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► To cite this version:

Marion Couderc, Géraldine Bart, Guillaume Coiffier, Sophie Godot, Raphaele Seror, et al.. 2020 French recommendations on the management of septic arthritis in an adult native joint. *Joint Bone Spine*, 2020, 87 (6), pp.538-547. 10.1016/j.jbspin.2020.07.012 . hal-03426419

HAL Id: hal-03426419

<https://hal.science/hal-03426419v1>

Submitted on 15 Dec 2022

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2020 French recommendations on the management of septic arthritis in an adult native joint

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Abstract

Septic arthritis (SA) in an adult native joint is a rare condition but a diagnostic emergency due to the morbidity and mortality and the functional risk related to structural damage. Current management varies and the recommendations available are dated. The French Rheumatology Society (SFR) Bone and Joint Infection Working Group, together with the French Language Infectious Diseases Society (SPILF) and the French Orthopaedic and Trauma Surgery Society (SOFCOT) have worked according to the HAS methodology to devise clinical practice recommendations to diagnose and treat SA in an adult native joint. One new focus is on the importance of microbiological documentation (blood cultures and joint aspiration) before starting antibiotic treatment, looking for differential diagnoses (microcrystal detection), the relevance of a joint ultrasound to guide aspiration, and the indication to perform a reference X-ray. A cardiac ultrasound is indicated only in cases of SA involving *Staphylococcus aureus*, oral streptococci, *Streptococcus gallolyticus* or *Enterococcus faecalis*, or when infective endocarditis is clinically suspected.

Regarding treatment, we stress the importance of medical and surgical collaboration. Antibiotic therapies (drugs and durations) are presented in the form of didactic tables according to the main bacteria in question (staphylococci, streptococci and gram-negative rods). Probabilistic antibiotic therapy should only be used for patients with serious symptoms.

Lastly, non-drug treatments such as joint drainage and early physical therapy are the subject of specific recommendations.

Keywords: Recommendation, Septic arthritis, Bone and joint infection

1. Introduction

Septic arthritis (SA) is defined as the presence of a culturable microorganism in the synovium and the joint cavity responsible for an inflammatory reaction in the joint. Although rare, this is the primary diagnostic concern for the clinician when faced with a patient with acute arthritis due to the morbidity and mortality and the functional risks involved. The latest French recommendations available are from 1991 (1) and needed to be updated.

The recommendations proposed relate to the diagnosis and treatment of peripheral SA in adults in a native joint involving a pyogenic bacterial infection. These recommendations do not cover mycobacterial infectious arthritis, Lyme arthritis, viral, parasitic and fungal arthritis, diabetic foot infection, Whipple's disease or reactive arthritis.

2. Methodology used to compile the recommendations

The methodology was inspired by the HAS recommendations (2). The working group was made up of 14 rheumatologists, 2 infectious disease specialists, 1 orthopaedic surgeon, 1 physiatrist, 1 general practitioner and 1 microbiologist.

The group devised several pragmatic questions for the diagnosis and treatment of SA. A critical analysis of the literature was carried out to provide answers to these questions. Three general principles and 16 specific recommendations were formulated and then graded according to the level of scientific evidence [Appendix A, Table S1; See the supplementary material associated with this article online].

The recommendations were first reviewed by the review group made up of 30 rheumatologists (21 working in hospitals and 9 in private practice) proposed by the French Rheumatology Society (SFR), 7 infectious disease specialists proposed by the French Language Infectious Diseases Society (SPILF) and 5 orthopaedic surgeons proposed by the French Orthopaedic and Trauma Surgery Society (SOFECOT). After an initial review, 8 recommendations proposed did not obtain the consensus defined as an average of ≥ 8.0 and/or $\geq 80\%$ of reviewers with a score ≥ 8 . These recommendations were therefore adapted to the review group's proposals while still conforming with the data in the literature and then resubmitted to the review group for validation. The antibiotic therapies proposed by the working group were validated by the SPILF recommendations group.

3. General principles and recommendations

Table 1 summarizes all of the recommendations with their level of evidence and their level of consensus.

3.1. General principles

Principle A- *Septic arthritis is a diagnostic emergency due to the morbidity and mortality and the functional risk related to structural damage.*

SA is a serious disease with a mortality rate of around 7% at 3 months, which increases with age (3). It is often associated with osteochondral complications responsible for a secondary functional disability (4–6). In animal models, this irreversible anatomical damage appears after 7 to 15 days (7,8) and a human study demonstrated better outcomes when antibiotic therapy was initiated within 10 days (9).

Principle B- *Efforts should be made to provide microbiological documentation (blood cultures and joint aspiration) of the septic arthritis before starting antibiotic treatment.*

Treatment of SA is based on antibiotic therapy adapted to the bacterial microorganism in question and then bacterial sensitivity tests (Recommendation 9). The bacterial microorganism is identified by synovial fluid (SF) analyses and/or blood cultures, which must be performed systematically (Recommendations 3 and 5).

The bacteria involved in SA are, in order of frequency, staphylococci, streptococci and gram-negative rods (4,5,8–13). In France, SA involving gonococci and methicillin-resistant *Staphylococcus aureus* (MRSA) is rare (12).

Almost 20% of cases of arthritis that clinicians consider septic and treat with antibiotics have no microbiological documentation, especially in cases of prior antibiotic therapy (14). SA is therefore diagnosed even in the absence of documentation.

Principle C- *Septic arthritis must be managed from the start by a medical and surgical team that has experience with this condition.*

Except in special cases (SA in a small, non-weight-bearing joint with sensitive bacteria, without any comorbidity), hospitalization is usually necessary to optimize the initial diagnostic and therapeutic management of SA and to help manage the patient's comorbidities.

