in preventing cartilage damage. Therefore, corticosteroids in combination with antibiotics may help protect the joint from proteolytic degradation. In a murine model, Sakiniene *et al* evaluated the effect at day 14 of adding intraperitoneal dexamethasone (DXM) to antibiotics to treat *S. aureus* SA.[359] They observed that mice in the DXM group had higher cure rates (78 vs 52%), fewer T-cells and macrophages in the SF and decreased serum levels of interferon-gamma at the end of the study.

Another murine model evaluated receptor activator of nuclear factor κB ligand (RANKL)-targeted therapy using osteoprotegerin (OPG) as decoy receptor to bind to RANKL.[355] In the complex system of bone remodelling, the RANK/RANKL/OPG pathway is the coupling factor between bone formation and bone resorption. RANKL binds to the RANK receptor of pre-osteoclasts and mature osteoclasts and stimulates their activation and differentiation. Consequently, modulation of this pathway may be useful in osteomyelitis and SA. Verdrengh *et al* induced *S. aureus* SA in mice and divided them in 3 groups: one group was treated with OPG alone (OPG-Fc), another was treated with OPG-Fc + antibiotics, and the last group was treated with RANK-Fc. A control group was treated with huFc alone to rule out an immune response towards the human Fc fragment in the OPG supplied. Mice treated with RANK-Fc or OPG-Fc preserved total bone mineral density and trabecular bone as compared to treatment with huFc or antibiotics. Treatment with RANK-Fc or OPG-Fc decreased the levels of bone resorption markers (osteocalcin, CTX-I, and TRACP5b). Nevertheless, neither RANK-Fc nor OPG-Fc significantly influenced the frequency and severity of SA.[355] The same group previously analysed the effect of treatment with bisphosphonate (zoledronic acid) in combination with antibiotics, or antibiotics in combination with DXM in *S. aureus*-induced SA in mice, showing their usefulness in the prevention of skeletal destruction by decreasing osteoclast activity.[354]

IL-10 has anti-inflammatory effects by promoting the T helper cell response and subsequently down-regulating the cell-mediated immune response. It may also have antibacterial activity. Puliti M et al evaluated the cytokine production of mice with group B streptococci SA and showed that both pro-inflammatory (IL-1, Il-6, TNF) and anti-inflammatory cytokines (IL-10) were increased.[356] The addition of anti-IL-10 antibodies to a group of mice at the time of infection resulted in worsening joint damage and a 60% increase in mortality, associated with early production of pro-inflammatory cytokines. Administration of IL-10 just after infection had a beneficial, dose-dependent effect on infected joints. Pro-inflammatory cytokine levels were lower in the IL-10 groups, with limited periarticular inflammation and little cell influx into the SF.[356]

Other studies using animal models focused on modulation of anti/pro-inflammatory cytokines (such as anti-TNF) found it useful in neutralising pro-inflammatory cytokines.[357]

Based on the results in these animal models, modulating inflammation in SA may have important benefits for subjects with this infection. Most of these studies were developed in *S. aureus* SA models, in which inflammatory activity is more pronounced.

b) Human studies

Several studies have evaluated the effect of corticosteroids on the outcome of SA in children.

A randomised, placebo-controlled study was performed in Costa Rica to evaluate the effect of treatment with antibiotics -in association with DXM or placebo for 4 days- on the outcome of 100 children with bacteriologically confirmed SA.[360] Treatment with DXM shortened the duration of symptoms; after one year of follow-up, limping, joint pain, and restricted range of movement were found in 26% of patients who received placebo but only 2% in patients treated with DXM. In that study, children under 3 months of age were excluded; *S. aureus* was responsible for 67% of cases and *H. influenzae* for 13%. Worthy of note was the high rate of sequelae in the placebo group, mainly in patients with *S. aureus* SA.

A second randomised trial conducted in Israel involved 49 children (mean age, 33 months) with SA.[361] DXM was given for the first 4 days of antimicrobial therapy and compared to placebo. Children in the DXM group had fewer days of fever, pain, and days of parenteral antibiotics, although there were no differences in long-term outcome. All *S. aureus* isolates in the study were methicillin-susceptible, and *K. kingae* was the most common pathogen identified; consequently, the results observed here may not apply to SA caused by MRSA.

A third randomised, double-blind, placebo-controlled clinical trial conducted in Pakistan evaluated the effect of DXM on children with SA.[362] In that study, 60 children older than 6 months were enrolled; those in the DXM group had a significant reduction in days of inflammation, redness, and days of hospitalisation, as well as improved motion of the affected joint and a reduction in ESR and CRP. Nevertheless, follow-up was very short and the aetiology of SA was not indicated.