A large number of risk factors for a poor outcome (antibiotic failure, joint sequelae or mortality) have been reported (*Appendix A, Table S2*).

SA can be considered as a complex bone and joint infection in certain cases, depending on: the patient's disposition (allergy, pregnancy, kidney or liver failure), the microorganism identified (polymicrobial, suspected contaminant), local septic complications (fistulization, abscess, osteitis, joint destruction) or general complications (endocarditis) or treatment (antibiotic resistance, drug intolerance, recurrence).

The management of complex SA requires discussion between rheumatologists, orthopaedists, microbiologists and infectious disease specialists.

3.2. *Specific recommendations*

Recommendation 1- *Septic arthritis should be considered in all cases of acute monoarthritis whether the patient is febrile or not. Oligo- or polyarthritis does not rule out the diagnosis.*

SA must be systematically considered in cases of acute monoarthritis (characterized by painful swelling with joint stiffness) that has generally been active for less than 2 weeks. However, symptoms can vary hugely (5,10) (*Appendix A, Table S3*). Several differential diagnoses are possible in cases of acute arthritis (Table 2). The absence of a fever does not rule out the diagnosis of SA as it is only observed in around half of the cases (5,10,15,16). Polyarticular involvement can be encountered (10–17%). It is often accompanied by sepsis or septic shock, and is a factor for poor prognosis (10,17).

Recommendation 2- *Suspected septic arthritis justifies looking for signs of immediate severity (quick SOFA ≥ 2).*

One third of patients with SA have initial sepsis (15,16,18). Sepsis is defined as an inappropriate host response to an infection that causes organ dysfunction (18).

In the presence of at least 2 of the following signs: respiratory rate $>22/\text{min}$, impaired alertness and/or SBP $<100 \text{ mmHg}$ (quick SOFA ≥ 2), the SOFA (Sepsis-related Organ Failure Assessment) immediate severity score must be assessed (19) (Table 3). If the SOFA score is ≥ 2 , probabilistic antibiotic therapy and close monitoring are necessary and possibly transfer to a specialized unit (intensive care or critical care) (Figure 1).

Recommendation 3- *It is essential to perform joint aspiration before administering antibiotics for a cytobacteriological analysis of the synovial fluid. The additional inoculation of the synovial fluid in blood culture bottles is recommended, in particular in cases of prior antibiotic therapy or long waiting times.*

Prior antibiotic therapy decreases the detection sensitivity for a microorganism in the SF (20). Purulent SF is suggestive of SA, but not specific, as it may be encountered during metabolic or reactive arthritis (10). SF must be injected into an EDTA or heparinized tube (to avoid SF coagulation a dry tube should not be used), shipped quickly (in under 2 hours) to the laboratory for cytological analysis and in a dry tube for the microbiological analysis (Gram staining direct examination (DE), culture) and microcrystal detection (21). Inoculating the SF in a blood culture bottle in the laboratory or at the patient's bed is thought to increase microbiological identification capabilities by 20%, especially in the case of prior antibiotic therapy (22).

After Gram staining, the DE is only positive in about 1/3 of SA cases (5,10,13,21). A negative DE therefore does not rule out SA.

In case of prior antibiotic therapy, there is no recommended antibiotic window before performing a joint aspiration. If the first aspiration is negative, it can be repeated (after 48 hours of culture for example).

Synovial needle biopsies are not thought to improve bacteriological identification compared to SF (23). They should be considered in second place, in particular when the SF cannot be aspirated (synovitis) (23).

Recommendation 4 *Based on the analysis of synovial fluid, microcrystal detection must be carried out in addition to the cytobacteriological analysis but their presence does not rule out the diagnosis of septic arthritis.*

The main differential diagnosis of SA is metabolic arthritis (gout, chondrocalcinosis), the diagnosis of which is based on the detection of crystals in the SF. However, metabolic and septic arthritis can coexist (24). The presence of crystals in the SF should therefore not rule out the diagnosis of SA at the outset and in such cases the SF should always be sent to the laboratory for microbiological analysis.

The white cell count and differential of the SF can guide the diagnosis of acute arthritis but no threshold is discriminating (*Appendix A, Table S4*). The higher the SF white cell count, the more likely it is to be septic (5). This is all the more true in the absence of crystals in the synovial fluid (25).

No biochemical SF marker (lactate, glucose, etc.) is currently sufficiently effective for diagnosing SA to be recommended systematically (*Appendix A, Table S5*).

Broad-range 16S rDNA PCR on SF has been disappointing when it comes to diagnosing SA. The only study conducted on native joints reported that 16S rDNA PCR was less effective than direct examination, blood cultures or SF culture, with a very low sensitivity (26) (*Appendix A, Table S6*). Therefore a negative 16S rDNA PCR on SF does not rule out SA.

Recommendation 5 *At least 2 sets of blood cultures should be performed before proposing antibiotic therapy, even in the absence of fever.*

Blood cultures are positive in 9 to 36% of SA cases and are sometimes the only test to identify the bacteria (14,21). At least 2 pairs of aerobic and anaerobic bottles are necessary, and if possible the blood should be drawn before antibiotic therapy (27,28). There is no rationale for preferring blood cultures in the event of a spike in fever (27). Blood culture bottles should be full enough (≥ 8 mL/bottle) to reduce the risk of false negatives.

As for the other biological blood parameters, none are sufficiently effective to be recommended for diagnostic purposes. An elevated white cell count and an inflammatory syndrome are common but not specific (4,5,10,29). A procalcitonin level <0.5 ng/mL does not rule out SA therefore this test is not recommended (28,29,30).