Fogel et al performed a retrospective study of 116 children with SA with the aim of evaluating the effect of DXM outside a clinical trial.[363] The DXM group had a more rapid clinical improvement and decrease in CRP, with shorter duration of intravenous antibiotics and hospital stay. *K. kingae* was also the most frequently isolated agent. No long-term follow-up was reported. Four children in the DXM group had a mild relapse of symptoms.

A Cochrane systematic review included the first two clinical trials with a total of 149 children aged 3-18 years.[364] In that review, the authors observed a more rapid recovery in the DXM group, with a relative risk of 1.33 for absence of pain, and 1.33 for normal function of the affected joint. There was an overall reduction of 2.77 days in the number of days of intravenous antibiotics. Although the authors acknowledged that DXM might be useful to speed up clinical recovery in children with SA, they also stated that the evidence was of low-quality, with small numbers of study participants and incomplete outcome data, and therefore recommended further clinical trials in children with relevant outcomes. Another systematic review including all 3 clinical trials and the retrospective study mentioned above

evaluated a total of 348 children (142 in the DXM group, 207 in the placebo group), with similar results to the Cochrane review.[353] In the second review, the authors strongly recommended the use of DXM in children with SA. The corticosteroid dose most commonly given was dexamethasone administered intravenously (ranging from 0.15 to 0.2 mg/kg/dose every six to eight hours) for four days.

The European Society for Paediatric Infectious Diseases (ESPID) Bone and Joint Infection Guidelines have not recommended the widespread adoption of steroids until larger prospective studies are conducted[28], as corticosteroids may delay the diagnosis of non-infectious inflammatory arthritis, resulting in delayed treatment and a possible increase in complications or sequelae. Furthermore, the studies that used DXM did not compare the possible effect of NSAIDs on the outcome of children with SA. In conclusion, DXM may be considered for use in children with highly inflammatory and symptomatic SA when the bacterial aetiology is highly probable or confirmed.

No appropriate studies in adults have been performed.

RECOMMENDATIONS

1. In children, nonsteroidal anti-inflammatory drugs may be beneficial during the acute phase while the signs of inflammation are present (**A-III**).
2. In children with confirmed SA, early administration of a short course of intravenous corticosteroids may accelerate clinical recovery and reduce hospital stay (**B-I**). **Comment**: The potential impact of diagnostic delay on non-infectious arthritis and the long-term effects in SA are unclear.
3. In adults, corticosteroid use is not recommended for SA due to the lack of clinical evidence on its effects (**D-III**).

*Joint drainage*

**XV. What joint drainage procedures are recommended in patients with SA?**

Joint decompression and removal of purulent material from the affected joint is one of the most urgent and important measures for treatment of SA. In any joint, an advanced stage of the disease is associated with poor functional outcome; consequently the time between the onset of initial symptoms and surgery directly affects functional outcome.[365,366] Joint drainage procedures in patients with SA include conservative measures, such as closed needle aspiration (repeated as necessary), and surgical interventions, such as arthroscopy with irrigation and debridement and arthrotomy (open surgical drainage).[367–372] When closed needle aspiration or arthroscopy with irrigation and debridement are not effective, arthroscopic or open surgical drainage, respectively, should be used, depending on the joint, previous surgeries and patient morbidity.[373] In general, the quality of the evidence in studies comparing different joint drainage procedures is low; most are retrospective and multivariate adjustment was not performed in several studies.

a) <u>In adults</u>

The best method for draining joints is not well defined. Serial aspiration and open arthrotomy have long been used to treat SA. In more recent years, multiple studies have been conducted to assess arthroscopic surgery for the treatment of SA but the vast majority have been retrospective, often involving different joints, and small or medium-sized cohorts. Based on the results of the analysed studies, outcomes can vary depending on the affected joint and the drainage procedure:

- For SA of the **knee**: needle aspiration, arthroscopy, or open surgery can be used to drain the joint.[245,365,374] A meta-analysis published in 2021 evaluated the overall efficacy of arthrotomy versus arthroscopy for the treatment of adults with SA in any joint.[375] A sub-analysis (including twelve retrospective studies) showed that patients with knee SA who underwent arthroscopy had a lower risk of reinfection, fewer complications and hospitalisation days.[375] In a more recently published meta-analysis, management of SA of the knee by arthroscopy and arthrotomy showed similar rates of reinfection, length of hospital stay, operative times and mortality rates, [376] although arthroscopy