Recommendation 6 *An X-ray is useful for diagnosing a pre-existing arthropathy and for structural monitoring, but should not delay joint aspiration. No further imaging is required to make a positive diagnosis of septic arthritis.*

X-ray is not particularly effective for diagnosing SA as signs are not usually visible on an X-ray for at least ten days (10). However, this imaging enables an anatomical analysis of the joint which may offer a differential diagnosis and serve as a reference for monitoring (31).

MRI can reveal soft tissue abscesses, oedema and bone erosions during SA (32,33). However, limited access to this examination makes its use inappropriate for the diagnosis of SA in an emergency. MRI is the preferred imaging method for certain specific sites such as septic arthritis of the sacroiliac joints and pubic symphysis. Data on an ¹⁸FDG PET/CT for SA in a native joint is very limited and its accessibility makes it as unsuitable for SA as an MRI (34).

Recommendation 7 *There is no indication for the systematic use of a joint ultrasound. Joint ultrasound is nevertheless useful to confirm the presence of intra-articular effusion in case of clinical uncertainty and can be used to guide aspiration.*

In cases of SA, ultrasound can reveal joint effusion and/or synovitis, which can be useful for a deep joint (35). With an ultrasound it is not possible to distinguish between SA and other types of arthritis, although it can provide indirect information suggesting metabolic arthritis (tophus, double contour sign, 'snowstorm' appearance) (36).

It can be used to distinguish between arthritis and a periarticular disorder (bursitis or tenosynovitis), which can be hard to tell apart upon clinical examination (*Appendix A, Table S7*). Lastly, ultrasound can help guide joint aspiration in a difficult-to-access joint.

Recommendation 8 *A cardiac ultrasound should be used to screen for infective endocarditis in cases of septic arthritis caused by *Staphylococcus aureus*, non-groupable oral streptococci, *Streptococcus galloyticus* or *Enterococcus faecalis*.*

Infective endocarditis (IE) should be considered in the event of a heart valve insufficiency murmur with positive blood cultures. However, even when a blood culture is negative, certain bacterial species such as *Streptococcus sp.* call for screening for IE (37). The frequency of peripheral SA associated with IE (around 5%) is lower than that of spondylodiscitis. The most frequent clinical presentation is acute monoarthritis predominant in the large joints of the lower limbs (38). They are often the source of *Staphylococcus aureus* IE complications (16). Although rare, acute *Staphylococcus aureus* oligoarthritis associated with IE is particularly serious (17,27).

Recommendation 9 *Except where there are signs of immediate severity (sepsis with SOFA ≥ 2), antibiotic therapy should not be prescribed before joint aspiration is performed to analyze the synovial fluid. Antibiotic therapy will be initiated upon receipt of positive microbiological results (direct examination, synovial fluid culture or blood culture). Probabilistic antibiotic therapy can also be considered in the case of clearly purulent synovial fluid without crystals.*

The clinical situations calling for antibiotic therapy are presented in the algorithm (Figure 1). Given the small number of clinical trials published, the main scientific evidence comes from retrospective series (16,39,40) or prosthetic joint infections (41,42).

Initially, a bactericidal antibiotic (β -lactam) is needed, especially when there is concomitant bacteraemia, but dual therapy is not indicated from the outset (except for *Pseudomonas aeruginosa*). In the absence of septic shock, there is no indication to add an aminoglycoside (except for infections with *Enterococcus sp.* or *Pseudomonas aeruginosa*) (43,44).

First-line antibiotics according to the main microorganisms encountered are recapped in Table 4 (*Appendix A, boxes text S1, S2 and S3*).

If the patient is allergic to penicillin, a cephalosporin can be considered as there is little risk of a cross-allergy between penicillins and cephalosporins (45).

If it is necessary to start probabilistic antibiotic therapy before the microbiology results are available (signs of immediate severity with SOFA ≥ 2), it is advisable to prescribe an injectable 1st generation cephalosporin (1GC) (cefazolin) for patients under the age of 70 (to cover at least *Staphylococcus aureus* and *Streptococcus sp.*), and prioritize an injectable third generation cephalosporin (3GC) (ceftriaxone or cefotaxime) for patients over 70 because of the higher likelihood of GNR arthritis (46) (Figure 1).

In cases of SA without bacteriological documentation despite repeating microbiological testing, switching to oral therapy is not possible and the IV β -lactam initially prescribed must be continued for the entire duration of treatment.

Table 5 summarizes the practical methods for using the proposed antibiotics to treat SA and their potential side effects.

Recommendation 10 *The total duration of antibiotic therapy (IV then oral) should be 4 to 6 weeks for pyogenic bacterial septic arthritis. A total duration of 7 days is sufficient in cases of *Neisseria gonorrhoeae* arthritis.*

The duration of antibiotic therapy currently accepted to treat SA in a native joint is between 4 and 6 weeks. This duration depends on the speed of diagnosis and antibiotic treatment initiation, the clinical response to antibiotic therapy, and the bacterial species isolated (5,47,48). A treatment duration of 4 weeks has been suggested in cases of streptococcal SA, and 6 weeks for *Staphylococcus* (26). There are currently no well-conducted randomized studies to answer this question, but a French clinical trial is in progress (SHASAR study). One randomized study has shown the non-inferiority of a duration of 6 vs 12 weeks of antibiotic therapy in infectious pyogenic spondylodiscitis (49).

Shorter antibiotic therapy could be considered in cases of SA in small joints (fingers, wrist) together with articular lavage/synovectomy surgery. One open-label randomized study has demonstrated the non-inferiority of 2 versus 4 weeks of antibiotic treatment in this particular context (50). However, this study did not treat haematogenous SA, but mainly SA in small joints (fingers or toes), involving sensitive bacteria (*S. aureus* in only 1/3 of cases), after direct inoculation (bite or wound), with bacteraemia in only 4%. Therefore these results cannot be transposed in practice to the management of haematogenous SA in native joints. One study has reported a significantly higher rate of infection relapse with 14 days of antibiotic therapy compared to 3 to 6 weeks of treatment for large native joint SA (4).

Seven days of antibiotic therapy is sufficient for infections with *Neisseria gonorrhoeae* and by extrapolation, other *Neisseria sp.* like *Neisseria meningitidis*, which can be responsible for SA (51).

In cases of concomitant bacteraemia without IE, antibiotic treatment should be administered for SA for at least 5 days intravenously, and at least 7 days for *S. aureus* SA (16). In the absence of signs of sepsis (SOFA ≥ 2), of sustained *S. aureus* bacteraemia, IE or multi-resistant bacteria (MRSA, *P. aeruginosa*, etc.), a randomized study recently confirmed the non-inferiority of an early switch to oral therapy (after 7 days) in the treatment of a bone and joint infection (52).

Recommendation 11- *The joint should be drained for as long as there is abundant effusion. Repeat joint aspiration drainage and surgical lavage (if possible arthroscopic) are equally recommended, based on the hospital's resources.*

During SA, 2 phases can be distinguished: the initial *congestive phase* with fluid that can be aspirated from the joint cavity, associated with weak to moderate hypervascularized tissue synovitis, and the *synovial phase* with significant, more or less vascularized synovial tissue hypertrophy, without fluid that can be aspirated (8).

In the *congestive phase*, the main purpose of drainage is to decrease the intra-cavity bacterial inoculum to enhance the effect of antibiotic therapy and limit cartilage damage. Incomplete joint drainage has been identified as an independent risk factor for treatment failure (18). No negative impact on mortality has been observed if surgical drainage is performed at least 48 hours after initiating treatment compared to earlier treatment (53). No functional benefits of early surgical lavage/synovectomy have been demonstrated (54). No longitudinal study has demonstrated the superiority of early surgery over needle aspiration drainage in the treatment of SA in a native joint (9,55–57). In fact, surgical joint drainage (open surgery or arthroscopy) has been associated with a worse functional prognosis and higher mortality (58), while percutaneous drainage has been associated with better functional recovery (9,18).

British guidelines in 2006 recommended repeat SF drainage until the joint dries “as often as necessary”, with no preference given between repeat aspiration and arthroscopic lavage (48).

For large joints, arthroscopic lavage is recommended if the response to repeat percutaneous needle aspiration is insufficient (48), in particular with persistently positive cultures despite suitable antibiotic therapy.

Recommendation 12 *An additional surgical procedure (joint lavage and/or synovectomy) should be considered if the infection is not controlled systemically or locally despite appropriate antibiotic therapy and repeat joint aspiration drainage.*

Synovectomy surgery is not relevant for first-line treatment of SA in a native joint, especially in the congestive phase. This procedure has a stiffening effect that delays short-term functional recovery and does not improve the functional prognosis in the medium term (16,48).

However, it should be considered in cases of persistent synovial hypertrophy with poor infection control despite appropriate antibiotic therapy, and after ruling out a differential diagnosis. Synovectomy can be performed by arthrotomy or arthroscopy depending on the hospital's technical resources.

The efficacy of the two techniques seems to be equivalent, but functional recovery in the medium term is inferior with arthrotomy and there are more complications (58–60). Arthroscopy should be preferred for the shoulder or knee, while open synovectomy should be considered when arthroscopic access poses technical difficulties.

As an indication, arthroscopic lavage should be considered in case of persistent purulent fluid and/or a positive culture after 5 to 7 days of suitable antibiotic therapy and synovectomy can be considered in cases of persistent inflammatory synovial hypertrophy after 15 days of appropriate antibiotic therapy and after ruling out a differential diagnosis (other coexisting inflammatory rheumatism, especially metabolic).

Recommendation 13 *Early physical therapy adapted to the patient's pain level is essential to maintain then improve passive joint range. Immobilization can be offered for pain relief for as short a time as possible.*

The absolute priority as far as physical therapy is concerned is recovering or maintaining joint range, initially by passive mobilization adapted to the patient's pain level, then active mobilization. Muscle therapy is secondary and can be started later.

There are no comparative studies evaluating the different methods of physical therapy during or after SA, but certain surgical trials have reported the importance of starting the day after surgery, under the supervision of the physical therapy team (60). No studies have evaluated the relevance of systematic joint immobilization.

Recommendation 14 *In cases involving a weight-bearing joint, partial weight-bearing with 2 canes (normal gait simulation) is possible as soon as the pain allows and the infection is in check.*

The recommended period to avoid weight-bearing for a weight-bearing joint (hip, knee or ankle) is not specified in the literature. No studies have shown the effectiveness of non-weight-bearing for preventing chondrolysis or epiphyseal osteonecrosis during SA.

Walking should be progressively encouraged based on pain levels during hospitalization (non-weight-bearing using 2 canes), gradually recovering weight-bearing over 4 to 6 weeks (60).

Recommendation 15- *Septic arthritis must be monitored both clinically and by lab tests (CRP). The purpose of monitoring is to keep track of the infection, find and eradicate the portal of entry (if identified), and assess functional sequelae. An X-ray is necessary at the end of antibiotic treatment to assess any structural damage.*

There is no data in the literature on the frequency or duration of SA monitoring. At least 6 months of follow-up is suggested.

The clinical information to consider is fever, pain, joint range, joint swelling, muscle atrophy and functional repercussions.

A poor functional outcome is not synonymous with a relapse or treatment failure. Structural joint damage is frequently observed after SA (almost 50%), even when healed. A type 1 complex regional pain syndrome (formerly known as reflex sympathetic dystrophy) can complicate and modify functional recovery, especially in wrist and ankle SA.