was associated with a significantly increased knee range of motion and a lower complication rate compared with arthrotomy treatment.[376] Thirteen retrospective studies, published between 2001 and 2021, were included in the meta-analysis;[365,366,373,377–385] nine had a moderate risk of bias and four a high risk of bias. Since none of the included studies were randomised controlled trials, and had significant biases, the results of the two meta-analyses mentioned above should be interpreted with caution. In a randomised clinical trial with a very small sample size (21 patients), the effectiveness of treatment of knee SA by arthroscopy and arthrotomy was similar.[374] A more recent retrospective study, based on a Nationwide Readmissions Database in the US, identified 14,365 patients with native knee SA who were undergoing irrigation and debridement. On multivariate analysis, arthroscopic surgery was associated with a reduction in hospital costs and length of stay, as well as fewer overall complications, while the risk of revision surgery did not differ between arthroscopic and open approaches.[386] Although some different conclusions were drawn from the studies reviewed, taking into account their limitations, arthroscopy seems to have some overall advantages over arthrotomy surgery for treating SA of the knee. An electronic survey distributed to all academic orthopaedic faculties across the United States showed that arthroscopic drainage of the knee in SA was the preferred method of treatment (70%); however, there was no consensus on a gold-standard treatment or the role of synovectomy.[383]

- For SA of the **wrist**: the joint can be drained by needle aspiration, arthroscopy or open surgical drainage. A retrospective comparison of 40 episodes of SA of the wrist initially treated with open or arthroscopic irrigation and debridement at a single institution showed that patients treated arthroscopically had fewer operations and a shorter hospital stay.[387]

- For SA of the **ankle**: the joint can be drained by needle aspiration, arthroscopy or open surgical drainage. In a retrospective study of 23 patients with SA of the ankle treated with arthroscopic drainage, the outcomes were similar to those found in previous studies of patients treated with the open surgical approach, with fewer complications.[388] A recently published retrospective study included 168 patients undergoing arthroscopy and 794 undergoing arthrotomy for SA of the ankle.[389] Patients were identified in a national data set from 2015-2020. There were no significant differences in 90-day reoperation rates between patients who underwent open arthrotomy versus arthroscopy, but the incidence of surgical-site infections and hospital readmissions was higher in the open arthrotomy cohort.[389]

- For SA of the **elbow:** the joint can be drained by needle aspiration, arthroscopy or open surgical drainage. Two case series analysed the outcomes of 11 and 12 patients, respectively, with SA of the elbow treated with arthroscopic surgery. [390,391] Based on the results, arthroscopy appears to be a reasonable possible alternative to open surgical treatment, although limited data preclude a firm conclusion.

- For SA of the **hip:** the joint can be drained by arthroscopy or open surgical drainage. In a systematic review, De Sa et al identified 65 patients with SA of the hip treated with arthroscopic irrigation and debridement.[392] The initial rate of infection eradication was 100% and all studies reported improvements in patient pain and function. No complications were reported, and only 1 of 65 hips (1.5%) required revision arthroscopy for recurrence. More recently, 421 patients with SA of the native hip joint were analysed: 387 (91.9%) and 34 (8.1%) were treated with open arthrotomy and arthroscopy, respectively.[393] Patients had similar short-term complication rates and re-operations regardless of treatment with open arthrotomy or arthroscopy, which suggests that arthroscopic management may be a safe option for the treatment of SA of the hip with potentially limited morbidity.

- For SA of the **shoulder**: several studies have not shown the superiority of arthroscopic treatment to open arthrotomy. In a systematic review, a high reoperation rate was observed, which could correlate with poor patient prognosis. In the early stages of the disease, arthroscopic irrigation and debridement appear to be safe and efficient.[394–400]

b) In children

Purulent joint effusion often increases intraarticular pressure, which can lead to epiphyseal avascular necrosis, and purulent products can directly damage the cartilage. Surgical drainage (however it is performed) reduces the bacterial load, as well as the risk of bone necrosis and permanent cartilage damage.[401] Drainage should be considered especially in neonates and infants <18 months of age with SA of the hip or shoulder joint.[28]

Joint drainage by arthrocentesis plays a key role in the management of SA in children. In addition to the therapeutic effect, biological samples can be obtained to identify the causative pathogen and guide selection of the correct antimicrobial therapy. [28,366,401]

Needle joint aspiration and irrigation/lavage has been reported to be safe and effective in SA of the shoulder, [402] knee, [403] and hip. [199,404] This procedure may lead to fewer sequelae than arthrotomy.[32]

Despite the fact that most authors use needle joint aspiration only as a diagnostic test for SA of the knee, it seems to be a useful procedure in septic knee arthritis for patients younger than 1 year old.[403] However, in patients between 1 and 3 years with CRP > 20 mg/L or those older than 3 years, the failure rates are 16% and 38%, respectively, and in these cases, arthroscopy or arthrotomy should be considered.[403]