The standard weight-bearing X-ray makes it possible to assess the osteochondral structural damage.

It is useful to monitor complete blood count, kidney function and transaminases with lab tests to assess tolerance to antibiotic therapy.

It can be useful to monitor changes in CRP, although a persistent inflammatory syndrome does not mean that the infection has not healed. It is important to be able to look for other causes of inflammatory syndrome in this context (thrombophlebitis, lymphangitis due to an IV catheter, non-eradication of a persistent portal of entry (bedsore, cancer, etc.), concomitant IE, or non-infectious synovitis in the infected or another joint (metabolic, chronic progressive inflammatory rheumatism, post-infectious reactive synovitis, etc.).

The portal of entry responsible for haematogenous SA must always be sought and eradicated based on bacteriological documentation (*Appendix A, Box text S4*).

Recommendation 16- *In cases of joint destruction responsible for painful and debilitating functional disability, a prosthetic joint or arthrodesis (depending on the joint site) should be considered and discussed in a multidisciplinary meeting.*

There are few studies analyzing post-SA arthroplasty in native joints. This possibility can be considered as soon as the infection subsides, particularly in a hip, which is especially vulnerable, carries a high risk of sequelae (rapid chondrolysis, osteonecrosis) and is difficult to access for surgical lavage/synovectomy. One prospective study has described certain cases of hip arthroplasty immediately following SA with a good functional prognosis (61).

The timeline and methods of perioperative care must be discussed on a case-by-case basis in a local multidisciplinary meeting. In a complex context (comorbidities, bacterial resistance or surgical difficulties), it is best to refer the patient to a reference centre for complex bone and joint infections.

Conflicts of interest:

The authors declare that they have no conflicts of interest in relation to the content of the recommendations.

Acknowledgements

The working group wishes to thank the SFR for its logistical support and all the reviewers who made it possible to compile these recommendations. The working group thanks SPILF and SOFCOT for their contribution to these recommendations.

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Appendix A. Supplementary data

Supplementary data (Tables S1-S7, boxes text S1-S4) associated with this article can be found in the online version at ...

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Table 1: General principles and recommendations for the management of septic arthritis in an adult native joint.

		Level of evidence	Level of agreement		
			*	Average	≥8/10
General principles					
A	Septic arthritis is a diagnostic emergency due to the morbidity and mortality and the functional risk related to structural damage.	3a - C	R1	9.50 ±1.4	95.0%
B	Efforts should be made to provide microbiological documentation (blood cultures and joint aspiration) of the septic arthritis before starting antibiotic treatment.	2b - C	R1	9.43 ±1.5	90.0%
C	Septic arthritis must be managed from the start by a medical and surgical team that has experience with this condition.	5 - D	R2	8.91 ±1.5	90.6%
Specific recommendations					
1	Septic arthritis should be considered in all cases of acute monoarthritis whether the patient is febrile or not. Oligo- or polyarticular involvement does not rule out the diagnosis.	2a - B	R1	9.30 ±1.4	87.5%
2	Suspected septic arthritis justifies looking for signs of immediate severity (quick SOFA ≥2).	3b - C	R2	9.09 ±1.5	87.5%
3	It is essential to perform joint aspiration before administering antibiotics for a cytobacteriological analysis of the synovial fluid (except where there are immediate severity signs of sepsis with a SOFA ≥2). The additional inoculation of the synovial fluid in blood culture bottles is recommended, in particular in cases of prior antibiotic therapy or long waiting times.	2a - B 4 - C	R1	9.13 ±1.8	80.0%
4	Based on the analysis of the synovial fluid, microcrystal detection must be carried out in addition to the cytobacteriological analysis but their presence does not rule out the diagnosis of septic arthritis.	2a - B 3b - C	R1	8.93 ±1.3	80.0%
5	At least 2 sets of blood cultures should be performed before proposing antibiotic therapy, even in the absence of a fever.	2a - B	R2	9.53 ±0.8	96.9%
6	An X-ray is useful for diagnosing a pre-existing arthropathy and for structural monitoring, but should not delay the joint aspiration. No further imaging is required to make a positive diagnosis of septic arthritis.	3b - C	R1	9.15 ±1.4	87.5%
7	There is no indication for the systematic performance of a joint ultrasound. Joint ultrasound is nevertheless useful to confirm the presence of intra-articular effusion in case of clinical uncertainty and can be useful to guide aspiration.	2b - B	R1	9.53 ±0.8	95.0%
8	A cardiac ultrasound should be used to screen for infective endocarditis in cases of septic arthritis caused by <i>Staphylococcus aureus</i> , non-groupable oral streptococci, <i>Streptococcus gallolyticus</i> or <i>Enterococcus faecalis</i> .	3b - C	R2	8.97 ±1.6	90.6%
9	Except where there are signs of immediate severity (sepsis with SOFA ≥2), antibiotic therapy should not be prescribed before joint aspiration is performed to analyze the synovial fluid. Antibiotic therapy will be initiated upon receipt of positive microbiological results (direct examination, synovial fluid culture or blood culture). Probabilistic antibiotic therapy can also be considered in the case of clearly purulent synovial fluid without crystals.	3b - C	R2	8.50 ±2.2	81.5%
10	The total duration of antibiotic therapy (IV then oral) should be 4 to 6 weeks for pyogenic bacterial septic arthritis. A total duration of 7 days is sufficient in cases of <i>Neisseria gonorrhoeae</i> arthritis.	3b - C	R1	8.85 ±1.6	82.5%
11	The joint should be drained for as long as there is abundant effusion. Surgical lavage (if possible arthroscopic) and repeat joint aspiration drainage are equally recommended, based on the hospital's resources.	3b - C	R2	9.06 ±1.3	93.8%
12	An additional surgical procedure (joint lavage and/or synovectomy) should be considered if the infection is not controlled systemically or locally despite appropriate antibiotic therapy and repeat joint aspiration drainage.	3b - C	R2	9.19 ±1.5	90.6%
13	Early physical therapy adapted to the patient's pain level is essential to maintain then improve passive joint range. Immobilization can be offered for pain relief for as short a time as possible.	4 - D	R1	8.75 ±2.2	85.0%
14	In cases involving a weight-bearing joint, partial weight-bearing with 2 canes (normal gait simulation) is possible as soon as the pain allows and the infection is in check.	5 - D	R1	8.90 ±1.9	90.0%
15	Septic arthritis must be monitored both clinically and by lab tests (CRP). The purpose of monitoring is to keep track of the infection, find and eradicate the portal of entry (if identified), and assess functional sequelae. An X-ray is necessary at the end of antibiotic treatment to assess any structural damage.	5 - D	R2	9.44 ±1.0	96.9%
16	In cases of joint destruction responsible for painful and debilitating functional disability, a prosthetic joint or arthrodesis (depending on the joint site) should be considered and discussed in a multidisciplinary meeting.	4 - D	R1	8.75 ±1.3	82.5%

*Round of review according to the Delphi method of consensus (R1: 1st round, R2: 2nd round)

Table 2: Main differential diagnoses of septic arthritis in cases of acute febrile mono- or oligoarthritis.

Soft tissue inflammation and infections	Bursitis (septic or microcrystalline) Acute resorption of apatite calcification Infectious dermohypodermatitis (erysipelas)
Microcrystalline and metabolic arthropathies	Acute arthritis with monosodium urate deposits (gout) Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease (chondrocalcinosis) Acute resorption of apatite calcification
Inflammatory rheumatic disorders	Peripheral spondyloarthritis including psoriatic arthritis Rheumatoid arthritis Auto-inflammatory diseases (AOSD ^a , FMF ^b , CAPS ^c etc.) Vasculitis (Henoch Schönlein Purpura, Behçet's disease) Systemic autoimmune diseases
Infectious or post-infectious arthropathies	Post-venereal or post-dysenteric reactive arthritis Post-streptococcal arthritis or rheumatic fever Fungal or parasitic arthritis Viral arthritis (hepatitis A, B C, rubella, parvovirus B19, HIV, arbovirus)
Other arthropathies	Episodic attacks of synovitis (intermittent hydarthrosis) Haemarthrosis

^a AOSD: *Adult onset Still's disease*. ^b FMF: *Familial Mediterranean Fever (recurrent illness)*, ^c CAPS: *Cryopyrin-Associated Periodic Syndrome*.

Table 3: SOFA (Sequential Organ Failure Assessment) immediate severity score.
Should be calculated if quick-SOFA ≥ 2 (confusion or respiratory rate $>22/\text{min}$, or SBP $<100\text{ mmHg}$)

	0	1	2	3	4
PaO₂/FiO₂, mmHg (kPa)^a	≥ 400 (53.3) SaO ₂ $\geq 95\%$	$<400/53.3$ SaO ₂ 90–94%	<300 (40) SaO ₂ $<90\%$	<200 (26.7) with ventilatory assistance	<100 (13.3) with ventilatory assistance
Platelets (G/L)	≥ 150	<150	<100	<50	<20
Bilirubin ($\mu\text{mol/L}$)	<20	20–32	33–101	102–204	>204
Cardiovascular	MAP ≥ 70 mmHg	MAP <70 mmHg	Dopamine <5 or Dobutamine (any dosage)	Dopamine 5.1–15 or Adrenaline ≤ 0.1 or Noradrenaline ≤ 0.1	Dopamine >15 or Adrenaline >0.1 or Noradrenaline >0.1
Glasgow score	15	13–14	10–12	6–9	<6
Creatinine ($\mu\text{mol/L}$)	<110	110–170	171–299	300–440	>440
Urine output (mL/24h)	≥ 500	≥ 500	≥ 500	<500	<200

^a Adapted to the patient's assessment excluding critical care (SaO₂ added)

Definition of sepsis if SOFA ≥ 2 and of septic shock if sepsis + filling and vasopressor + lactates $>2\text{ mmol/L}$

Table 4. Antibiotic therapies proposed for the treatment of septic arthritis in an adult native joint based on the main bacterial species isolated.

<i>Bacterial species</i>	First-line IV antibiotic	Switch to oral antibiotic (according to bacterial sensitivity test)	Antibiotic if contraindication
Methicillin-sensitive <i>Staphylococcus aureus</i>	cloxacillin, oxacillin or cefazolin	Rifampicin ^c + FQ ^d or FQ ^d + Clindamycin ^e	Infectious disease consult Choice between Daptomycin, Rifampicin + others (cotrimoxazole, cyclins, linezolid)
Methicillin-resistant <i>Staphylococcus aureus</i>	Vancomycin or Teicoplanin	Rifampicin ^c + FQ ^d or FQ ^d + Clindamycin ^e	
Streptococci	Amoxicillin	Amoxicillin	Clindamycin or anti-streptococcal FQ ^d
Enterococci	Amoxicillin + Gentamicin ^f or Amoxicillin + Ceftriaxone (Infectious disease consult)	Amoxicillin	Infectious disease consult
Group 1 and 2 Enterobacteriaceae	Cefotaxime or Ceftriaxone	FQ ^d (if strain sensitive to nalidixic acid)	Infectious disease consult
Group 3 Enterobacteriaceae ^a	Cefepime	Infectious disease consult according to bacterial sensitivity test	Infectious disease consult
<i>Pseudomonas aeruginosa</i>	Ceftazidime + Ciprofloxacin ^b	Infectious disease consult according to bacterial sensitivity test	Infectious disease consult
Anaerobes	Amoxicillin if sensitive or Metronidazole	Clindamycin or Amoxicillin	Infectious disease consult
<i>Neisseria gonorrhoeae</i>	Ceftriaxone or Cefotaxime	FQ ^d	Infectious disease consult

^a Group 3 Enterobacteriaceae (*Enterobacter* sp., *Citrobacter freundii*, *Serratia* sp., *Morganella* sp., *Providencia* sp.) should not be treated using a 3GC antibiotic (cephalosporinase is induced, making the antibiotic inactive), but with a 4th generation cephalosporin such as cefepime.