The success rate of needle aspiration and lavage in SA of the hip has been reported as 85%.[199] For a successful outcome, these basic principles should be followed: aspiration should remove the amount of pus consistent with what would be expected based on ultrasound results, and lavage should be continued until a clear fluid is obtained. Any difficulties in draining the SF would suggest the presence of pseudomembranes, which are difficult to remove by needle aspiration. In this case, or if recovery is slow, another lavage method —either arthroscopy or arthrotomy— should be performed, depending on the surgical team. Repeated ultrasound controls are mandatory in order to decide whether to perform repeated needle aspiration or one of the more aggressive alternatives.[405] Compared to other joints, there is a higher percentage of open arthrotomy in SA of the hip.[32]

The limited use of arthroscopic lavage is probably attributable to the historical lack of training in arthroscopic techniques given to paediatric orthopaedic surgeons. The technique has been found to be safe and effective for the treatment of SA of the hip,[406,407] knee,[366,407–409] shoulder, elbow, wrist and ankle, [407] with low failure rates or need for conversion to arthrotomy. Compared to hip arthrotomy with drainage, arthroscopic lavage has been associated with shorter duration of hospital stay, faster reduction of post-surgical pain, quicker recovery of both passive and active movements of the affected joint, and earlier return to activity.[406] This is due to the minimally invasive nature of arthroscopic drainage of the septic joint with minimal soft tissue disruption. However, surgical drainage by arthrotomy should be considered in SA of the hip or shoulder in young children due to the high incidence of associated osteomyelitis.[32,202]

Some orthopaedic surgeons prefer to perform an open arthrotomy because they are accustomed to the procedure. With this approach, removal of the pus is theoretically more complete. As mentioned above, surgical drainage by arthrotomy should be considered for SA of the hip or shoulder in young children. [32,202] Arthrotomy is also indicated when the response to repeated needle aspiration or arthroscopic lavage is unsatisfactory.[404] Arthrotomy can also be considered the first choice in acute osteoarticular infections caused by MRSA or PVL+, because these bacteria are associated with a more aggressive clinical course and a higher rate of development of complications and sequelae. [28,401] There is little evidence to leave a drain in place on a routine basis. If considered due to the extent of infection or difficulty of debridement, drains should be inserted for as short a time as possible.

In cases of SA of the knee, it would appear that unsuccessful treatment correlates with time between the onset of infection and time of surgery, and not with type of procedure.[366]

RECOMMENDATIONS

1. Joint drainage to treat SA can be performed by closed-needle aspiration (repeated as necessary), arthroscopy or arthrotomy (open surgery) (**A-III**). We recommend tailoring the optimal drainage procedure to age, affected joint, extent of involvement, time course and other clinical data (**A-III**).
2. In adults, arthroscopic joint drainage with synovectomy is the suggested first-line procedure for SA of the knee (**B-II**). Needle aspiration is another treatment option (**B-II**). For the ankle, elbow or wrist, initial joint drainage may be by needle aspiration or arthroscopy (**B-III**). For the hip and shoulder, arthroscopy or arthrotomy is the suggested initial procedure (**B-II**). Open surgery is suggested for cases of unfavourable evolution after repeated aspiration or arthroscopic drainage (**B-III**).
3. In children, the suggested initial treatment procedure for uncomplicated SA of joints other than the hip is needle aspiration (**B-I**). For SA of the hip, knee, ankle, shoulder, elbow or wrist, arthroscopy is preferable to open surgery (**B-II**). We suggest joint drainage by arthrotomy as the first option for hip and shoulder SA in young children, and after more conservative procedures (needle aspiration or arthroscopy) have failed (**C-III**).

*Additional measures*

**XVII. What additional measures may be useful to improve functional outcome in a patient with septic arthritis?**

While there are a large number of published studies on the best joint drainage technique to treat SA, there are few on which additional measures should be implemented after surgery to improve clinical outcomes.

No randomised clinical trials have compared the efficacy of different postoperative treatments. To our knowledge, an experimental trial in rabbits,[410] clinical guidelines by the European Society of Paediatric Infectious Diseases,[28] three prospective studies,[23,406,411] six retrospective studies,[366,373,397,412–414] and one systematic review[392] have been published on this topic.