^b A dual therapy comprised of Ceftazidime + amikacin can be used for the first 48 hours (decrease in bacterial inoculum) pending the final bacterial sensitivity test (sensitivity to ciprofloxacin)

^c Rifampicin should not be used as a monotherapy.

^d FQ: the following fluoroquinolones can be used in the treatment of septic arthritis: ofloxacin, levofloxacin, ciprofloxacin and moxifloxacin. All of these FQs are effective against staphylococci, Enterobacteriaceae and gonococci. Levofloxacin and moxifloxacin are effective against streptococci. Ciprofloxacin and levofloxacin are effective against *Pseudomonas aeruginosa*. Moxifloxacin should be used with caution due to its cardiac toxicity (heart rhythm disorders) and potential liver toxicity.

^e Clindamycin monotherapy can be proposed as an alternative (second-line treatment), according to US recommendations, in staph infections sensitive to erythromycin and clindamycin, in particular if resistant to FQ and/or rifampicin.

^f Gentamicin is offered for a period of 3 to 5 days in the absence of concomitant endocarditis.

Table 5. Practical methods for using the main antibiotics for the treatment of septic arthritis in adult native joints: dosages (in the absence of renal impairment), route of administration and main adverse reactions to look for.

Antibiotic	Dosage (CKD-EPI >60 ml/min)	Route of administration	Monitoring
Cloxacillin Oxacillin	IV: 150 mg/kg/day ^a without exceeding 16 g/day	IV to divide into 4 to 6 infusions/day or continuous infusion after a loading dose of 2 g over 1 hour then syringe pump ^b	Drug eruption Acute tubulopathy (drug-induced crystalluria) GI disorders Acute cytolytic hepatitis
Amoxicillin	IV: 150 to 200 mg/kg/day ^a without exceeding 16 g/day Oral: 4.5 to 6 g/day in 3 doses	IV to divide into 6 infusions/day or continuous infusion (daily dose divided into three 8-hour infusions) after a loading dose of 2 g over 1 hour then syringe pump ^b	Drug eruption GI disorders Encephalitis (confusion/epilepsy) Acute interstitial nephritis Acute tubulopathy (drug-induced crystalluria)
Cefazolin	IV 80 to 100 mg/kg/day ^a	IV to divide into 4 to 6 infusions/day or continuous infusion (daily dose divided into two 12-hour infusions) after a loading dose of 2 g over 1 hour then syringe pump ^b	Cytopenia Acute cytolytic hepatitis
Ceftriaxone	IV: 2 to 4 g/day	Flash IV 2 g every 12 h (if total dose 4 g) or every 24 h (if total dose 2 g)	Cytopenia Acute cytolytic hepatitis GI disorders (risk of PMC)
Cefotaxime	IV: 150 to 200 mg/kg/day ^a	IV to divide into 6 infusions/day or continuous infusion after a loading dose of 2 g over 1 hour then syringe pump ^b	
Ceftazidime	IV: 75 to 100 mg/kg/day ^a	IV to divide into 3 infusions/day or continuous infusion after a loading dose of 2 g over 1 hour then syringe pump ^b	
Cefepime	IV: 75 to 100 mg/kg/day ^a	IV to divide into 3 infusions/day or continuous infusion after a loading dose of 2 g over 1 hour then syringe pump ^b	
Vancomycin	IV: 40 mg/kg/day ^a , to adapt to assays	Loading dose of 1 g over 1 h then syringe pump, to be adapted to assays ^b	<i>For vancomycin:</i> 'Red man' syndrome if infused too fast. Vascular toxicity: requires central line or adapted dilutions by peripheral line.
Teicoplanin	IV: 10 mg/kg ^a with loading and then maintenance dose to adapt to assays	Loading dose 10 mg/kg/12 h the first 3 days then 1 slow IV injection of 10 mg/kg/day over 30 min ^b IM route possible (same doses)	<i>For all glycopeptides:</i> Ototoxicity and nephrotoxicity Drug eruption
Rifampicin	10 to 15 mg/kg/day ^a 600 mg once daily (<45 kg) 900 mg once daily (45 to 60 kg) 600 mg twice daily (>60 kg)	Taken orally on an empty stomach, once a day if total dose <900 mg, in 2 doses if total dose >900 mg	Enzyme induction: many combinations contraindicated (anticoagulants, antiretrovirals, calcineurin inhibitors, etc.) GI disorders Acute cytolytic hepatitis Orange coloration of secretions Never as a monotherapy
Ofloxacin	200 mg twice daily (monotherapy) 200 mg twice daily (combination with rifampicin)	Always oral	Neutropenia (combination with rifampicin) Tendinopathy (risk of rupture) Photosensitization
Levofloxacin	500 mg once daily (<60 kg) 750 mg once daily (>60 kg)		Risk of QT prolongation (moxifloxacin) GI disorders (risk of PMC)
Ciprofloxacin	500 mg twice daily (<60 kg) 750 mg twice daily (>60 kg)		
Moxifloxacin	400 mg once daily		
Clindamycin	600 mg three times a day (60 to 90 kg) 900 mg three times a day (>90 kg)	Oral (or IV)	GI disorders (risk of PMC) Frequent rashes Risk of QT prolongation (IV use)
Gentamicin	6 to 8 mg/kg once daily	IV over 30 minutes, once daily	Nephrotoxicity ^c Ototoxicity
Amikacin	20 to 30 mg/kg once daily		