Except for the experimental trial and the clinical guidelines, all the other studies evaluated the outcome of a complete protocol for surgery and subsequent rehabilitation. Most of these protocols opt for early mobilisation to favour the functional outcome of the joint.[6,28,366,373,392,410,411,414] Type of mobilisation is specified in only two studies.[373,411] In a prospective review evaluating 28 patients with SA of the hand, Boustred *et al.* advocate starting active mobilisation early.[411] In that study, better results were obtained in patients when debridement was performed early and when rehabilitation involved early active mobilisation. On the other hand, Böhler et al. evaluated 70 patients with monoarthritis and supported early but passive movements.[373] Better results were obtained in patients debrided by arthroscopy and those following a rehabilitation protocol of passive joint mobility. These results are consistent with those described in 1981 by Salter *et al*.[410] in the only experimental trial conducted in SA. That study compared three types of postoperative measures in 51 rabbits with SA: 1) immobilisation, 2) intermittent active motion, and 3) continuous passive motion. They concluded that the best results in rabbits were obtained with continuous passive motion, as it prevented adhesions, increased purulent drainage, improved chondrocyte nutrition, stimulating them for synthesis of matrix components. While early reviews recommended joint immobilisation in the acute phase of infection, animal models of SA observed greater cartilage degeneration and more adhesions in immobilised animals versus animals treated with continuous passive motion devices. Consequently, early rehabilitation is currently considered essential to prevent joint contractures and muscle atrophy.[14] Patients should be mobilised as soon as pain permits. A consensus strategy for early rehabilitation management of SA in the native knee joint was published very recently, although prospective validation of this strategy is needed.[415] It specifies that mobilisation should be performed according to the patient's tolerance and pain, and that weight-bearing can be considered as soon as pain and muscle control permit, but should be progressive and carried out with technical aids.

Another topic of debate in the protocols mentioned above is how much weight bearing should be allowed on the lower limbs after surgical debridement of the affected joint. In adults, all the reviewed literature suggests avoiding full weight bearing on the operated limb. The paediatric guidelines also do not recommend loadbearing until after a reasonable period of time has elapsed, which is not specified but is related to pain control.[81] For SA of the hips, most studies discourage early weight bearing, including partial weight bearing,[392,406] while weight bearing as tolerated is recommended for SA of the knee, and should be progressive and carried out with a technical aid.[373] The El-Sayed study in children between 3 and 12 years of age with SA of the hip recommended avoiding weight bearing on the affected limb for 2 weeks after the procedure.[406] The European guidelines for children published by Saavedra *et al* also recommended avoiding any weight bearing in this situation.[28] In a retrospective study comparing open and arthroscopic treatments for acute native knee SA, following the procedure, all patients were routinely visited by the physiotherapist; they were allowed to bear weight as tolerated with a walking aid (e.g., crutches) and started range-of-motion exercises approximately 48 hours postoperatively.[414] In the recently published consensus strategy for early rehabilitation of SA of the knee, weight-bearing can be resumed as soon as pain and muscle control permit.[415]

RECOMMENDATIONS

Suggestions include**:**

1. Initiating physiotherapy after surgical joint drainage (**B-III**).
2. Early mobilisation of the affected joint, initially with passive movement (**B-III**). In children with hip arthritis, immobilisation in an abduction spica cast is reserved for cases of severe infection at risk of joint dislocation (**B-II**).
3. Early weight bearing -including partial weight bearing- is discouraged when the hip joint is affected (**D-III**).
4. Early partial weight bearing is suggested for patients with knee SA, once the pain is controlled (**B-III**).

## RECOMMENDATIONS FOR CLINICAL FOLLOW-UP

### XVIII. How should patients be followed up and for how long?

Once patients are progressing satisfactorily, with improvement of inflammatory signs and progressive decrease of acute phase responses, they can be discharged from hospital and continue treatment on an outpatient basis, as described in the previous sections.[12] Most studies detail the patient's progress and the development of sequelae, and specify a follow-up period (most are between 6 and 24 months), although almost none describe how this was done. The British Guidelines published in 2006 by Coakley *et al* [31] are silent on this point. More recently, Memon *et al* and Meier *et al* [394,416] concluded with the need to standardise follow-up, although they acknowledge the lack of relevant evidence due to the heterogeneity of patients and the need to individualise each case according to evolution. It should be noted that the need for follow up was recognised by paediatric societies, and both the Spanish and European guidelines recommend a periodic clinical and analytical follow-up. [26,28] Whenever possible, this follow-up should be performed by an orthopaedic surgeon and an infectious disease specialist around 2 weeks after discharge and for at least 12 months.[26,28]

There is very little high-quality evidence on how to follow up patients with SA. However, it would seem advisable to perform at least a complete blood count and CRP every 7-14 days while antibiotic treatment is administered to monitor infection and check for potential adverse effects (especially neutropenia). Symptoms, signs, and acute phase responses are useful to guide the decision to discontinue antibiotics.[12,394,417] After completion of antimicrobial treatment, follow-up by orthopaedic and infectious disease specialists is recommended at approximately 1-2 weeks, 4–6 weeks and 3 months. A follow-up period of at least 1 year is suggested in adults at risk of long-term adverse outcomes and sequelae (such as those with impaired joint function and/or concomitant osteomyelitis) and in children, preferably conducted by an experienced orthopaedic surgeon. Follow-up may be longer in patients at high risk of sequelae: those with more severe deterioration of joint function or suspected osteomyelitis and when infection is caused by MRSA.[23,418,419]