^a Weight dose calculated using the ideal body weight if BMI >25. Ideal weight using Lorentz formula = height (cm) - 100 - (height (cm) - 150)/X, (where X = 2 if woman and X = 4 if man)

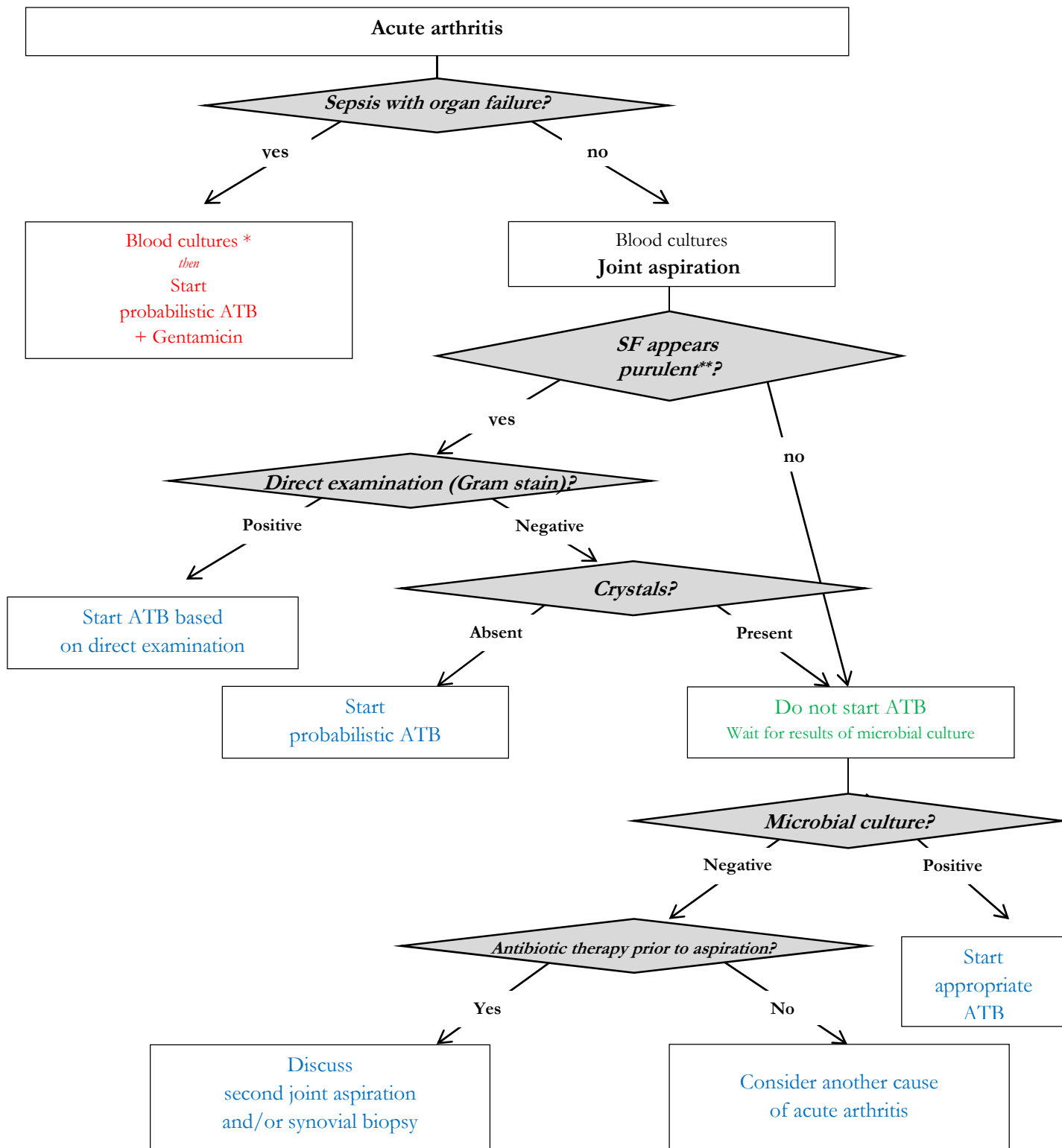
^b The use of a syringe pump for antibiotic therapy requires drug monitoring by assaying the trough level 48 to 72 hours after changing the dosage.

Target assay between 20 and 50 µg/mL for β-lactams and between 30 and 50 µg/mL for glycopeptides.

^c No need to determine the trough level of aminoglycosides for short-term treatment (<5 days) for patients without renal impairment (CKD-EPI >60 ml/min). The trough level assay is only recommended if an aminoglycoside is needed in patients with renal impairment and/or for prolonged treatment, such as with concomitant endocarditis.

IV: Intravenous, PMC: Pseudomembranous colitis

Figure 1. Algorithm aid for the initiation of antibiotic therapy during septic arthritis in an adult native joint



* Organizing the joint aspiration should not delay the start of antibiotic therapy in this situation. ** SF= Synovial fluid

ATB: Antibiotic

Probabilistic ATB: Cefazolin (age <70 years) or Ceftriaxone/Cefotaxime (age ≥70 years)

ATB based on direct examination:

- . Gram + in clusters (*Staphylococcus sp.*): Cloxacillin or Cefazolin
- . Gram + in chains (*Streptococcus sp./ Enterococcus sp.*): Amoxicillin
- . Gram -: Ceftriaxone/Cefotaxime