In children, the main objective of follow up is to try and prevent the development of sequelae. Bone deformities such as avascular necrosis of the femoral head, physeal involvement or joint cartilage destruction in SA can lead to dysmetria, limping, chronic pain, joint instability or rigidity.[103,420,421] Children with SA should be followed until functional or radiological sequelae can be ruled out, especially bone destruction or physeal involvement, as they may lead to functional sequelae later on. Long-term orthopaedic follow-up once antibiotic treatment is finished and the infection has been cured is crucial to deal with any ongoing bone or joint sequelae in growing children.[103,421]

In the short term, follow-up should be performed to confirm that the infection is resolved. Prospective studies in children with SA have shown that antibiotics can be safely discontinued once the patient is asymptomatic or has only minor symptoms and CRP is normal after a minimum duration of treatment (2 weeks for non-complicated SA).[26,28] In general, there is no need to repeat inflammatory markers once they are normalised and the child is on oral therapy, unless new clinical findings appear. However, children with complex diseases, underlying problems or immunodeficiency need careful consideration.

After hospitalisation, follow-up by orthopaedists and paediatricians with experience of musculoskeletal disorders is recommended at about 1-2 weeks, 4-6 weeks, 3 months, and 12 months after discharge. The first follow-up is important to ensure adherence and antibiotic tolerance. Long-term beta-lactam therapy can result in leukopenia, usually mild to moderate, and a control CBC may be necessary in children with longer duration of therapy (e.g., every 7-14 days). Experienced orthopaedic surgeons should follow children for a variable length of time depending on the severity of the infection, age, and the area affected [103,421]. Longer follow up should be considered in children at higher risk for sequelae, such as young infants and newborns, infections caused by MRSA, PVL-positive strains or *Salmonella*, those with longer duration of symptoms before initiation of therapy, hip involvement, osteomyelitis-associated SA or if the physis is affected. A large retrospective Spanish study showed that hip involvement and osteomyelitis-associated SA were the most important parameters related to sequelae in children with SA.[32]

Normal activity without pain is an important endpoint before discharge from follow up. Most studies follow children for 6-12 months; only rarely do sequelae develop that were not noticed in the first 6 months after completion of antibiotic therapy. Radiography or MRI may be needed to assess complications or sequelae depending on the severity of the disease or clinical outcome during follow-up of these children. Some authors suggest radiological follow-up at least 6 weeks after resolution of symptoms to evaluate ongoing bone involvement.[103,421]

RECOMMENDATIONS

1. Outpatient follow-up with oral antimicrobial therapy (or outpatient parenteral antimicrobial therapy, if oral treatment is not possible) is suggested once a favourable clinical and analytical evolution is established (**B-III**).
2. Clinical (joint pain, inflammation and function) and analytical (blood count, CRP and erythrocyte sedimentation rate) monitoring is suggested (**B-III**). While patients are receiving antibiotics, we suggest monitoring for possible associated adverse effects (**B-III**).
3. We suggest outpatient follow-up by orthopaedic and infectious disease specialists at 1-2 weeks, 4–6 weeks and 3 months after discharge (**C-III**). We suggest a follow-up period of at least 1 year in adults at risk of long-term adverse outcomes and sequelae (such as those with impaired joint function and/or concomitant osteomyelitis) and in children (preferably by an experienced orthopaedic surgeon) (**B-III**). In infants with hip/physeal involvement, a longer follow-up may be necessary (**B-III**).

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**Table 1. Criteria used to evaluate the strength of the recommendation and the quality of the evidence**

| Category/grading strength of recommendations | Definition |
|---|---|
| ***A*** | Strongly supports a recommendation for use |
| ***B*** | Moderately supports a recommendation for use |
| ***C*** | Marginally supports a recommendation for use |
| ***D*** | Supports a recommendation against use |
| ***Quality of evidence*** | |
| **I** | Evidence from at least one well-designed randomised, controlled trial |
| **II** | Evidence from at least one well-designed clinical trial, without randomisation; from cohort or case-controlled analytical studies (preferably from 1 centre); from multiple time series; or from dramatic results of uncontrolled experiments |
| **III** | Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies |

**Table 2. Differential diagnosis of septic arthritis of a native joint: alternative diagnoses to septic arthritis**

*In adults and children*

- Trauma (traumatic injuries, penetrating wounds, hemarthrosis)
- Viral arthritis
- Bursitis

*In adults*

- Crystal arthritis (gout, chondrocalcinosis, and others)
- Spondyloarthropathies
- Rheumatoid arthritis
- Other systemic inflammatory diseases (systemic lupus, sarcoidosis, Behçet disease)
- Osteoarthritis

*In children*

- Transient synovitis of the hip
- Juvenile idiopathic arthritis
- Other bacterial infections: pyomyositis, osteomyelitis, cellulitis
- Post-infectious arthritis: post-streptococcal and reactive arthritis
- Malignancy
- Henoch-Schönlein purpura
- Perthes disease
- Slipped capital femoral epiphysis
- Sickle cell anaemia, infarction

**Table 3. Main microorganisms (in percentages) identified in contemporary series of septic arthritis in adults**

| | *S. aureus* (methicillin-susceptible) | *S. aureus* (methicillin-resistant) | CoNS | Streptococci | Enterobacterales | *Pseudomonas* and non-fermenting gram-negative bacilli | Others |
|---|---|---|---|---|---|---|---|
| Clerc (2011)[17*] | 45 | 5 | 3 | 14 | 9 | 5 | 3 |
| Khan (2013)[20] | 35 | 0 | 12 | 12 | 18 | 5 | 18 |
| Dubost (2014)[316†] | 45 | 8 | 10 | 16 | 10 | 3 | 9 |
| Muñoz-Egea (2014)[422] | 53 | 5 | 0 | 18 | 10 | 0 | 14 |
| Madruga (2014)[224] | 36 | 18 | 0 | 25 | 4 | 7 | 9 |
| Nolla (2015)[6] | 49 | 6 | 1 | 29 | 7 | 4 | 4 |
| Ben-Chetrit (2020) | 35 | 8 | 9 | 24 | 16 | | 9 |
| Ross (2020) | 42 | 18 | 1 | 17 | 6 | | 16 |

CoNS: coagulase-negative staphylococci

[*] The percentage does not add up to 100% because polymicrobial infections and those of unknown aetiology are not included

[†] Including 111 cases from 1999-2008

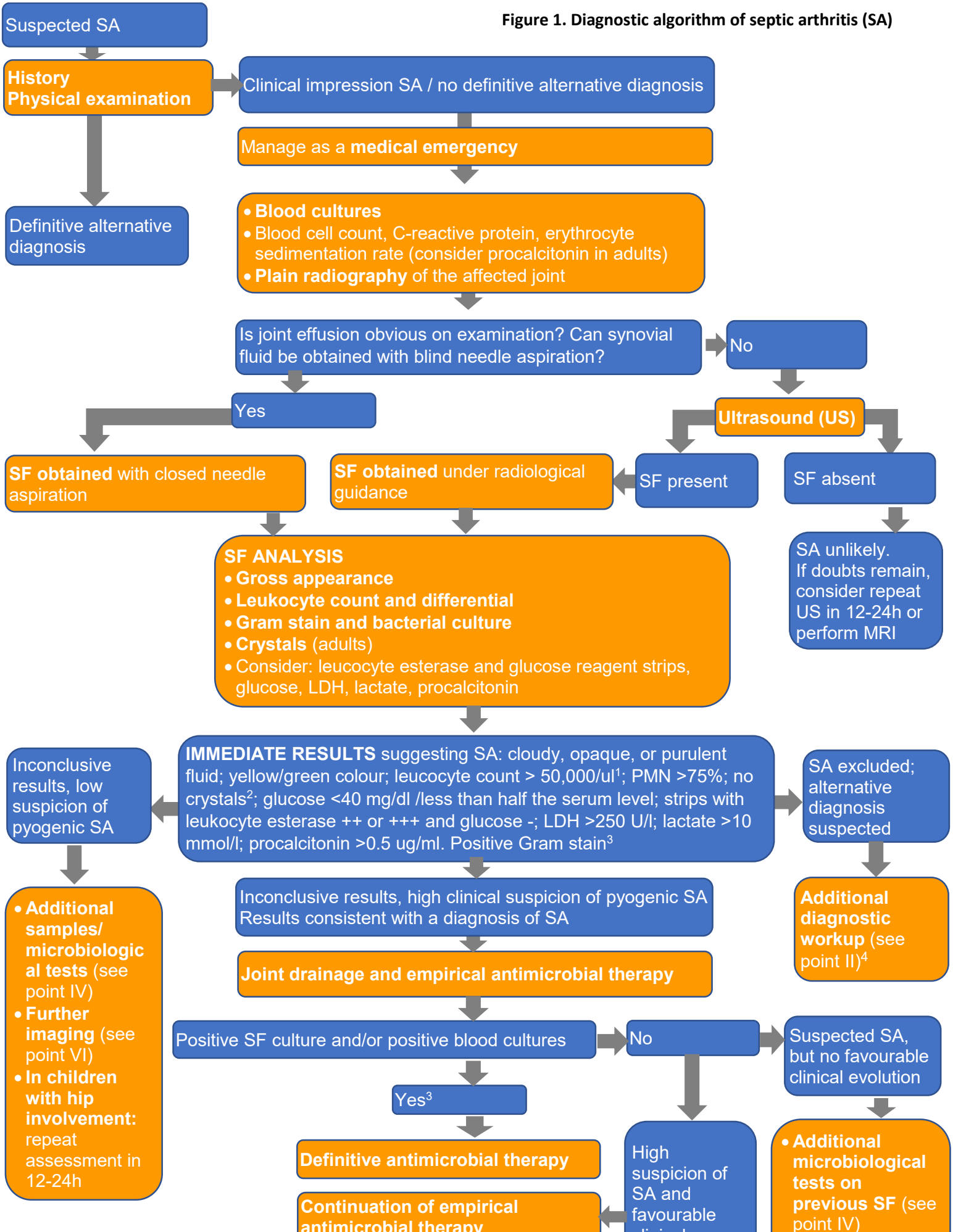
**Table 4. Expected pathogens and empirical antibiotic treatment recommended for septic arthritis in specific epidemiological contexts**

| | **Main aetiological agents** | **Empirical treatment** | **Comments** |
|---|---|---|---|
| Nosocomial acquisition | *S. aureus* (susceptible or resistant to methicillin), gram-negative bacilli | Daptomycin or vancomycin + cefepime or meropenem (aztreonam o ciprofloxacin in beta-lactam allergy) | Multiple aetiologies and resistance mechanisms |
| History of joint surgery or puncture | CoNS, *Staphylococcus aureus* (susceptible or resistant to methicillin), streptococci, Enterobacterales, *Pseudomonas aeruginosa* | Daptomycin or vancomycin + cefepime or meropenem (aztreonam o ciprofloxacin in beta-lactam allergy) | CoNS are the most common cause of SA after cruciate ligament surgery or meniscectomy.<br>Outbreaks of SA caused by streptococci and other oral microbiota organisms have been described after intraarticular steroid injections without appropriate aseptic measures |
| Plant thorn injury | Enterobacterales (*Pantoea agglomerans*)<br><br>*Nocardia* spp. | Ceftriaxone or ertapenem (ciprofloxacin in beta-lactam allergy).<br>No (definitive treatment if isolated) | |
| Shoe puncture wound | *P. aeruginosa, S. aureus* | Cloxacillin + antipseudomonal beta-lactam (ceftazidime) or piperacillin-tazobactam or meropenem | Concomitant osteomyelitis should be ruled out and careful debridement performed |
| Human bite | *Eikenella corrodens*, anaerobes, streptococci | Amoxicillin-clavulanic acid (clindamycin + ciprofloxacin in beta-lactam allergy) | |
| Animal bite | *Pasteurella multocida*, *Capnocytophaga spp.,* anaerobes | Amoxicillin-clavulanic acid (clindamycin + ciprofloxacin in beta-lactam allergy) | |
| Farm or animal exposure | *Bartonella, Brucella, Coxiella* | Directed treatment after aetiological diagnosis is recommended (consider doxycycline or quinolones) | |
| Suspected STI | *Neisseria gonorrhoeae* | Ceftriaxone or cefotaxime | Screening for other STI. Consider treatment for *Chlamydia* |
| **Specific paediatric conditions** | | | |
| Chronic granulomatous disease | *S. aureus, Serratia, Aspergillus* | Meropenem or piperacillin-tazobactam | |
| Sickle cell disease | *S. aureus, Salmonella, S. pneumoniae* | Third-generation cephalosporin + cloxacillin | |

| | **Main aetiological agents** | **Empirical treatment** | **Comments** |
|---|---|---|---|
| Gamma interferon pathway immunodeficiency | Mycobacteria | No empirical treatment recommended (definitive treatment if isolated) | |
| Chickenpox, skin wounds | *Group A streptococcus* | Cefazolin | |

1. The choice would depend on the local epidemiology. CoNS=coagulase negative staphylococci; STI=sexually transmitted infection

**Figure 1. Diagnostic algorithm of septic arthritis (SA)**




MRI= Magnetic resonance imaging, SA=septic arthritis, SF=synovial fluid, S=Ultrasound
1. Leucocyte count usually > 20,000; > 100,000 highly suggestive of SA
2. SA and crystalline arthritis may occur simultaneously
3. Diagnosis of SA
4. Assessment by a rheumatologist and/or orthopaedic surgeon is suggested